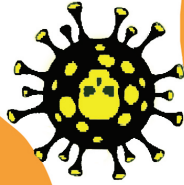


برنامه آموزش مجازی

تازه های کرونا - ۱

دارای ۱۶ امتیاز بازآموزی



دانشگاه پزشکی تهران



دانشگاه علوم پزشکی تهران



دانشگاه علوم پزشکی تهران



دانشگاه علوم پزشکی تهران



دانشگاه علوم پزشکی تهران





رئیس کنگره
دکتر محمد رئیس زاده



دبیر علمی
دکتر بابک شکارچی



دبیر اجرایی
دکتر محمدرضا عزیزی



دوسال از پاندمی کووید ۱۹ در دنیا می گذرد، هنوز زوایای بسیاری از این بیماری که تاثیرات بیشماری در تمام کشورهای جهان داشته ناشناخته مانده است. سازمان نظام پزشکی براساس وظیفه ذاتی خود و با تاکید بر گسترش آموزشهای عمومی ، اختصاصی و افزایش سطح سواد سلامت و هم چنین بازآموزیهای علمی ویژه ارایه دهندگان خدمات سلامت ، مبادرت به برگزاری دوره آموزشی جامع کووید ۱۹ نموده است. این همایش به صورت مجازی و با حداکثر امتیاز بازآموزی برگزار می شود. موضوعات مختلف از جمله تشخیص و تظاهرات بالینی، واکسیناسیون، توانبخشی، چالشهای درمان و ابعاد حقوقی آن می پردازد.

دکتر بابک شکارچی
دبیر علمی برنامه



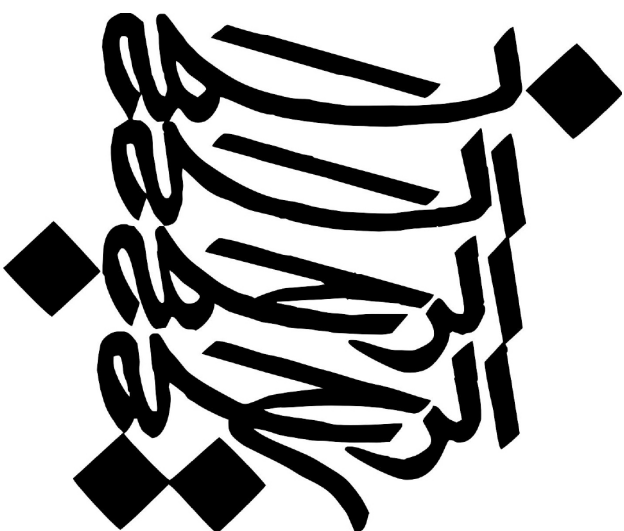
اعضای کمیته اجرایی

مینا اخوان، دکتر بابک پورقلیچ، الهه چراغی،
دکتر محمد دائمی، دکتر بابک شکارچی،
سحر صالحی، دکتر محمد رضا عزیزی، الهام
کریمی صارمی، مژگان کارکردی، دکتر علی
اصغر هنرمند



اعضای کمیته علمی

| | |
|---------------------------|---------------------------------|
| دکتر منصور ابوالقاسمیان | دکتر علیرضا خوشدل |
| دکتر بهنام ثبوتی | دکتر احسان مصطفوی |
| دکتر سید علیرضا فهیم زاد | دکتر مسعود سلیمانی دودران |
| دکتر محمد طاهر | دکتر مرضیه نجومی |
| دکتر علیرضا جلالی فراهانی | دکتر کتایون طائری |
| دکتر محمد جلیلی | دکتر حسن ابوالقاسمی |
| دکتر اتابک نجفی | دکتر طلعت مختاری آزاد |
| دکتر مجید مختاری | دکتر ژیلایاوریان |
| دکتر رامین ابریشمی | دکتر محمد وجگانی |
| دکتر کامران رودینی | دکتر محمدعلی برومند |
| دکتر حمید عمادی کوچک | دکتر حسن هاشمی |
| دکتر پیمان دادخواه | دکتر اردا کیانی |
| دکتر نفیسه حسینی یکتا | دکتر مصطفی قانعی |
| دکتر احمد علی نور بالا | دکتر اسماعیل ایدنی |
| دکتر زهرا وهابی | دکتر فرزاد فاتحی |
| دکتر معصومه ذوقعلی | دکتر مسعود مهرپور |
| دکتر محمد رضا اسدی | دکتر زهرا بدرخواهان |
| دکتر محمد حسین پور غریب | دکتر محمد جواد عالم زاده انصاری |
| دکتر غلامرضا نوروزی | دکتر بهزاد عین الهی |
| دکتر مجید روانبخش | دکتر علیرضا استقامتی |
| دکتر مهرناز رسولی نژاد | دکتر اشرف آل یاسین |
| دکتر سعید بیرودیان | دکتر نسرين چنگیزی |
| دکتر محمد تقدسی | دکتر مصطفی اسماعیلی |
| | دکتر حسین فودازی |



تازه های کووید با رویکرد واکسیناسیون، تشخیص و تظاهرات بالینی

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تظاهرات بالینی و بیماریهای همراه

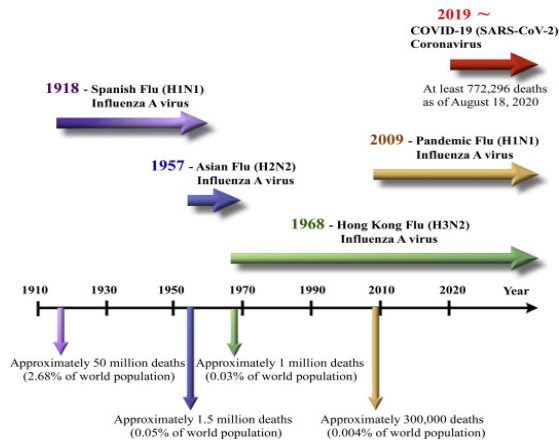
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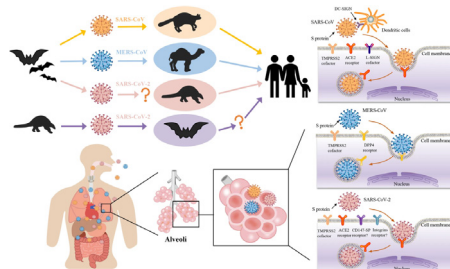
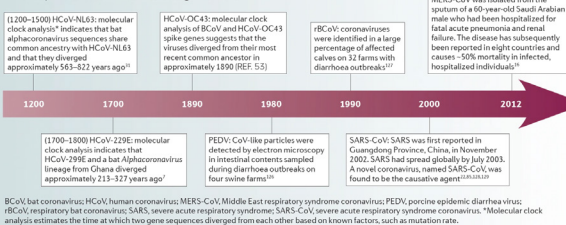
Professor Ali Reza Khoshdel

MD, PhD in Epidemiology

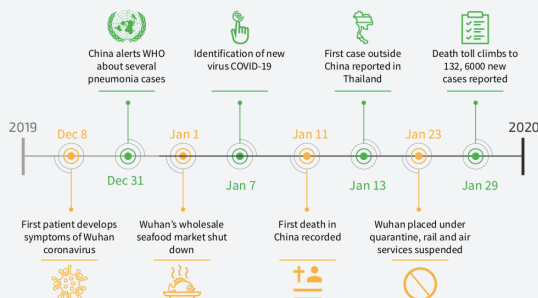
December 2021



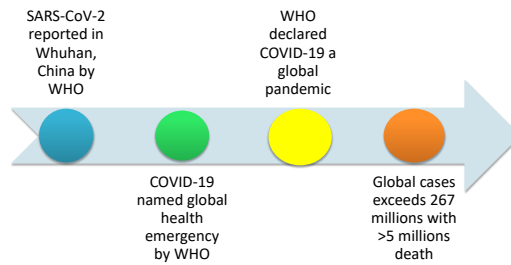
Timeline | Timeline of coronavirus emergence events



Coronavirus Timeline: The Beginning

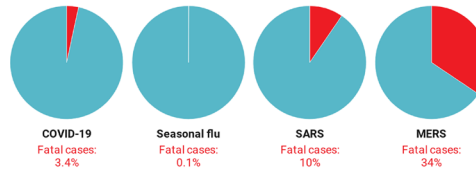


- Compared to SARS and MERS, COVID-19 has spread strikingly fast: While MERS took two and a half years to infect 1,000 people, and SARS took roughly four months to hit that figure, COVID-19 reached 1,000 cases in just 48 days.

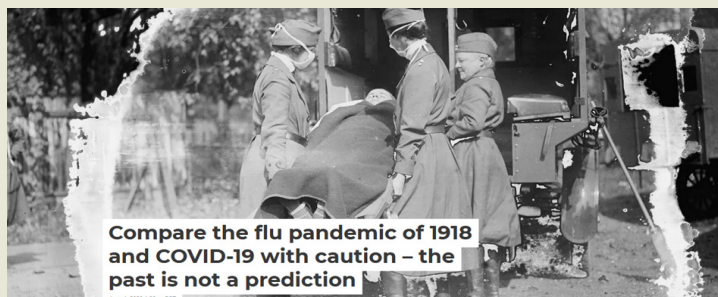


COVID-19 looks a lot closer to the season flu than to previous coronavirus outbreaks

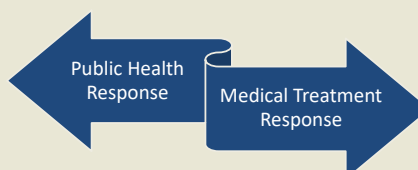
Fatal cases Non-fatal cases



COVID-19, SARS, and MERS data are global and total to date. Seasonal flu data are U.S., for the 2018-2019 season. Chart: Elijah Wolfson for TIME • Source: CDC and WHO • Created with Datawrapper

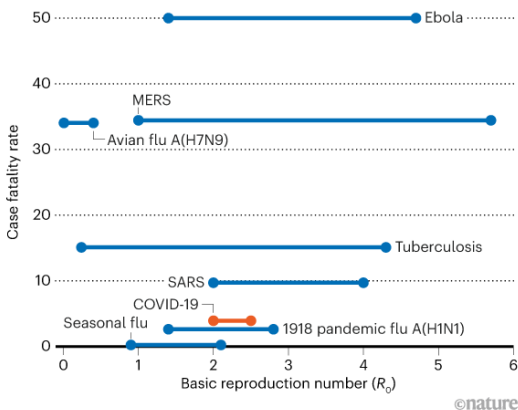


Compare the flu pandemic of 1918 and COVID-19 with caution – the past is not a prediction



COVID-19 VS OTHER DISEASES

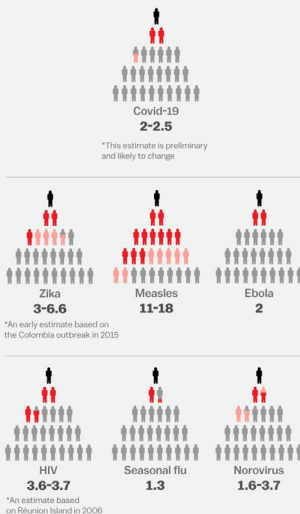
Estimates suggest the COVID-19 coronavirus is less deadly than the related illnesses SARS or MERS, but more infectious (R_0) than seasonal influenza.



Contagious, resistant, mostly mild or asymptomatic, long transmission period, sometimes severe complication, no medication, not yet vaccination, etc...

How contagious is a disease?

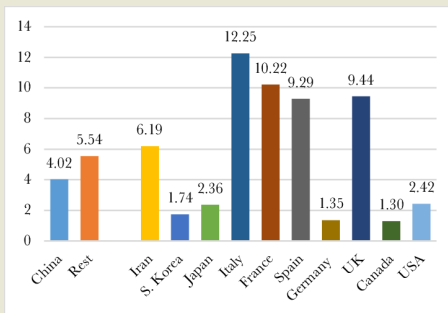
Scientists use "R naught," or R_0 , to estimate how many other people one sick person is likely to infect



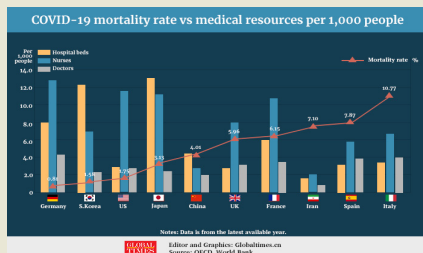
SOURCES: Travel Medicine, PLOS One, JAMA Pediatrics, MOP, NCBI, New England Journal of Medicine, "The Spread and Control of Norovirus Outbreaks Among Hospitals in a Region"

Vox

Case Fatality Rate (CFR)



Mortality and Resources

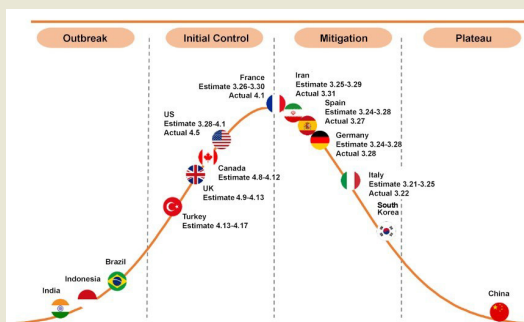
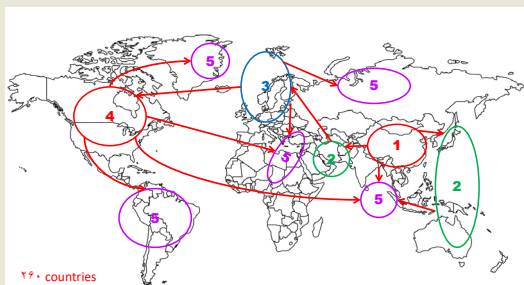


تازه های کووید

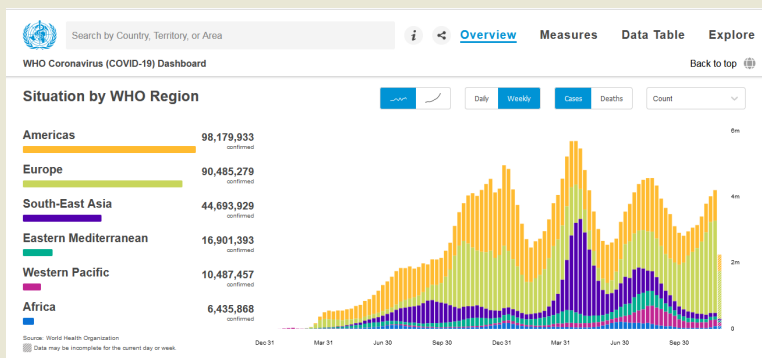
Covid 19

The Comprehensive National Congress On Covid 19

Case Fatality Rate (CFR)



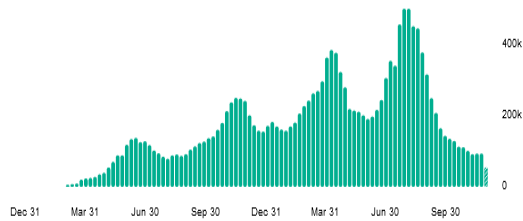
10 December 2021



Globally, as of 4:08pm CET, 9 December 2021, there have been **267,184,623** confirmed cases of COVID-19, including **5,277,327** deaths, reported to WHO. As of 8 December 2021, a total of **8,158,815,265** vaccine doses have been administered.

Eastern Mediterranean

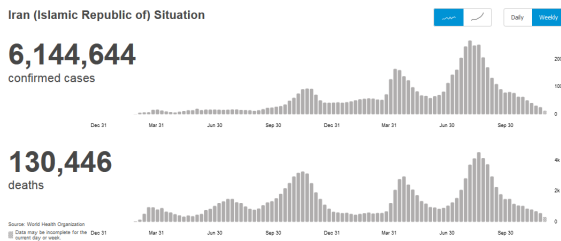
16,901,393
confirmed cases



Iran (Islamic Republic of) Situation

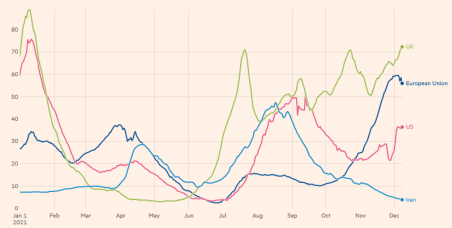
6,144,644
confirmed cases

130,446
deaths



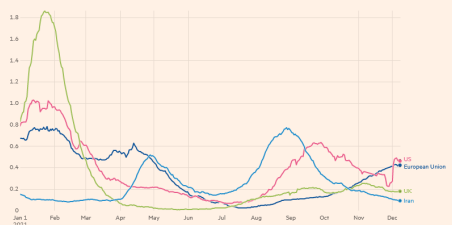
New confirmed cases of Covid-19 in European Union, US, UK and Iran

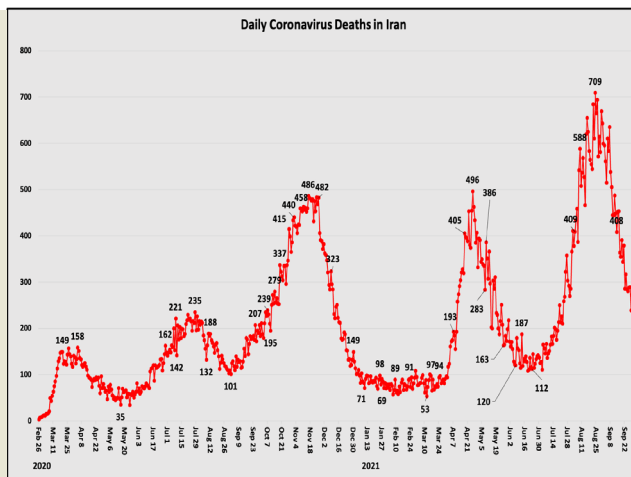
Seven-day rolling average of new cases (per 100k)



New deaths attributed to Covid-19 in European Union, US, UK and Iran

Seven-day rolling average of new deaths (per 100k)

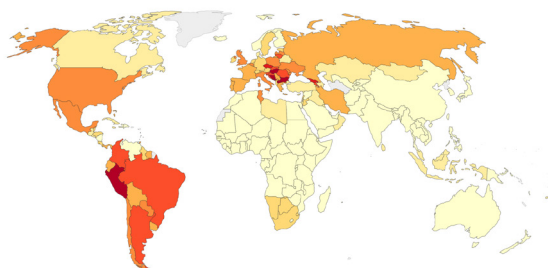




Cumulative confirmed COVID-19 deaths per million people

Due to limited testing and challenges in the attribution of the cause of death, confirmed deaths can be lower than the true number of deaths.

Our World in Data



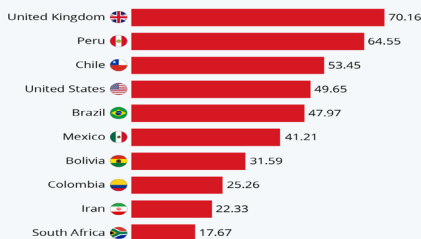
No data 0 500 1,000 1,500 2,000 2,500 3,000 3,500 >4,000

Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

COVID-19 Deaths Per 100,000 Inhabitants: A Comparison

COVID-19 deaths per 100,000 of the population in the 10 worst affected countries*

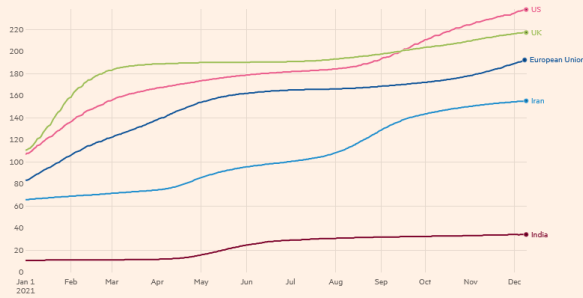


* As of August 09, 2020 at 03:00 AM EDT
Source: Johns Hopkins University



statista

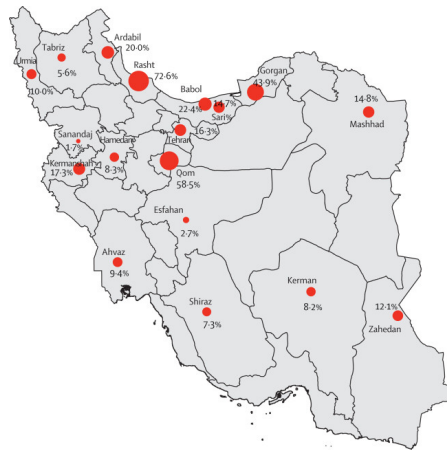
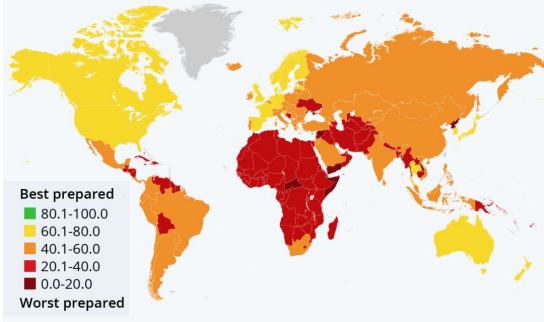
Cumulative deaths attributed to Covid-19 in European Union, US, UK, Iran and India
Cumulative deaths (per 100k)



Source: Financial Times analysis of data from Johns Hopkins CSSE, World Health Organization, UK Government coronavirus dashboard, Government of Iran, Public Health France, Iranian Ministry of Health and the Swedish Public Health Agency. Data updated December 9 2021 3:23pm GMT. Interactive version: ft.com/covid19

The Countries Best And Worst Prepared For A Pandemic

Country score in the 2021 Global Health Security Index rating the ability to respond to epidemics/pandemics*



تازه های کووید

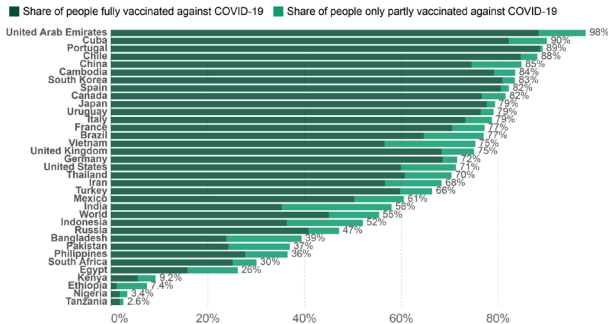
Covid 19

The Comprehensive National Congress On Covid 19

Share of people vaccinated against COVID-19, Dec 8, 2021

Alternative definitions of a full vaccination, e.g. having been infected with SARS-CoV-2 and having 1 dose of a 2-dose protocol, are ignored to maximize comparability between countries.

Our World
in Data



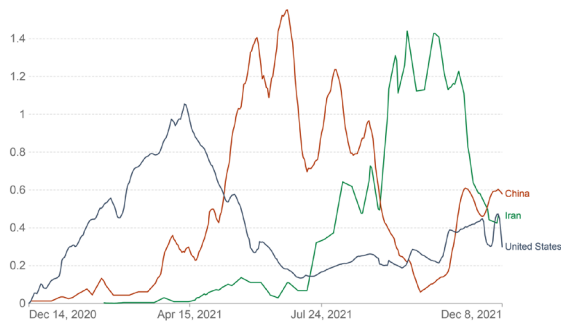
Source: Official data collated by Our World in Data. This data is only available for countries which report the breakdown of doses administered by first and second doses in absolute numbers.
CC BY

تاکنون ۸۵ درصد جمعیت هدف بالای ۱۲ سال دوز اول را تزریق کرده‌اند و پوشش کامل واکسیناسیون در جمعیت هدف به ۷۱ درصد رسیده است. استان قم با ۷۰ درصد تزریق دوز اول کمترین میزان استقبال از واکسیناسیون در کشور را به خود اختصاص داده است و در جایگاه‌های بعدی استان کردستان با ۷۴ درصد، البرز با ۷۷ درصد، بوشهر و سیستان و بلوچستان با ۷۸ درصد کمترین میزان استقبال از واکسیناسیون را داشتند.

Daily COVID-19 vaccine doses administered per 100 people

Number of daily doses administered (rolling 7-day average), divided by the total population of the country. All doses, including boosters, are counted individually.

Our World
in Data

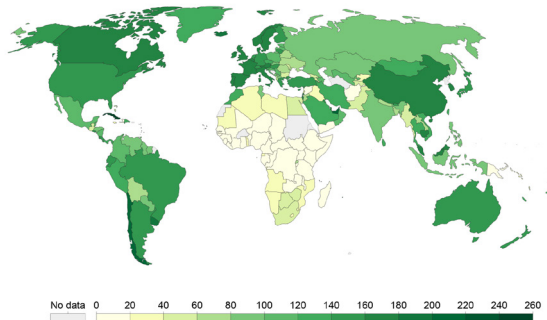


Source: Official data collated by Our World in Data - Last updated 9 December 2021, 10:20 (London time)
OurWorldinData.org/coronavirus - CC BY

COVID-19 vaccine doses administered per 100 people

All doses, including boosters, are counted individually. As the same person may receive more than one dose, the number of doses per 100 people can be higher than 100.

Our World
in Data

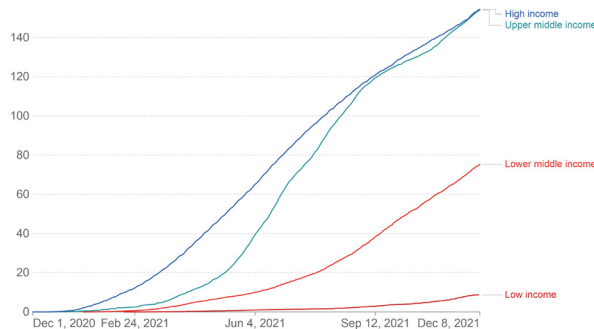


Source: Official data collated by Our World in Data – Last updated 9 December 2021, 10:20 (London time)
OurWorldinData.org/coronavirus • CC BY

COVID-19 vaccine doses administered per 100 people, by income group

All doses, including boosters, are counted individually. As the same person may receive more than one dose, the number of doses can be higher than the number of people in the population.

Our World
in Data



Source: Official data collated by Our World in Data, World Bank
Note: Country income groups are based on the World Bank classification.

OurWorldinData.org/covid-vaccinations • CC BY

How Effective Are The Covid-19 Vaccine Candidates?

Estimated effectiveness at Covid-19 prevention based on interim data from late-stage clinical trials*



* As of Nov 23, 2020, Phase III trials for BNT162b2 are complete.
Other trials are ongoing and findings have not been peer-reviewed.
Sources: Respective companies, Russian health ministry



statista

تازه های کووید

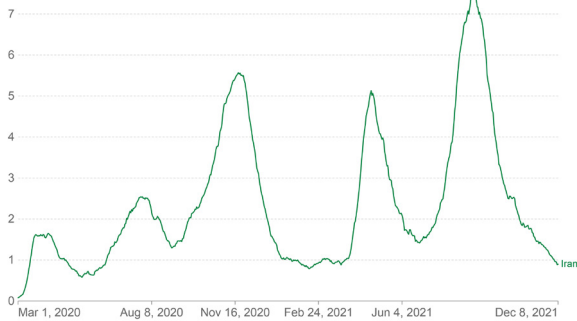
Covid 19

The Comprehensive
National Congress On Covid 19

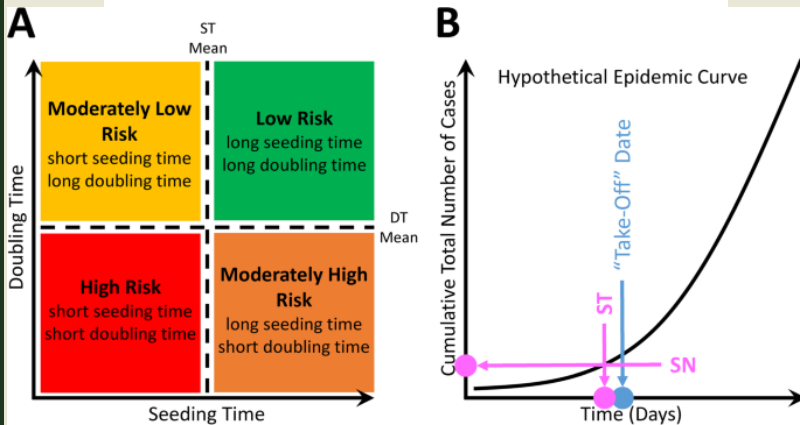
۱۸

Daily new confirmed COVID-19 deaths per million people

7-day rolling average. Due to limited testing and challenges in the attribution of the cause of death, confirmed deaths can be lower than the true number of deaths.

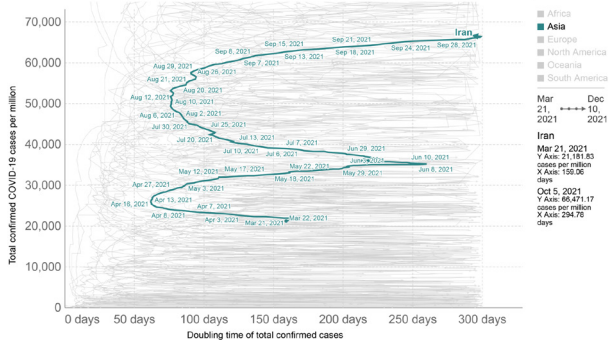


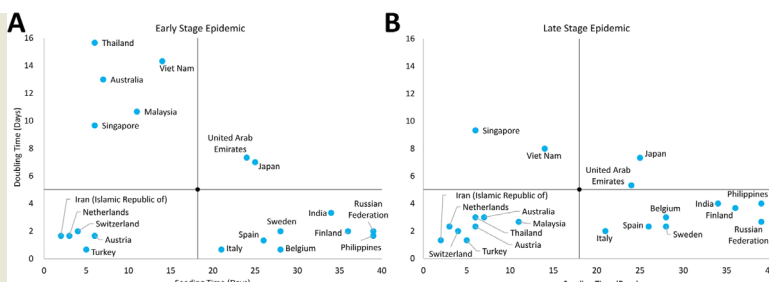
Predict Trajectories



Total confirmed COVID-19 cases per million vs. Doubling time of total confirmed cases, Mar 21, 2021 to Dec 10, 2021

The number of confirmed cases is lower than the number of total cases. The main reason for this is limited testing.



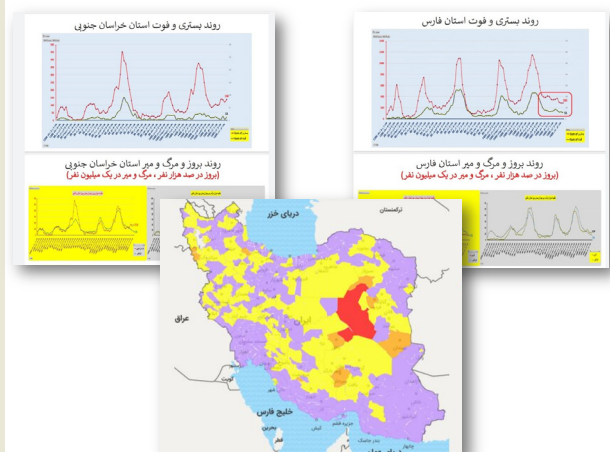


Determination of mean seeding time (ST) and mean doubling time (DT) and ST/DT Model sensitivity analysis. a With seeding number (SN) set to 12 cases for all countries and seeding time (ST) for each country calculated as the number of days required to reach SN = 12, early epidemic stage doubling time (DT) for each country was calculated as the mean number of days required to observe case doubling to 24, 48, and then 96 cases. All 20 countries were plotted on the ST/DT Model coordinate plane and overall mean ST was found to be 18 days (Horizontal line) and overall mean DT was found to be 5 days (Vertical line). b For sensitivity analysis, later epidemic stage DT was calculated as the mean number of days for each country to observe case doubling to 192, 384, and 768 cases. The countries with the largest changes from early to later stage epidemic were Australia, Malaysia, and Thailand, all of which moved from moderately low risk to high risk. Viet Nam also had a marked reduction in DT but remained moderately low risk. All countries in the moderately high risk quadrant moved closer to the mean DT line but did not cross over into the low risk quadrant. The only country that did not move at all (ie, had no change in DT) was Switzerland

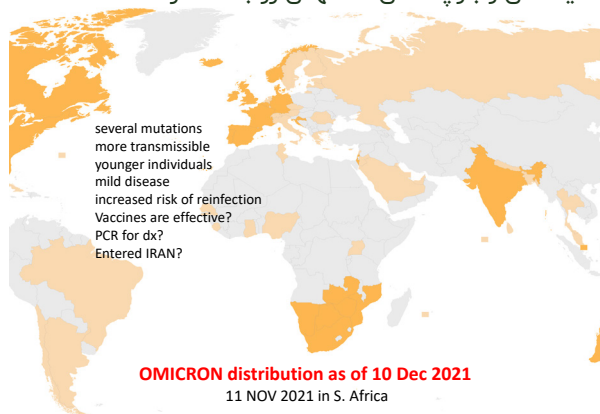
روند درصد رعایت دستور العمل های بهداشتی در کشور



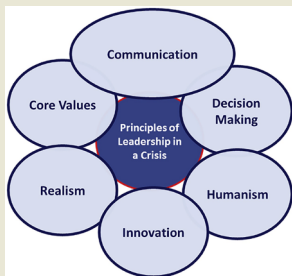
دستورعمل های بهداشتی شامل رعایت بهداشت فردی، استفاده از ماسک، رعایت فاصله گذاری اجتماعی و رعایت تهویه مناسب می باشند.



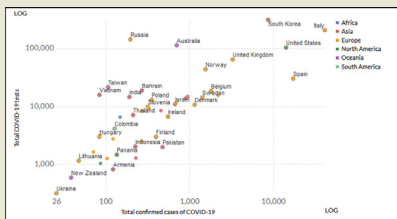
خراسان شمالی، یزد، کرمان، گلستان، سمنان، مازندران، گیلان، اردبیل، خراسان رضوی، فارس، قم، هرمزگان، بوشهر، سیستان و بلوچستان، اصفهان رو به خطر هستند



Crisis Management

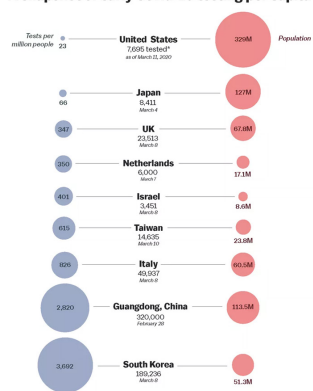


Test and Trace



NOTE:
Timely
Easy Access

A snapshot of early Covid-19 testing per capita

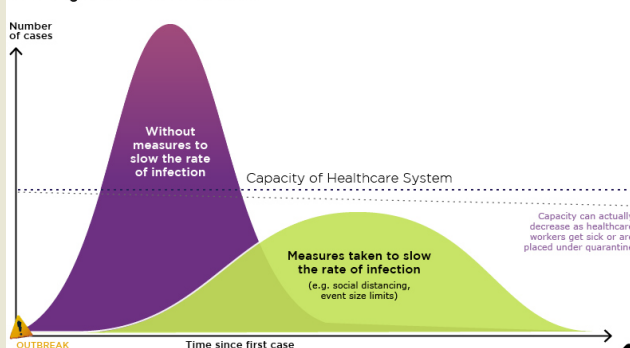


*Test counts do not include full reporting from all US states
Source: Covid Tracing Project, Business Insider, the Atlantic, Taiwan CDC

Vox

Mitigation

Flattening the COVID-19 Case Curve



Source: Adapted from Drew Harris, CDC

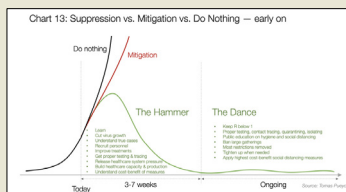
تازه های کووید

Covid 19

The Comprehensive National Congress On Covid 19

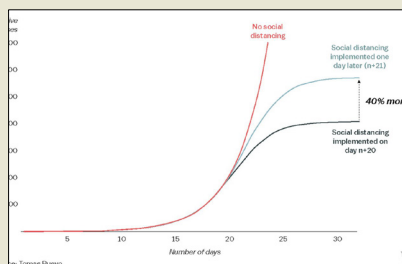
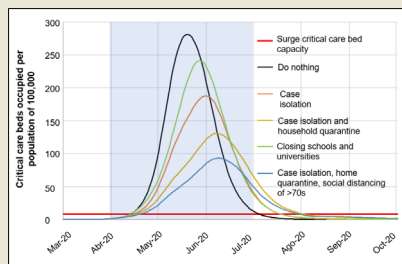
۲۲

Suppression

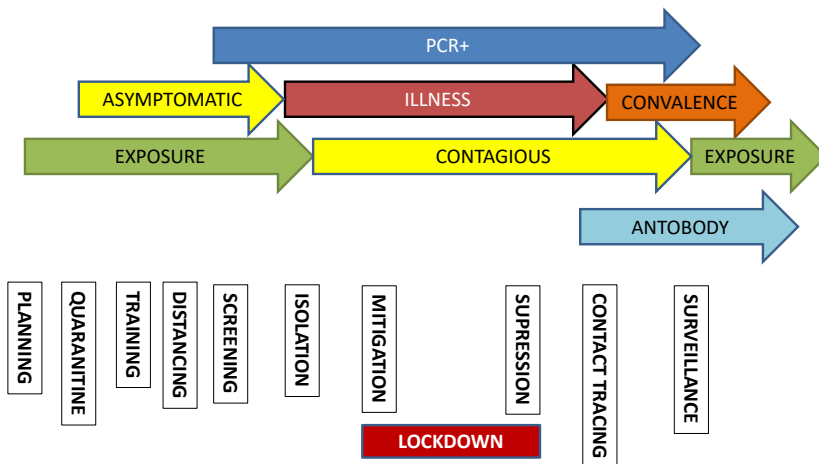


MOST EFFECTIVE NPIs

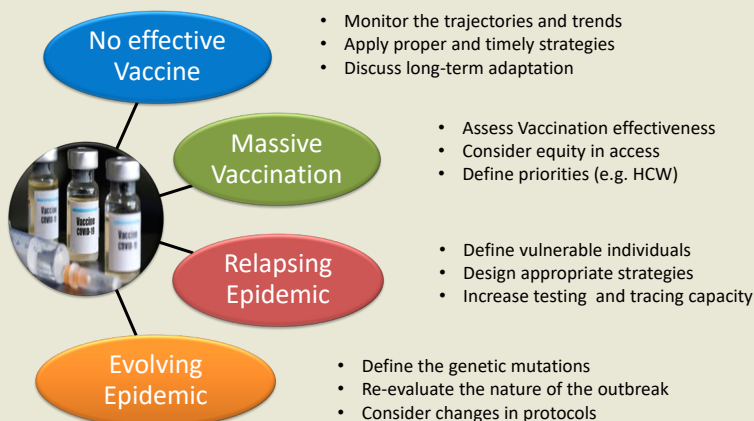
Case Isolation
Home Quarantine
Social Distancing



Summarizing Strategies



Possible Future Scenarios



Action Plan





دکتر احسان مصطفوی

**اپیدمیولوژیست، مدیر پروژه کارآزمایی بالینی واکسن مشترک
انستیتو پاستور ایران و انستیتو فینلای کوبا**

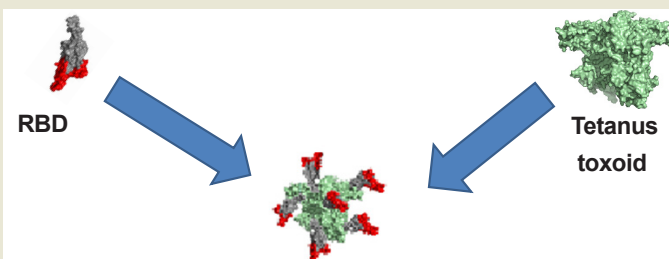
نتایج، فرصت ها و چالش های کارآزمایی بالینی واکسن پاستوکوک در ایران



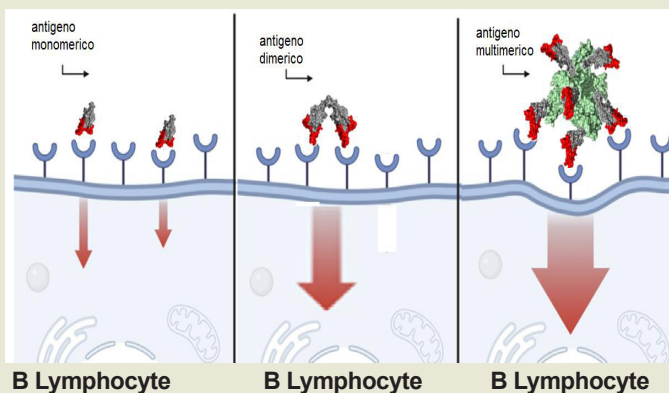
IFV INSTITUT
FINLAY
VACUN



سوبرانا 2 / پاستوکوک



نقش آنتی ژن چند ظرفیتی در خنثی سازی موثر ویروس



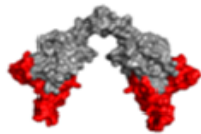
تازه های کووید

Covid 19

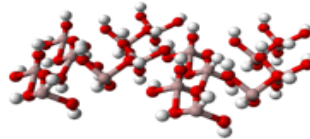
The Comprehensive
National Congress On Covid 19

سوبرانا پلاس / پاستوکوک پلاس

RBD dimer



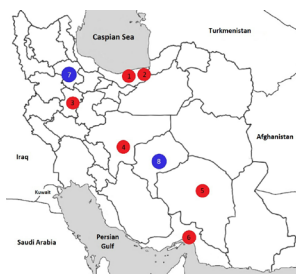
$Al(OH)_3$



طراحی مطالعه: 24 هزار داوطلب در 8 شهر کشور افراد تحت مطالعه

در 6 شهر (شامل اصفهان، بابل، بندرعباس، ساری، همدان و کرمان) این مطالعه رژیم واکسن 2 - دوز (از کاندید واکسن سوبرانا - 2) در روزهای صفر و 28 تزریق شد.

در 2 شهر (شامل زنجان و یزد) علاوه بر دو دوز واکسن سوبرانا - 2، یک دوز بوستر از واکسن سوبرانا-1 با فاصله 28 روز از دوز دوم تزریق شد.

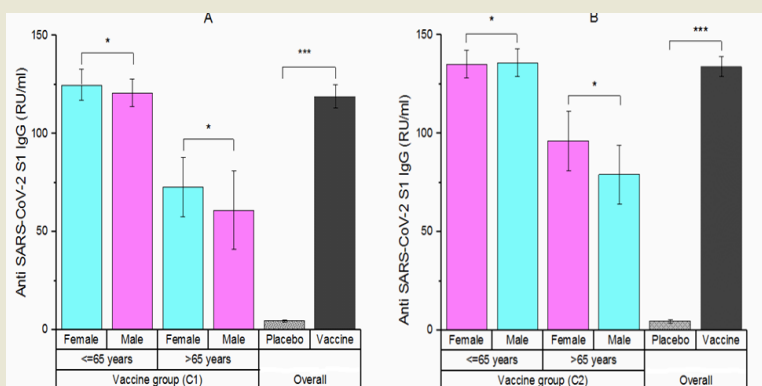




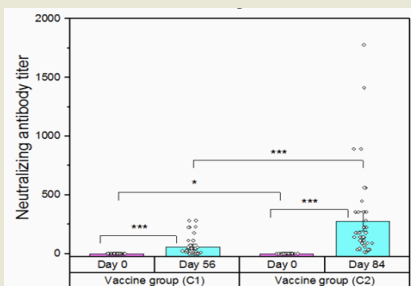
مقایسه سطح آنتی بادی افراد واکسینه شده در مقایسه با روز صفر

| زمان مطالعه | تعداد نمونه بررسی شده | درصد افزایش ۴ برابری یا بیشتر |
|------------------|-----------------------|-------------------------------|
| روز ۵۶ (دو دوزه) | ۲۶۰۸ نفر | ٪۸۶/۵ |
| روز ۸۴ (سه دوزه) | ۹۹۶ نفر | ٪۹۸/۸ |

میانگین هندسی آنتی بادی تولیدی در شرکت کنندگان مطالعه



مقایسه سطح آنتی بادی افراد واکسینه شده در مقایسه با روز صفر

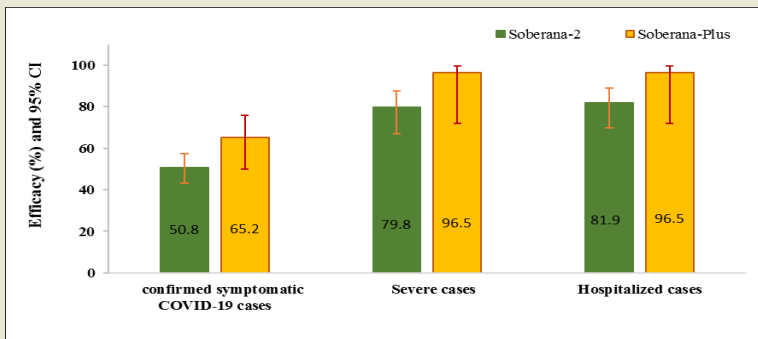


ایمنی سلولی در رژیم دو دوزه

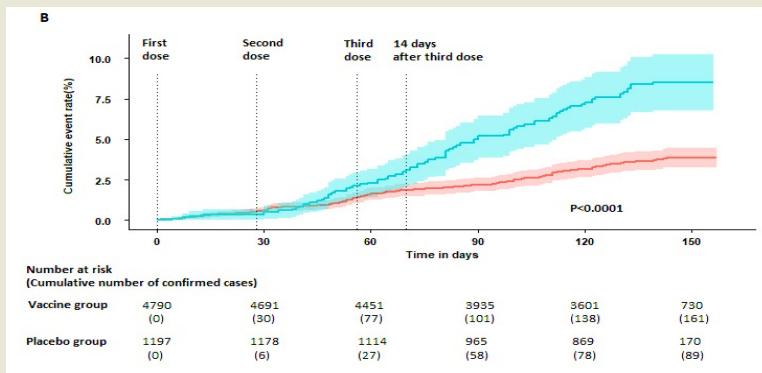
- اطلاعات ایمنی سلولی با استفاده از کیت اینترفرون گاما بر روی 424 نفر در شهرهای ساری و بابل در روز 56 (یک ماه بعد از تزریق دوز دوم واکسن) اندازه گیری شد.

- در 90/7 درصد از افراد مطالعه که واکسن دریافت کرده بودند، پاسخ ایمنی سلولی و هومورال در روز 56 مشاهده شد.

مقایسه اثربخشی رژیم دو دوزه و سه دوزه واکسن سوبرانا - 2



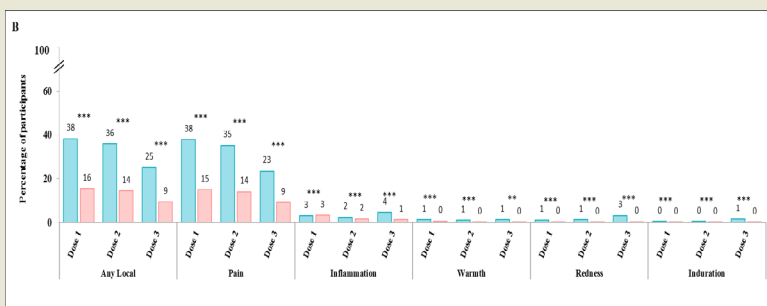
اثربخشی رژیم سه دوزه واکسن سوبرانا



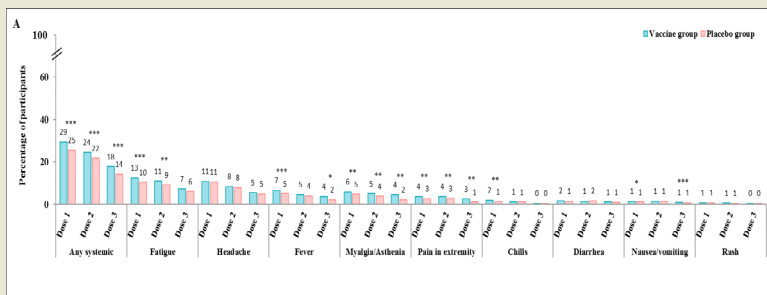
اثر بخشی واکسن در پیشگیری از مرگ ناشی از کووید-19

در رژیم دو دوزه یک مورد مرگ در گروه واکسن نما مشاهده شد ولی هیچ مورد مرگی در گروه واکسن تا پایان زمان مطالعه اثربخشی مشاهده نگردید. در رژیم سه دوزه هیچ مورد مرگی در گروه واکسن و واکسن نما مشاهده نگردید.

درصد شیوع عوارض موضعی در شرکت کنندگان مطالعه



درصد شیوع عوارض سیستمیک در شرکت کنندگان مطالعه



کمیته‌های نظارتی مطالعه

- کمیته ملی اخلاق در پژوهش های زیست پزشکی
- سازمان غذا و دارو
- کمیته پایش و ایمنی مطالعه (DSMB)
- کمیته پایش



همکارانی که در به ثمر نشستن این مطالعه همکاری داشتند



| | |
|------|--|
| ۷۵ | سطح ملی (انستیتو پاستور ایران، کمیته های علمی و نظارتی، ...) |
| ۱۰۲ | دانشگاه علوم پزشکی اصفهان |
| ۱۴۵ | دانشگاه علوم پزشکی بابل |
| ۱۸۲ | دانشگاه علوم پزشکی مازندران |
| ۱۵۴ | دانشگاه علوم پزشکی زنجان |
| ۹۱ | دانشگاه علوم پزشکی کرمان |
| ۷۳ | دانشگاه علوم پزشکی هرمزگان |
| ۱۵۶ | دانشگاه علوم پزشکی همدان |
| ۱۰۱ | دانشگاه علوم پزشکی یزد |
| ۱۰۷۹ | |

سپاس از داوطلبان شرکت کننده در مطالعه



چالش ها و فرصت های کارآزمایی بالینی واکسن در ایران

مطالعه فاز 3 کوبا

مقاله فاز سوم کارآزمایی بالینی واکسن سوبرانا که در کشور کوبا انجام شده است به صورت پری پرینت در دسترس است. در این مطالعه اثربخشی ۹۲ درصدی واکسن در پیشگیری از فرم های علامت دار بیماری و همچنین بیخطری آن نشان داده شده است. در مطالعه اثربخشی رژیم سه دوزه این واکسن هیچ مرگی در گروه واکسن اتفاق نیفتاد و ۳ مورد مرگ در گروه واکسن نما گزارش شد.

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Efficacy and Safety of SOBERANA 02, a COVID-19 conjugate vaccine in heterologous three doses combination

① M. Eugenia Toledo-Romani, M. Garcia-Carmenate, ② C. Valenzuela Silva, W. Baldoquin-Rodriguez, M. Martinez Pérez, M. C. Rodriguez Gonzalez, B. Paredes Moreno, J. C. Mendoza Hernández, R. Gonzalez-Mujica Romero, O. Samón Tabio, P. M. Velazco Villares, J. P. Bacallao Castillo, E. Licea Martín, ③ M. Rodriguez Ortega, ④ N. L. Herrera Marrero, ⑤ E. Caballero Gonzalez, L. I. Egues Torres, R. Duarte Gonzalez, S. Garcia Blanco, S. Pérez Cabrera, S. Huete Ferreira, K. Idalmis Cisneros, O. Fonte Galindo, D. Meliá Pérez, L. Rojas Remedios, S. Fernandez Castillo, ⑥ Y. Climent Ruiz, Y. Valdes-Balbin, ⑦ D. Garcia-Rivera, ⑧ V. Verez Bencomo, SOBERANA Phase 3 team

doi: <https://doi.org/10.1101/2021.10.31.21265703>

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should not be used to guide clinical practice.

[Abstract](#)

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[Metrics](#)

[Preview PDF](#)

کارآزمایی بالینی فاز 1 و 2 در کودکان

- در این بالینی 350 کودک 3 تا ۱۸ ساله وارد مطالعه شدند.
- متعاقب تزریق 2 دوز از کاندید واکسن سوبرانا-2 هیچ عارضه جدی یا شدید منتسب به واکسن مشاهده نشد. الگوی بیخطری واکسن در این گروه سنی مشابه بالغین 19 تا 29 ساله بود.
- بعد از دریافت 2 دوز واکسن، افزایش 4 برابری تیتر آنتیبادی در 99/3% کودکان 3 تا 11 سال و 92/9% کودکان 12 تا 18 سال مشاهده گردید.
- نتایج سایر شاخصهای ایمنولوژیک (شامل غلظت آنتیبادی IgG، مهار اتصال RBD به گیرنده ACE2 و تولید آنتیبادی نوترالیزاسیون) در این گروه سنی مشابه پاسخ ایمنولوژیک در بالغین گروه سنی 19 تا 29 سال بود.

سوبرانا پلاس به عنوان تک دوز

- در این مطالعه به افراد با سابقه ی قبلی کووید-۱۹ یک دز از واکسن سوبرانا پلاس تزریق شده است.
- هیچ عارضه جدی متعاقب تزریق واکسن گزارش نشده است.
- میانه تیتر آنتی بادی مهارکننده سه برابر افراد با سابقه ی قبلی کووید-۱۹ بوده است.
- تیتر ۱:۱۶۰ آنتی بادی خنثی کننده در 80 درصد داوطلبین دیده شده است.
- افزایش سلولهای تی اختصاصی و تولید کننده اینترفرون گاما و آلفا دیده شده است.
- یک ظرفیت بازمهندسی برای سوبرانا-پلاس وجود دارد و با ایجاد برخی تغییرات، ایمنی را در برابر انواع جهش‌ها ایجاد کرد.

THE LANCET Regional Health Americas

VOLUME 4, 100079, DECEMBER 01, 2021

PDF [1 MB]

A single dose of SARS-CoV-2 FINLAY-FR-1A vaccine enhances neutralization response in COVID-19 convalescents, with a very good safety profile: An open-label phase 1 clinical trial

Arturo Chang-Monteagudo ^{a, b} • Rolando Ochoa-Azze ^{a, b} • Yanet Climent-Ruiz ^a •

Consuelo Macías-Abraham ^a • Laura Rodríguez-Noda ^a • Carmen Valenzuela-Silva • et al. Show all authors

تازه های کووید

Covid 19

The Comprehensive National Congress On Covid 19

آخرین وضعیت مجوزهای واکسن در ایران

- مجوز استفاده در افراد زیر 18 سال
- مجوز استفاده به عنوان دوز بوستر سایر واکسن ها





دکتر مسعود سلیمانی دودران
مرکز کارآزمایی بالینی دانشگاه علوم پزشکی
ایران - IUMS-CTC

اطمینان از انجام صحیح و بدون سوگیری ارزیابی های ایمنولوژیک

مشکلات

- مشخص نبودن آزمایشات ایمنوژنیسیته ضروری در ابتدای کار و
- انجام آزمایشات ایمنوژنیسیته توسط سازنده واکسن و
- نبود آزمایشگاه رفرنس در سازمان غذا و دارو

راه حل ها

- کورسازی نسبت به مداخله
- کورسازی نسبت به پیامد ها، استفاده از جفت کد آشکار و پنهان

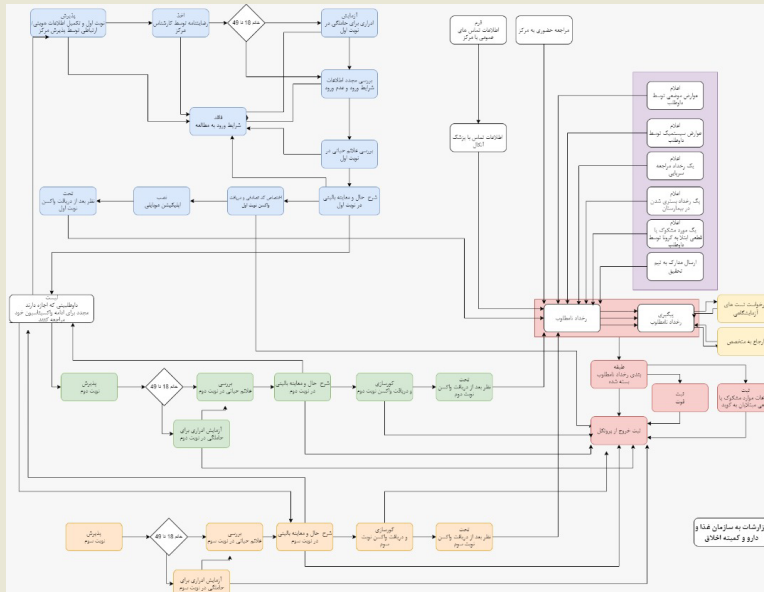
اطمینان از انجام صحیح و بدون سوگیری ارزیابی های ایمنولوژیک

مشکلات

- تعداد بالای شرکت کنندگان در فاز 3 و حجم زیاد داده ای که تولید می شود
- ضرورت انجام پیگیری فعال Active
- ضرورت سرعت عمل در انجام و گزارش آنالیز های بینابینی
- ضرورت شناسایی و ثبت همه رخداد های نامطلوب (قبل از اینکه معلوم شود واکنش نامطلوب به واکسن هستند)

راه حل ها

- ایجاد ارتباط دو طرفه بین داوطلب و تم پیگیری از طریق اپلیکیشن موبایلی
- طراحی نرم افزار مناسب برای ثبت و مدیریت داده و پیگیری بلند مدت
- ایجاد سیستم یکپارچه و مرتبط



سایر مشکلات

- بی اعتمادی مردم برای شرکت در مطالعه حتی در مطالعات Non inferiority بصورت blind
- بسته شدن پنجره انجام مطالعه سوپریوریته با در دسترس قرارگرفتن واکسن
- نبود CRO مستقل
- کمبود وقت برای طراحی، آماده سازی و اجرا
- هزینه بسیار زیاد انجام مطالعات کارآزمایی و نامانوس بودن مقررات حاکم بر انجام کارآزمایی با استانداردهای ICH برای قاطبه محققین کشور
- معضل کارت واکسن



Marzieh Nojomi, MD, MPH

Professor of Community Medicine
IUMS

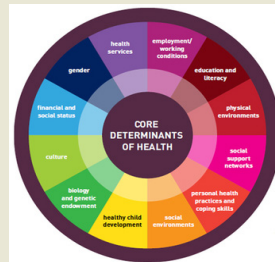
MSK Manifestations of COVID-19

Covid-19 Pandemic

- On December 31, 2019, cases of unexplained pneumonia were reported in Wuhan city, China
- After performing extensive investigations, isolation of a virus related to the genus coronaviruses was done and later named
- Novel coronavirus (COVID-19) by the world health organization on 12 January

Definition of SDH

- The social determinants of health (SDH) are the non-medical factors that influence health outcomes.
- They are the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life.



SDH Components



Examples of the social determinants of health

- Income and social protection
- Education
- Unemployment and job insecurity
- Working life conditions
- Food insecurity
- Housing, basic amenities and the environment
- Early childhood development
- Social inclusion and non-discrimination
- Structural conflict
- Access to affordable health services of decent quality.

Importance of SDH

- Recent estimates attribute 10 to 20 percent of health outcomes to medical care
- 30 percent to genetics,
- 40 to 50 percent to behavior,
- 20 percent to the social and physical environment.

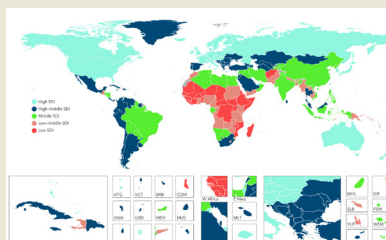
Socio-demographic Index (SDI)

- Summary measure that identifies where countries or other geographic areas sit on the spectrum of development.
- SDI is a composite average of the rankings of the
Incomes per capita,
Average educational attainment, and
Fertility rates of all areas in the GBD study.

Socio-demographic Index (SDI)

- SDI is highly correlated with many of the health outcomes
- For example, fertility captures differences in the number of people in different age groups in a country, which is in turn linked with mortality patterns.
- In a country with a large number of older people, for example, more people die than in a country with greater numbers of young people.

Sociodemographic-Index groupings by country



COVID-19 and income inequality in OECD countries

| | Mean | sd | Min | Max |
|---------------------------------------|-----------|-----------|---------|------------|
| Cases per-million | 2474.21 | 2077.79 | 136.02 | 7413.36 |
| Deaths per-million | 175.03 | 214.06 | 4.08 | 841.27 |
| GDP per capita | 41,889.82 | 24,240.02 | 9370.18 | 116,639.89 |
| Not in Europe | 0.28 | 0.45 | 0.00 | 1.00 |
| Days since first case reported | 112.31 | 18.56 | 88.00 | 148.00 |
| Proportion of population aged over 65 | 17.75 | 4.01 | 7.22 | 27.58 |
| Life Expectancy at birth | 80.72 | 2.56 | 74.80 | 84.20 |
| Days from first case to lockdown | 31.11 | 25.42 | 2.00 | 115.00 |
| Maximum lockdown stringency index | 78.80 | 11.89 | 46.00 | 96.00 |
| Gini | 32.70 | 5.22 | 24.20 | 45.40 |

COVID-19 and income inequality in OECD countries

- A strong association between income inequality and the number of COVID-19 deaths
- Wider income inequalities lead to worse health outcomes
- Income inequality could be a proxy for social capital and the investment in, and popular support of, public services

COVID-19 and income inequality in OECD countries

- Countries with low levels of income inequality were simply more prepared and were in a stronger position to cope with the COVID-19 crisis.
- It is also the case that stronger social capital also leads to individuals following lockdown restrictions more stringently.

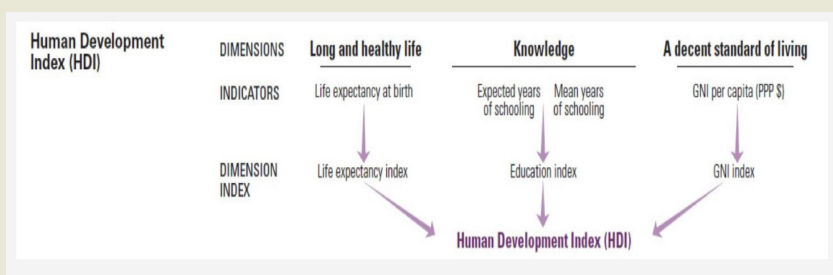
Human Development Index (HDI)

- The Human Development Index (HDI) is a summary measure of average achievement in key dimensions of human development:
- A long and healthy life, being knowledgeable and have a decent standard of living.
- The HDI is the geometric mean of normalized indices for each of the three dimensions.

Human Development Index (HDI)

- The health dimension is assessed by life expectancy at birth,
- The education dimension is measured by Mean of years of schooling for adults aged 25 years and more and expected years of schooling for children of school entering age.
- The standard of living dimension is measured by Gross national income per capita.

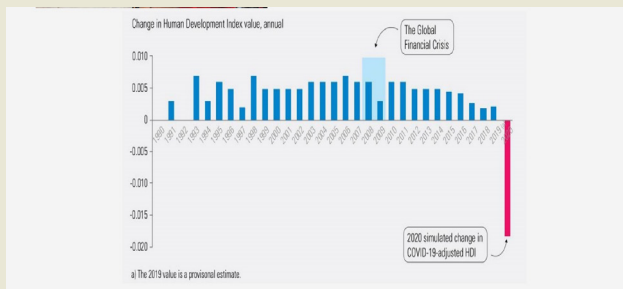
Human Development Index (HDI)



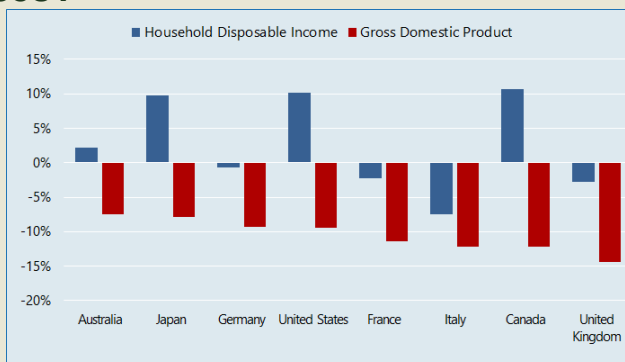
COVID-19: Human development on course to decline this year for the first time since 1990

- The world has seen many crises over the past 30 years, including the Global Financial Crisis of 2007-09.
- Each has hit human development hard but, overall, development gains accrued globally year-on-year,”
- “COVID-19 – with its triple hit to health, education, and income – may change this trend.”

COVID-19: Human development on course to decline this year for the first time since 1990



How did the first wave of the COVID-19 pandemic affect the household sector and public finances?



COVID-19 and the impact of Social Determinants of Health

- COVID-19 has been termed a Great equalizer
- Social inequalities in health are profoundly, and unevenly, impacting COVID-19 morbidity and mortality.

COVID-19 and the impact of Social Determinants of Health

- Many social determinants of health including
- Poverty, physical environment (eg, smoke exposure, homelessness), and race or ethnicity—can have a considerable effect on COVID-19 outcomes.

COVID-19 and the impact of Social Determinants of Health

- Homeless families are at higher risk of viral transmission because of crowded living spaces and scarce access to COVID-19 screening and testing facilities.
- In a study of 408 individuals residing in a shelter, 147 (36%) had a positive SARS-CoV-2 PCR test.

COVID-19 and the impact of Social Determinants of Health

- Smoke exposure and smoking has been linked to adverse outcomes in COVID-19.
- Current or former smokers were more likely to have severe COVID-19 symptoms than non-smokers (about 4 times)
- An increased risk of intensive care unit (ICU) admission (2.4 times), mechanical ventilation (1.4), or COVID-19-related mortality (4 times)

COVID-19 and the impact of Social Determinants of Health

- The COVID-19 infection rate is three times higher in black than in white
- The mortality rate is six times higher
- In a report, Over 50% of COVID-19 cases and almost 70% of COVID-19 fatalities are disproportionately within the black population, who make up only 30% of that population

COVID-19 and the impact of Social Determinants of Health

- Physical distancing measures, are substantially more difficult for those with adverse social determinants
- School closures increase food insecurity for children living in poverty who participate in school lunch programs
- Malnutrition causes substantial risk to both the physical and mental health of these children, and increase of the risk of infectious disease

COVID-19 and the impact of Social Determinants of Health

- People who are homeless are at higher risk of infection during physical lockdowns especially if public spaces are closed, resulting in physical crowding
- Being able to physically distance is not simply accessible in some communities

COVID-19 and the impact of Social Determinants of Health

- The association of social inequalities and COVID-19 morbidity is further compounded in the context of underlying chronic respiratory conditions
Such as asthma, possible additive, or even multiplicative, effect on COVID-19 morbidity.

- Several adverse social determinants that impact the risk of COVID-19 morbidity also increase asthma morbidity
Including poverty, smoke exposure, and race or ethnicity

Influence of COVID-19 on lifestyle behaviors

- Among the multiple consequences of the current pandemic, there have been two significant impacts;
- Stockpiling food as a result of grocery restriction
- Spending more time indoor;
Including working from home, tele-education, and restricted outdoor physical activities

Influence of COVID-19 on lifestyle behaviors

- Besides, the frequent stressful exposure to visual and auditory news concerning COVID-19 can be linked to
- Overeating, in particular high-sugar foods, known as
“Food craving”

Influence of COVID-19 on lifestyle behaviors

- Sedentary habits attributable to lockdown measures as alternations in
- Sleeping, and smoking habits are substantially changing the lifestyle,
- Especially among health workers

Influence of COVID-19 on lifestyle behaviors

- Sleep disorders could be a risk factor for obesity, especially in young men
- Mental distress and social isolation may lead to an increase in the need for smoking
- During the lockdown, smoking will have a higher chance to impact second-hand smokers

Lifestyle changes in before and during COVID-19

| Items | Mean | SD | 95% CI | | t | Sig. (2-tailed) |
|---|------|------|--------|--------|---------|-----------------|
| | | | Lower | Upper | | |
| How many times do you smoke per day before? | 1.30 | 0.75 | - 0.02 | 0.00 | - 1.04 | 0.30 |
| How many times do you smoke per day during | 1.30 | 0.77 | | | | |
| How many hours do you sleep per day before? | 1.53 | 0.59 | - 0.33 | - 0.29 | - 28.81 | 0.00** |
| How many hours do you sleep per day during? | 1.84 | 0.75 | | | | |
| How many times do you practice physical activity per week before? | 2.22 | 1.43 | 0.02 | 0.10 | 3.09 | 0.00** |
| How many times do you practice physical activity per week during? | 2.16 | 1.43 | | | | |
| How many minutes do you spend per each exercise before? | 1.61 | 0.89 | 0.01 | 0.07 | 2.97 | 0.00** |
| How many minutes do you spend per each exercise during | 1.56 | 0.86 | | | | |
| Before confinement, what were your physical activities | 1.56 | 2.21 | - 0.37 | - 0.24 | - 6.91 | 0.00** |
| During confinement, what are your physical activities? | 1.86 | 2.41 | | | | |
| How many hours do you spend watching TV per day before? | 2.27 | 1.41 | - 0.69 | - 0.63 | - 43.56 | 0.00** |
| How many hours do you spend watching TV per day during? | 2.93 | 1.58 | | | | |
| How many hours do you spend on social media per day before? | 3.90 | 1.12 | - 0.45 | - 0.41 | - 39.94 | 0.00** |
| How many hours do you spend on social media per day during? | 4.33 | 0.95 | | | | |
| How many hours do you spend on the internet to study/work per day before? | 3.65 | 1.35 | - 0.34 | - 0.29 | - 26.36 | 0.00** |
| How many hours do you spend on the internet to study/work per day during | 3.97 | 1.31 | | | | |
| How many hours do you spend with your family before? | 3.67 | 1.33 | - 0.57 | - 0.52 | - 37.91 | 0.00** |
| How many hours do you spend with your family during | 4.21 | 1.14 | | | | |

Changes in time spent on TV, social media, internet, and with family before and during COVID-19

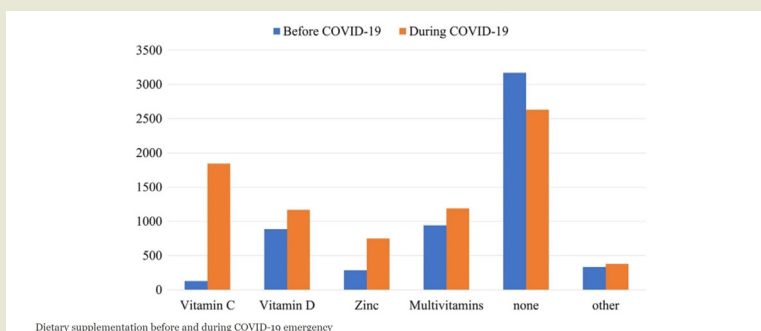
| | TV | | Social media | | Internet (study/work) | | Family | |
|-----------|--------------|-----------------|--------------|-----------------|-----------------------|-----------------|--------------|-----------------|
| | pre-COVID-19 | during COVID-19 | pre-COVID-19 | during COVID-19 | pre-COVID-19 | during COVID-19 | pre-COVID-19 | during COVID-19 |
| None | 2620 (44.4) | 1755 (29.8) | 176 (3) | 103 (1.7) | 547 (9.3) | 462 (7.8) | 554 (9.4) | 294 (5) |
| < 1 h/day | 1090 (18.5) | 852 (14.5) | 606 (10.3) | 255 (4.3) | 822 (13.9) | 589 (10) | 730 (12.4) | 323 (5.5) |
| 1 h/day | 794 (13.5) | 724 (12.3) | 1060 (18) | 548 (9.3) | 974 (16.5) | 616 (10.4) | 973 (16.5) | 540 (9.2) |
| 2 h/day | 776 (13.2) | 1132 (19.2) | 1808 (30.7) | 1624 (27.5) | 1292 (21.9) | 1206 (20.5) | 1497 (25.4) | 1391 (23.6) |
| > 2 h/day | 616 (10.4) | 1433 (24.3) | 2246 (38.1) | 3366 (57.1) | 2261 (38.3) | 3023 (51.3) | 2142 (36.3) | 3348 (56.8) |

Smoking habit before and during COVID-19

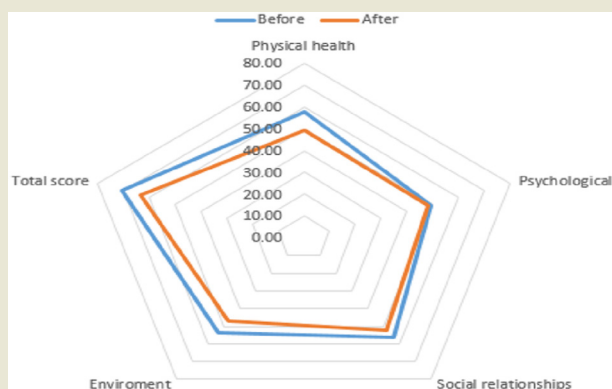
| | Smoking pre-COVID-19 | Smoking during COVID-19 |
|---------------------|----------------------|-------------------------|
| Never | 4910 (83.3) | 4928 (83.6) |
| < 5 cigarettes/day | 479 (8.1) | 439 (7.4) |
| 5-10 cigarettes/day | 234 (4) | 228 (3.9) |
| > 10 cigarettes/day | 273 (4.6) | 301 (5.1) |

Data presented as n (%)

Dietary supplementation before and during COVID-19 emergency



Change in WHOQOL-BREF scores according to COVID-19.

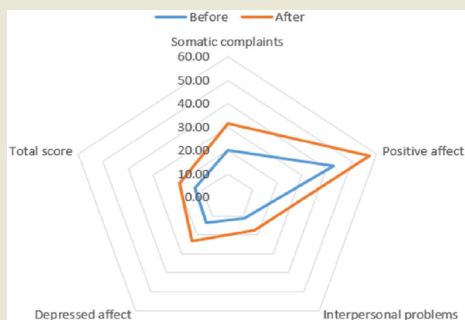


Change in quality of life due to COVID-19.

| | Before | | After | | t (95% Confidence interval) | p-value |
|----------------------|--------|-------|-------|-------|-----------------------------|---------|
| | M | SD | M | SD | | |
| Physical health | 20.15 | 3.35 | 17.29 | 3.94 | 8.47 (2.19–3.53) | p<0.001 |
| Psychological | 14.70 | 2.57 | 14.46 | 3.74 | 0.87 (-0.30–0.77) | 0.386 |
| Social relationships | 8.42 | 1.31 | 7.82 | 1.68 | 4.54 (0.33–0.86) | p<0.001 |
| Environment | 21.46 | 4.37 | 18.76 | 4.62 | 7.06 (1.95–3.47) | p<0.001 |
| General | 5.41 | 1.25 | 4.68 | 1.42 | 5.90 (0.49–0.98) | p<0.001 |
| Total score | 70.15 | 10.92 | 63.00 | 13.10 | 7.18 (5.17–9.12) | p<0.001 |

<https://doi.org/10.1371/journal.pone.0247970.t005>

Change in CES-D10 scores according to COVID-19.



Findings

- Sedentary lifestyle increased, spending more time on social media and television.
- Sleep time reduced and body weight increased
- There was a significant increase in the rate of dietary supplement consumption,

COVID-19 and the impact of Social Determinants of Health

- The effect of social determinants of health and COVID-19 morbidity is perhaps underappreciated
- Yet, the great public health lesson is that for centuries pandemics disproportionately affect the poor and disadvantaged

COVID-19 and the impact of Social Determinants of Health

- Additionally, mitigating social determinants
Improved housing, reduced overcrowding, and improved nutrition
- Reduces the effect of infectious diseases,

Tuberculosis, even before the advent of effective medications.

COVID-19 and the impact of Social Determinants of Health

- It is projected that recurrent outbreaks of SARS-CoV-2 will likely occur after this initial wave, necessitating ongoing planning over the next few years.
- Studies are required to measure the effect of COVID-19 on individuals with adverse social determinants and innovative approaches to management are required, and might be different from those of the broader population.

COVID-19 and the impact of Social Determinants of Health

- The effect of physical distancing measures, particularly among individuals with chronic conditions facing adverse social circumstances, needs to be studied
- Adverse determinants and physical distancing measures could compound issues, such as medication access and broader access to care.
- The long-term effect of school closures, among those facing adverse social circumstances, is also in need of study.

COVID-19 and the impact of Social Determinants of Health

- Measures that affect adverse determinants,
Reducing smoke exposure, regular income support to low-income households, access to testing and shelter among the homeless, and improving health-care access in low-income neighborhoods
- Have the potential to dramatically reduce future pandemic morbidity and mortality,

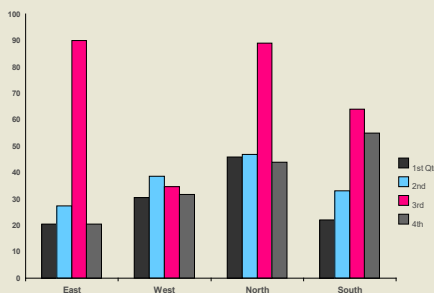
COVID-19 and the impact of Social Determinants of Health

- Moving forward, as the lessons of COVID-19 are considered, social determinants of health must be included as part of pandemic research priorities, public health goals, and policy implementation.



Conclusion

- Public health interventions should be developed to reduce these hazardous effects and avoid the emergence of a deadlier pandemic.



دکتر کتایون طایری
متخصص بیماری های عفونی، فلوشیپ HIV/AIDS بالینی

تأثیر پاندمی کووید 19- بر سیستم بهداشتی و مراقبت بیماری ها

بحران های بهداشتی

- میتوان ادعا کرد که اساسا در تمام دنیا، بدلیل تثبیت نسبی وضعیت سلامت، سیستم های بهداشتی بر پایه مقابله با بحران ها طراحی نشده بوده است

- بحران بهداشتی، یک واقعه غیر منتظره با چالش های بزرگ بهداشتی که نیازمند بسیج سریع منابع بوده و بر تمام جمعیت عمومی تأثیر می گذارد - بحران کووید 19- در حقیقت تأثیرات بسیار عمیقی بر سیستم بهداشتی، حتی در کشورهای توسعه یافته داشته است

- بسیاری از سیستم های بهداشتی دنیا بر بیماری های غیر واگیر نظیر دیابت و بیماری های قلبی - عروقی متمرکز بوده است

- مواردی چون تغییر سبک زندگی و سالمندی و ...

- برای مثال تخمین زده می شد که با افزایش 48% در مبتلایان به دیابت، تا سال 2045 حدود 629 میلیون دیابتی در دنیا وجود خواهد داشت!

- به دلیل کنترل بیماری های واگیر در جهان و کنترل outbreak ها، بیشتر خدمات بهداشتی و مراقبتی، از بیمارستان به بخش های سرپایی شیفت داده شده است

- سرمایه گذاری در زمینه پیشگیری از بیماری های واگیر کاهش یافته بود.

کووید 19-

- یک بحران جهانی که گفته می شود :

- هر روزمان را برای اصلاح خطای دیروزمان گذرانیم!

- سیستم بهداشتی با چهار مشکل عمده مواجه شد:

- خستگی جسمی و روحی پرسنل بهداشتی

- کاهش منابع مالی

- هزینه های سنگین کووید

- بسته شدن بیمارستانهای فعال در سایر رشته ها

- افزایش روند به تعویق افتادن سایر خدمات بهداشتی-درمانی

- نظیر مراقبت بیماری های مزمن، بدخیمی ها و

- واکسیناسیون، مراقبت مادران، ...

- افزایش بیماری های مختلف

- اختلالات روانپزشکی (اضطراب، افسردگی)، افزایش مصرف مخدرها و الکل،

بیحرکتی، عوارض کووید 19- مزمن، aging؟!

تبعات تداوم بحران کووید- 19

- اقتصادی

- قرنطینه و تعطیلی مشاغل

- اجتماعی

- تغییرات روابط اجتماعی، فامیلی و خانوادگی

- بحران های عاطفی

- سیاسی

- اعتماد به ارگانهای جهانی نظیر WHO یا تصمیم برای تصمیم گیری فردی

- تکنولوژی

- تولیدات جدید با تمرکز بر اقدامات نظارتی و کنترلی

- تداوم پذیری ارائه خدمات مهم قبلی

- محیط زیست و ...

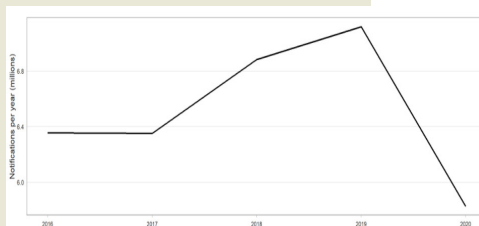
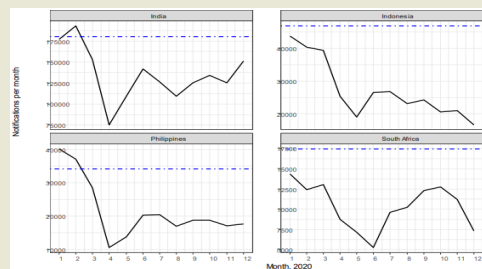
- مطالعات مختلف نشان داده است که در طی پاندمی کووید-19، در تمام دنیا

اطلاع رسانی در مورد اغلب بیماری های عفونی دیگر کاهش یافته است.

- برای مثال کاهش 12% بیماریابی سل در آلمان در سال گذشته کاهش یافته است.

Source, Global TB report,
WHO, 2021

رشد بیماریابی سل در 84 کشور، 2017-2020



تأثیر کووید بر بیماریابی سل

- در سال 2020 حدود 1.4 میلیون نفر شناسایی سل کمتر بوده است
- 4.9- میلیون در سال 2020 در مقایسه با 6.3 میلیون در 2019
- کاهش 21% در بیماریابی
- در 10 کشور اصلی که High burden برای سل هستند، کاهش بیماریابی 28% می باشد
- تخمین زده می شود که بیش از 500 هزار مرگ (اضافه بر موارد فوتی ناشی از سل) احتمالاً بدلیل سل رخ داده است
- در حقیقت جهان به یک دهه قبل، برگشته است، با سال 2010

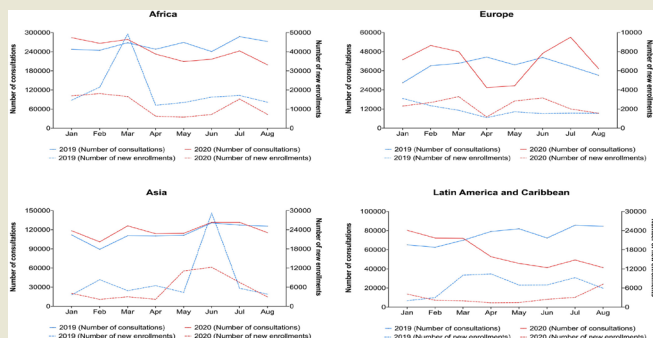
Estimated excess TB mortality globally



تأثیر کووید بر بیماریابی HIV

- در کشورهای مختلف دنیا در دوران پاندمی کووید-19، کاهش 40-50% در اقدامات تشخیصی HIV انجام تست HIV گزارش شده است
- تقریباً در بسیاری کشورهای اروپایی، علیرغم افت تشخیص، ارائه درمان ضد رتروویروسی حفظ شده است
- اما برخی کشورهای مناطق دیگر با کمبود داروها مواجه شده اند

Impact of coronavirus disease (COVID-19) on HIV testing and care provision across four continents



تأثیر کووید-19 بر برنامه های کنترل HIV



هیپاتیت های ویروسی (31 مرکز کبدی در پنج قاره)

- بین 24% تا 39% کاهش در انجام تست های HBV DNA و HBsAg

Ullrich A, Schranz M, Rexroth U, Hamouda O, Schaade L, Diercke

- کاهش 35% درمان HBV

M, Boender TS. The Impact of the COVID-19 Pandemic and As-

- کاهش 50% تست HCVAb

sociated Public Health Measures on Other Notifiable Infectious

- کاهش 49% درمان HCV

Diseases Under National Surveillance in Germany, Week 1-2016

Week 32-2020.

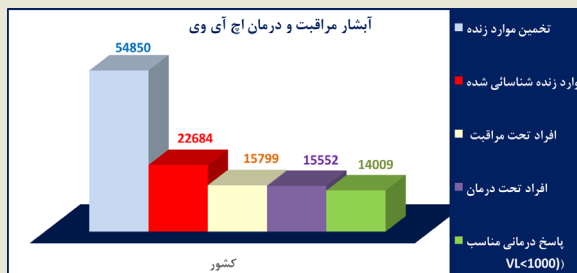
کووید مزمن

بروز انواع بیماری های مزمن:

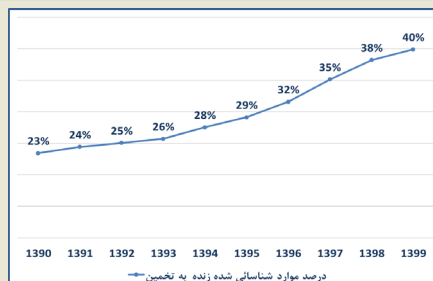
- تنفسی
- قلبی-عرقی
- روانی-خلقی
- دیابت
-

افزایش مراجعات به مراکز بهداشتی درمانی بدلیل کووید مزمن بیماری های دوران سالمندی را چندین سال زودتر خواهیم دید؟!

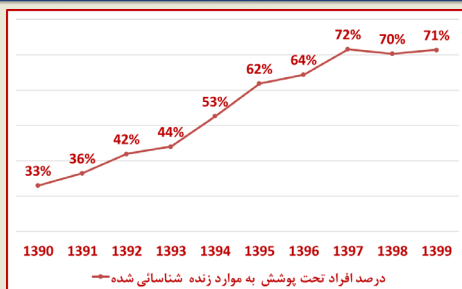
تاثیر کووید-۱۹ بر
شاخص های برنامه کنترل
اچ آی وی



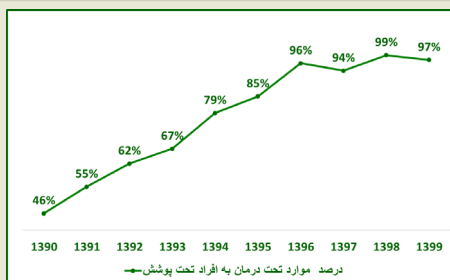
روند نسبت شناسائی به موارد تخمین



روند نسبت افراد تحت پوشش به موارد زنده شناسائی شده



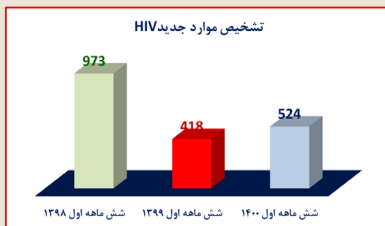
روند نسبت موارد تحت درمان به افراد تحت پوشش



تأثیر بر شاخص ها

- تشخیص موارد جدید
- درصد پرونده های فعال (حداقل یکبار مراجعه)
- تعداد موارد تحت درمان ARV
- درصد پوشش درمان ARV افراد تحت پوشش
- درصد تحویل به هنگام دارو
- درصد سنجش وایرال لود
- درصد وایرال لود ساپرس شده

تشخیص موارد جدید

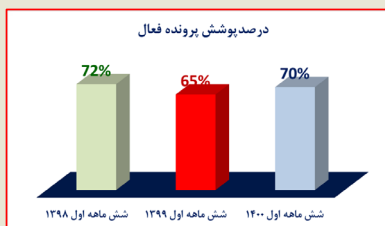


شش ماهه اول سال ۱۴۰۰ نسبت به زمان مشابه قبل از پاندمی کووید-۱۹

۴۶٪ کاهش یافته است

اگرچه نسبت به سال اول پاندمی افزایش یافته است

درصد پرونده های فعال (حداقل یکبار مراجعه)

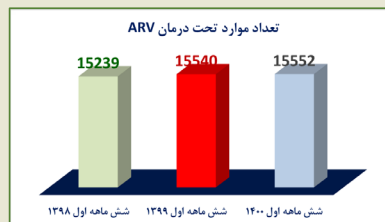


شش ماهه اول سال ۱۴۰۰ نسبت به زمان مشابه قبل از پاندمی کووید-۱۹

۳٪ کاهش یافته است

اگرچه نسبت به سال اول پاندمی افزایش یافته است

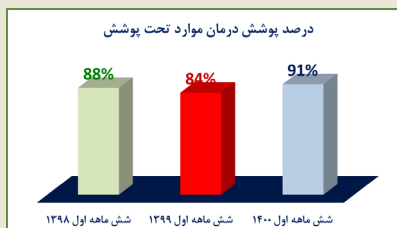
تعداد موارد تحت درمان ARV



شش ماهه اول سال ۱۴۰۰ نسبت به زمان مشابه قبل از پاندمی کووید-۱۹

۲٪ افزایش یافته است

درصد پوشش درمان ARV افراد تحت پوشش

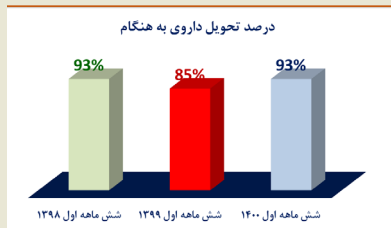


شش ماهه اول سال ۱۴۰۰ نسبت به زمان مشابه قبل از پاندمی کووید-۱۹

۳٪ افزایش یافته است

اگرچه در سال اول پاندمی کاهش داشته است.

درصد تحویل به هنگام دارو

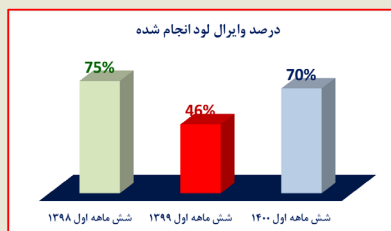


شش ماهه اول سال ۱۴۰۰ نسبت به زمان مشابه قبل از پاندمی کووید-۱۹

تغییری نکرده است

اگرچه در سال اول پاندمی کاهش داشته است.

درصد سنجش وایرال لود

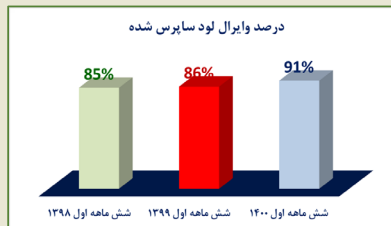


شش ماهه اول سال ۱۴۰۰ نسبت به زمان مشابه قبل از پاندمی کووید-۱۹

۷٪ کاهش یافته است

اگرچه نسبت به سال اول پاندمی افزایش یافته است

درصد وایرال لود ساپرس شده



شش ماهه اول سال ۱۴۰۰ نسبت به زمان مشابه قبل از پاندمی کووید-۱۹

۷٪ افزایش یافته است

تغییر شاخص ها در یک نگاه

| تغییر شش ماهه اول ۱۴۰۰ نسبت | شش ماهه اول ۱۳۹۹ | شش ماهه اول ۱۳۹۸ | تغییر شش ماهه اول ۱۴۰۰ نسبت |
|-----------------------------|------------------|------------------|-----------------------------|
| تشخیص موارد جدید HIV | 524 | 418 | 973 |
| درصد پوشش پرونده فعال | 70% | 65% | 72% |
| تعداد موارد تحت درمان ARV | 15552 | 15540 | 15239 |
| درصد پوشش درمان موارد فعال | 91% | 84% | 88% |
| درصد تحویل داروی به هنگام | 93% | 85% | 93% |
| درصد وایرال لود انجام شده | 70% | 46% | 75% |
| درصد وایرال لود ساپرس شده | 91% | 86% | 85% |

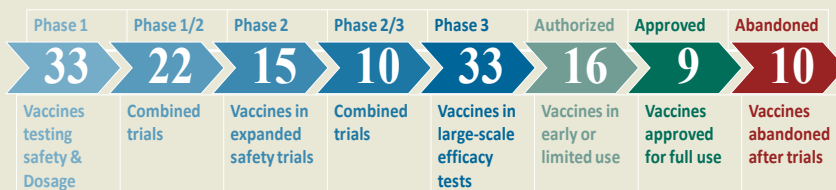
Dr Hassan Abolghassemi

Coronavirus Vaccine Status Worldwide & IRAN

Index

- Coronavirus Vaccine Tracker(Total)
- Economic insight of COVID-19 vaccines
- Genetic Vaccines
- Viral Vector Vaccines
- Protein-based Vaccines
- Inactivated or attenuated Vaccines
- Booster updates

Coronavirus Vaccine Tracker(Total)



- Currently testing: 111

Preclinical: 75

The New York Times

Leading vaccines

| Developer | How It Works | Phase | Status |
|--------------------|--------------|-------|--|
| Pfizer-BioNTech | mRNA | 2 3 | Approved in U.S., other countries. Emergency use in many countries. |
| Moderna | mRNA | 3 | Approved in Canada, Switzerland. Emergency use in many countries. |
| Oxford-AstraZeneca | ChAdOx1 | 2 3 | Approved in Brazil. Emergency use in many countries. |
| Johnson & Johnson | Ad26 | 3 | Approved in Canada. Emergency use in many countries. |
| Gamaleya | Ad26, Ad5 | 3 | Emergency use in many countries. |
| CanSino | Ad5 | 3 | Approved in China. Emergency use in other countries. |
| Vector Institute | Protein | 3 | Approved in Turkmenistan. Early use in Russia. |
| Novavax | Protein | 3 | Emergency use in Indonesia, Philippines. |
| Sinopharm | Inactivated | 3 | Approved in China, U.A.E., Bahrain. Emergency use in many countries. |
| Sinovac | Inactivated | 3 | Approved in China. Emergency use in many countries. |
| Sinopharm-Wuhan | Inactivated | 3 | Approved in China. Limited use in U.A.E. |
| Bharat Biotech | Inactivated | 3 | Emergency use in India, other countries. |

تازه های کووید

Covid 19

The Comprehensive National Congress On Covid 19

Current Status (Global)

Approved Genetic platform Vaccines

| Developer | Platform | Approvals | Brand | Country of Origin |
|--|---------------------|--|---|-------------------|
| Moderna mRNA-1273 | RNA | in 77 countries 32 trials in 8 countries | mRNA-1273 | US |
| Pfizer/BioNTech BNT162b2 | RNA | in 107 countries 45 trials in 21 countries | BNT162b2 | US, Germany |
| Takeda TAK-919 (Moderna formulation) | RNA | in 1 country 2 trials in 1 country | TAK-919 (Moderna formulation) | US, Japan |
| Zyudus Cadila ZyCoV-D | DNA | in 1 country 5 trials in 1 country | ZyCoV-D | India |



| Developer | Platform | Approvals | Brand/Project name | Country of Origin |
|--|--|---|-------------------------------|-------------------|
| CanSino | Non Replicating Viral Vector | in 9 countries 11 trials in 6 countries | Ad5-nCoV | China |
| Gamaleya | Non Replicating Viral Vector | in 19 countries 4 trials in 2 countries | Sputnik Light | Russia |
| Gamaleya | Non Replicating Viral Vector Ad26, Ad5 | in 73 countries 22 trials in 7 countries | Sputnik V | Russia |
| Janssen (Johnson & Johnson) | Non Replicating Viral Vector | in 78 countries 16 trials in 18 countries | Ad26.COV2.S | US, Israel |
| Oxford/AstraZeneca AZD1222 | Non Replicating Viral Vector | in 125 countries 49 trials in 23 countries | AZD1222 | UK, Sweden |
| Serum Institute of India Covishield (Oxford/AstraZeneca formulation) | Non Replicating Viral Vector | Approved in 46 countries 2 trials in 1 country | Covishield | UK, Sweden, India |

| Developer | Platform | Approvals | Brand | Country of Origin |
|---|---------------------------------|---|-------------------------------|----------------------|
| Anhui Zhifei Longcom ZF2001 | Protein Subunit | in 3 countries 10 trials in 5 countries | ZF2001 | China |
| Center for Genetic Engineering and Biotechnology (CIGB) CIGB-66 | Protein Subunit | in 4 countries 5 trials in 1 country | Abdala | Cuba |
| FBRI EpiVacCorona | Protein Subunit | in 2 countries 3 trials in 1 country | EpiVacCorona, Aurora-CoV | Russia, Turkmenistan |
| Medigen MVC-COV1901 | Protein Subunit | in 1 country 8 trials in 2 countries | MVC-COV1901 | Taiwan |
| Serum Institute of India COVOVAX (Novavax formulation) | Protein Subunit | in 2 countries 3 trials in 3 countries | Novavax, Covovax | US, India |
| Vaxine/CinnaGen Co. COVAX-19 | Protein Subunit | in 1 country 4 trials in 2 countries | Spikogen | Australia, Iran |
| Instituto Finlay de Vacunas Cuba Soberana 02 | Protein Subunit | in 4 country 3 trials in 2 countries | Soberana 02 | Cuba |
| Instituto Finlay de Vacunas Cuba Soberana Plus | Protein Subunit | in 2 country 5 trials in 2 countries | Soberana Plus | Cuba |
| Razi Vaccine and Serum Research Institute Razi Cov Pars | Protein Subunit | in 1 country 3 trials in 1 countries | Razi Cov Pars | Iran |

Current Status (Global) Approved Genetic platform Vaccines

| Developer | Platform | Approvals | Brand | Country of Origin |
|---|-------------|---|--|-------------------|
| Bharat Biotech | Inactivated | in 10 countries 7 trials in 1 country | Covaxin (also known as BBV152 A, B, C) | India |
| Chumakov Center KoviVac | Inactivated | in 1 country 2 trials in 1 country | KoviVac | Russia |
| Kazakhstan RIBSP QazVac | Inactivated | in 2 countries 3 trials in 1 country | QazVac | Kazakhstan |
| Minhai Biotechnology Co SARS-CoV-2 Vaccine (Vero Cells) | Inactivated | in 2 countries 5 trials in 1 country | KCONVAC, KconecaVac | China |
| Shafa Pharmed Industrial Co COVID-19 Inactivated Vaccine | Inactivated | in 1 country 6 trials in 1 country | COVIran Barekat | Iran |
| Sinopharm (Beijing) BBIBP-CorV (Vero Cells) | Inactivated | in 68 countries 19 trials in 10 countries | BBIBP-CorV | China |
| Sinopharm (Wuhan) Inactivated (Vero Cells) | Inactivated | in 2 countries 8 trials in 7 countries | Sinopharm Wuhan | China |
| Sinovac CoronaVac | Inactivated | in 43 countries 26 trials in 8 countries | CoronaVac (formerly PiCoVacc) | China |
| Organization of Defensive Innovation and Research FAKHRAVAC (MIVAC) | Inactivated | in 1 countries 3 trials in 1 countries | FAKHRAVAC (MIVAC) | Iran |

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Current Status (WHO) Approved platform Vaccines

| Developer | Platform | Approvals | Brand | Country of Origin |
|--|--|---|---|-------------------|
| Moderna mRNA-1273 | RNA | in 77 countries 32 trials in 8 countries | Moderna mRNA-1273 | US |
| Pfizer/BioNTech BNT162b2 | RNA | in 107 countries 45 trials in 21 countries | Pfizer/BioNTech | US, Germany |
| Janssen (Johnson & Johnson) | Non Replicating Viral Vector | in 78 countries 16 trials in 18 countries | Janssen (Johnson & Johnson) | US, Israel |
| Oxford/AstraZeneca AZD1222 | Non Replicating Viral Vector | in 125 countries 49 trials in 23 countries | AZD1222 | UK, Sweden |
| Serum Institute of India Covishield (Oxford/AstraZeneca formulation) | Non Replicating Viral Vector | Approved in 46 countries 2 trials in 1 country | Covishield | UK, Sweden, India |
| Bharat Biotech | Inactivated | in 10 countries 7 trials in 1 country | Bharat | India |
| Sinopharm (Beijing) BBIBP-CorV (Vero Cells) | Inactivated | in 68 countries 19 trials in 10 countries | BBIBP-CorV | China |
| Sinovac CoronaVac | Inactivated | in 43 countries 26 trials in 8 countries | CoronaVac (formerly PiCoVacc) | China |

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تازه های کووید

Covid 19

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The Comprehensive National Congress On Covid 19

Current Status (IRAN) Approveand Developing platformsd Vaccines

| Developer | Platform | Approvals | Brand | Country of Origin |
|--|---------------------------------|---|--|-------------------|
| Oxford/AstraZeneca AZD1222 | Viral Vector | in 125 countries 49 trials in 23 countries | AZD1222 | UK, Sweden |
| Serum Institute of India Covishield (Oxford/AstraZeneca formulation) | Viral Vector | Approved in 46 countries 2 trials in 1 country | Covishield | UK, Sweden, India |
| Gamaleya | Viral Vector | in 73 countries 22 trials in 7 countries | Sputnik V | Russia |
| Bharat Biotech | Inactivated | in 10 countries 7 trials in 1 country | Covaxin (also known as BBV152 A, B, C) | India |
| Sinopharm (Beijing) BBIBP-CorV (Vero Cells) | Inactivated | in 68 countries 19 trials in 10 countries | BBIBP-CorV | China |
| Sinopharm (Wuhan) Inactivated (Vero Cells) | Inactivated | in 2 countries 8 trials in 7 countries | Sinopharm Wuhan | China |
| Sinovac CoronaVac | Inactivated | in 43 countries 26 trials in 8 countries | CoronaVac (formerly PiCoVacc) | China |
| Shafa Pharmed Industrial Co COVID-19 Inactivated Vaccine | Inactivated | in 1 country 6 trials in 1 country | COVIran Barekat | Iran |
| Vaxine/CinnaGen Co. COVAX-19 | Protein Subunit | in 1 country 4 trials in 2 countries | Spikogen | Australi, Iran |

Current Status (IRAN) Developing Vaccines

| Developer | Platform | Approvals | Brand | Country of Origin |
|---|---------------------------------|--|---|-------------------|
| Shafa Pharmed Industrial Co COVID-19 Inactivated Vaccine | Inactivated | 1 approval in Iran 6 trials in 1 country | COVIran Barekat | Iran |
| Vaxine/CinnaGen Co. COVAX-19 | Protein Subunit | 1 approval in Iran 4 trials in 2 countries | Spikogen | Australia, Iran |
| Finlay Vaccine Institute/ Institute Pasteur of Iran Soberana 2, or PastoCoVac | Protein Subunit | Approved in 3 countries 4 trials in 2 countries | Soberana 2, or PastoCoVac | Cuba, Iran |
| Baqiyatallah University of Medical Sciences | Protein Subunit | 3 trials in Iran | Noora | Iran |
| Razi Vaccine and Serum Research Institute | Protein Subunit | 1 approval in Iran 3 trials in Iran | Razi Cov Pars | Iran |
| Iran's Ministry of Defence | Inactivated | 1 approval in Iran 2 trails in Iran | Fakhravac | Iran |

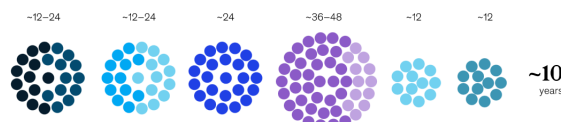
**Fast-forward:
Will the speed
of COVID-19
vaccine
development
reset industry
norms?**

<https://www.mckinsey.com/industries/life-sciences/our-insights/fast-forward-with-the-speed-of-covid-19-vaccine-development-reset-industry-norms>
May 13, 2021

Development times for COVID-19 vaccines were highly compressed compared with standard practice.

Vaccine development then and now, months

Sample baseline scenario,¹ (after multiple years of research)



Sample accelerated timeline,² (based on previous SARS/MERS research)

Development was simultaneous rather than sequential. Clinical phases were continued after subsequent steps were initiated.



¹Timelines can vary widely based on disease and trial designs.

²Patient safety was paramount despite the condensed timeline.

³Continuation of clinical development after emergency-use authorization.

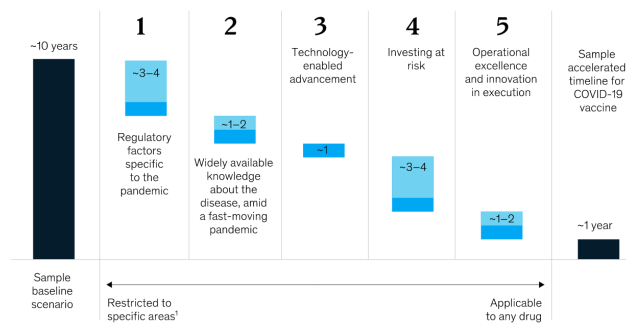
Fast-forward:
Will the speed
of COVID-19
vaccine
development
reset industry
norms?

May 13, 2021

McKinsey
& Company

Five factors affected the speed with which COVID-19 vaccines were developed.

Potential time savings associated with five key development factors, years



Note: Time savings across acceleration categories are not cumulative and depend on critical development path.
For instance, other pandemic situations or areas of high unmet medical need.

Current Status (Global) All combined trial genetic vaccines

| Developer | Platform | Brand | Country of Origin | Combined Phases |
|---|----------|---------------------|-------------------|-----------------|
| Pfizer/BioNTech BNT162b2 | RNA | Pfizer/ BioNTech | US, Germany | 2&3 |
| Arcturus Therapeutics and Duke-NUS Medical School | RNA | N/A | US & Singapore | 2&3 |
| Genexine | DNA | N/A | South Korea | 2&3 |
| AnGes, Osaka University and Takara Bio | DNA | N/A | Japan | 1&2 |
| Gennova Biopharmaceuticals and HDT Bio | RNA | N/A | India & US | 1&2 |
| GeneOne Life Science | DNA | N/A | South Korea | 1&2 |
| Takis Biotech and Rottapharm Biotech | DNA | N/A | Italy | 1&2 |
| Daiichi Sankyo and University of Tokyo | RNA | N/A | Japan | 1&2 |
| Elixirgen Therapeutics | RNA | N/A | US | 1&2 |
| Eyegene | RNA | N/A | South Korea | 1&2 |
| Vaccibody | DNA | N/A | Norway | 1&2 |

| Developer | Platform | Brand | Country of Origin | Combined Phases |
|---|------------------------------|------------|-------------------|-----------------|
| Oxford/AstraZeneca AZD1222 | Non-Replicating Viral Vector | AZD1222 | UK, Sweden | 2&3 |
| Serum Institute of India Covishield (Oxford/AstraZeneca formulation) | Non-Replicating Viral Vector | Covishield | UK, Sweden, India | 2&3 |
| ReiThera & Lazzaro Spallanzani National Institute for Infectious Diseases | Non-Replicating Viral Vector | N/A | India | 2&3 |
| Israel Institute for Biological Research | Non-Replicating Viral Vector | N/A | Israel | 2&3 |
| Washington University & Bharat Biotech | Non-Replicating Viral Vector | N/A | US & India | 2&3 |
| Cellid & LG Chem | Non-Replicating Viral Vector | N/A | South Korea | 1&2 |
| BIOCAD | Non-Replicating Viral Vector | N/A | Russia | 1&2 |

تازه های کووید
Covid 19

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The Comprehensive
National Congress On Covid 19

| Developer | Platform | Brand | Country of Origin | Combined Phases |
|--|---------------------------------|-------------|-------------------|-----------------|
| Clover Biopharmaceuticals & Dynavax | Protein Subunit | Inactivated | China & US | 2&3 |
| Shionogi & National Institute of Infectious Diseases & Kyushu University | Protein Subunit | Inactivated | Japan | 2&3 |
| Finlay Vaccine Institute Soberana 1 | Protein Subunit | Inactivated | Cuba | 1&2 |
| SpyBiotech | Protein Subunit | Inactivated | GB | 1&2 |
| EuBiologics | | | | 1&2 |
| VBI Vaccines | Protein Subunit | Inactivated | US | 1&2 |
| Akston Biosciences | Protein Subunit | Inactivated | US | 1&2 |
| Sinopharm | Protein Subunit | Inactivated | China | 1&2 |
| Icosavax & Seqirus | Protein Subunit | Inactivated | US & Australia | 1&2 |
| Research Institute for Biological Safety Problems | Protein Subunit | Inactivated | Kazakhstan | 1&2 |
| St. Petersburg Scientific Research Institute of Vaccines and Sera | Protein Subunit | Inactivated | Russia | 1&2 |
| HIPRA | Protein Subunit | Inactivated | Spain | 1&2 |
| Human Stem Cells Institute | Protein Subunit | Inactivated | US | 1&2 |

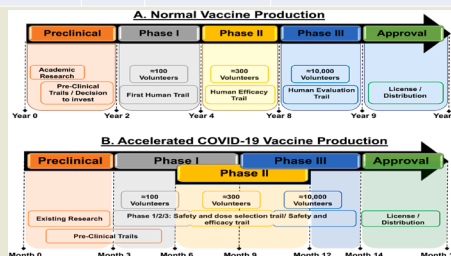
Current Status (Global) All combined trial Inactivated vaccines

| Developer | Platform | Brand | Country of Origin | Combined Phases |
|--|-------------|-------|-------------------|-----------------|
| Chumakov Center at the Russian Academy of Sciences | Inactivated | N/A | Russia | 1&2 |
| KM Biologics | Inactivated | N/A | Japan | 2&3 |

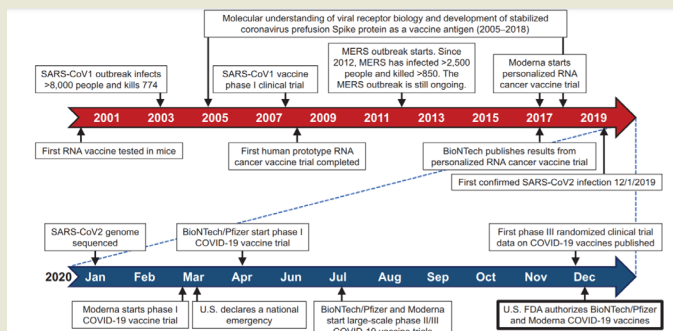
~ 32 studies are enjoying **combined-phase** developments

Super-rapid race for **saving lives** by developing COVID-19 vaccines

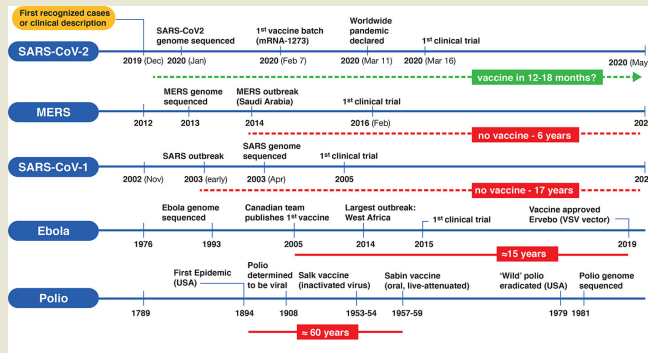
[Journal of Integrative Bioinformatics](#)



How Did We Get a COVID-19 Vaccine in Less Than 1 Year?

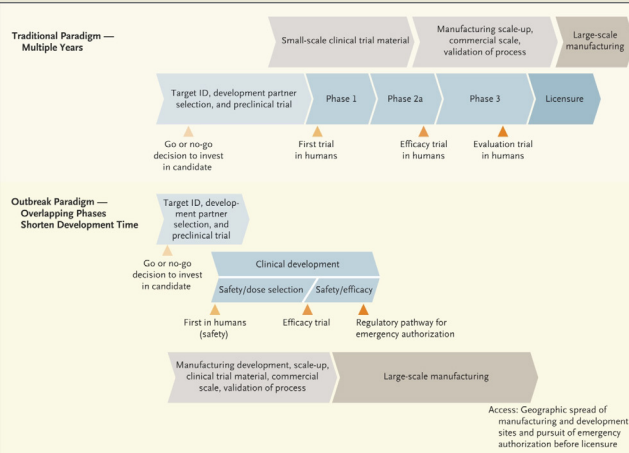


A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic



THE NEW ENGLAND JOURNAL of MEDICINE

Developing Covid-19 Vaccines at Pandemic Speed
Difference between Traditional Vaccine Development and Development Using a Pandemic Paradigm. May 21, 2020



U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾ PRS Login

Home ▾ Search Results ▾ Study Record Detail

Investigating a Vaccine Against COVID-19

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

Sponsor:
 University of Oxford

Information provided by (Responsible Party):
 University of Oxford

Study Details Tabular View No Results Posted Disclaimer How to Read a Study Record

Study Description

Brief Summary:
 A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in healthy UK volunteers.

ClinicalTrials.gov Identifier: NCT04400838

Recruitment Status: Active, not recruiting
 First Posted: May 26, 2020
 Last Update Posted: October 20, 2021

Economic insight of COVID-19 vaccines

2021 Financial Guidance⁽¹⁾

| | |
|---|--|
| Revenues | \$81.0 to \$82.0 Billion (previously \$78.0 to \$80.0 billion) |
| Adjusted Cost of Sales ⁽¹⁾ as a Percentage of Revenues | 39.1% to 39.6% (previously 39.0% to 40.0%) |
| Adjusted S&A Expenses ⁽¹⁾ | \$11.6 to \$12.1 Billion (previously \$11.5 to \$12.5 billion) |
| Adjusted R&D Expenses ⁽¹⁾ | \$10.4 to \$10.9 Billion (previously \$10.0 to \$10.5 billion) |
| Adjusted Other (Income)/Deductions ⁽¹⁾ | ~\$2.3 Billion (previously approximately \$2.2 billion of income) |
| Effective Tax Rate on Adjusted Income ⁽¹⁾ | Approximately 16.0% |
| Adjusted Diluted EPS ⁽¹⁾ | \$4.13 to \$4.18 (previously \$3.95 to \$4.05) |

Midpoint of Revenue Range Reflects 91% Op Growth Compared to 2020 Revenues;
Midpoint of Adjusted Diluted EPS⁽¹⁾ Range Reflects 80% Op Growth Compared to 2020

⁽¹⁾ See Slides 38 and 39 for definitions and for additional information regarding Pfizer's 2021 financial guidance



Third Quarter 2021 Earnings

Selected 2021 Financial Guidance⁽¹⁾ Ranges Excluding Comirnaty⁽¹⁾

| | |
|---|---|
| Revenue | \$45.0 to \$46.0 billion (previously \$45.0 to \$47.0 billion) |
| Adjusted Cost of Sales ⁽¹⁾ as a Percentage of Revenues | 21% to 22% |
| Adjusted Diluted EPS ⁽¹⁾ | \$2.60 to \$2.65 (previously \$2.55 to \$2.65) |

Midpoint of Revenue Range Reflects ~6% Op Growth Compared to 2020 Revenues Excluding Revenue Impacts of Comirnaty⁽¹⁾; Midpoint of Adjusted Diluted EPS⁽¹⁾ Range Reflects ~12% Op Growth Compared to Prior Year

⁽¹⁾ See Slides 38 and 39 for definitions and for additional information regarding Pfizer's 2021 financial guidance



Third Quarter 2021 Earnings

2022 Outlook for Potential Comirnaty⁽¹⁾ Sales

4B

Expected doses to be produced in 2022

1.7B

Expected doses to be delivered in 2022 based on contracts signed as of mid-October 2021

~\$29B

Direct sales and alliance revenues anticipated in 2022 based on contracts signed as of mid-October 2021

We Continue to Engage with Governments Regarding Potential Additional Orders for 2022

⁽¹⁾ See Slides 38 and 39 for definition of Comirnaty, which is the name for the Pfizer-BioNTech COVID-19 Vaccine



Third Quarter 2021 Earnings



Economic insight of COVID-19 vaccines

| | 2016 | 2017 | 2017 (restated) | 2018 | 2018 (represented) | 2019 | 2020 |
|--|-------------|-------------|--------------------|-------------|-----------------------|-------------|-------------|
| Operating results | | | | | | | |
| Revenue | 258,387,689 | 277,717,018 | 308,353,579 | 344,525,821 | 344,525,821 | 425,272,726 | 456,414,611 |
| Gross profit | 20,670,673 | 23,076,554 | 26,048,865 | 31,228,092 | 31,228,092 | 37,531,303 | 40,323,311 |
| Operating profit | 10,213,720 | 11,905,966 | 13,140,388 | 15,396,806 | 14,067,974 | 16,136,744 | 17,759,975 |
| Earnings before interest and tax | 10,856,642 | 12,706,623 | 13,996,518 | 16,321,803 | 14,992,971 | 16,903,274 | 18,545,111 |
| Profit for the year attributable to equity holders of the parent company | 4,647,344 | 5,283,091 | 5,575,584 | 5,835,842 | 5,835,842 | 6,252,537 | 7,187,278 |
| Profitability | | | | | | | |
| Gross margin | 8.00% | 8.31% | 8.45% | 9.06% | 9.06% | 8.83% | 8.83% |
| Operating margin | 3.95% | 4.29% | 4.26% | 4.47% | 4.08% | 3.79% | 3.89% |
| Net profit margin | 2.67% | 2.83% | 2.81% | 2.73% | 2.73% | 2.50% | 2.65% |
| Asset status | | | | | | | |
| Total assets | 157,711,590 | 169,539,028 | 190,693,400 | 235,771,077 | 235,771,077 | 269,888,371 | 311,236,706 |
| Equity attributable to equity holders of the parent company | 31,810,928 | 35,257,635 | 38,301,481 | 42,821,826 | 42,821,826 | 47,422,146 | 56,358,845 |
| Total liabilities | 113,179,154 | 118,269,374 | 132,746,210 | 167,495,310 | 167,495,310 | 192,949,004 | 221,289,385 |
| Cash and cash equivalents | 25,572,759 | 29,011,436 | 32,240,796 | 40,298,985 | 40,298,985 | 39,191,967 | 50,178,265 |
| Gearing ratio | | | | | | | |
| Liquidity ratio | 71.76% | 69.76% | 69.61% | 71.04% | 71.04% | 71.49% | 71.10% |
| Current ratio (times) | 1.33 | 1.31 | 1.31 | 1.28 | 1.28 | 1.29 | 1.31 |
| Inventory turnover ratio (days) | 37 | 37 | 37 | 38 | 38 | 36 | 39 |
| Trade receivables turnover ratio (days) | 95 | 95 | 92 | 99 | 99 | 98 | 107 |
| Trade payables turnover ratio (days) | 96 | 94 | 91 | 90 | 90 | 85 | 92 |
| Data per share (RMB) | | | | | | | |
| Earnings per share – Basic | 1.68 | 1.91 | 1.88 | 1.97 | 1.97 | 2.11 | 2.31 |
| Earnings per share – Fully diluted | 1.68 | 1.91 | 1.88 | 1.96 | 1.96 | 2.10 | 2.31 |

Leading Coronavirus Vaccines

The development cycle of a vaccine, from lab to clinic.

PRECLINICAL TESTING: Scientists test a new vaccine on cells and then give it to **animals** such as mice or monkeys to see if it produces an immune response.

PHASE 1 SAFETY TRIALS: Scientists give the vaccine to a **small number of people** to test safety and dosage, as well as to confirm that it stimulates the immune system.

PHASE 2 EXPANDED TRIALS: Scientists give the vaccine to **hundreds of people** split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety.

PHASE 3 EFFICACY TRIALS: Scientists give the vaccine to **thousands of people** and wait to see how many become infected, compared with volunteers who received a placebo. These trials can determine if the vaccine protects against the coronavirus, measuring what's known as the **efficacy rate**. Phase 3 trials are also large enough to reveal evidence of relatively rare side effects.

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EARLY OR LIMITED APPROVAL: Many countries have procedures for providing emergency authorizations for vaccines, based on preliminary evidence that they are safe and effective. In addition, some countries such as [China](#) and [Russia](#) began administering vaccines before detailed Phase 3 trial data was made public. Experts have warned of [serious risks](#) from jumping ahead of these results.

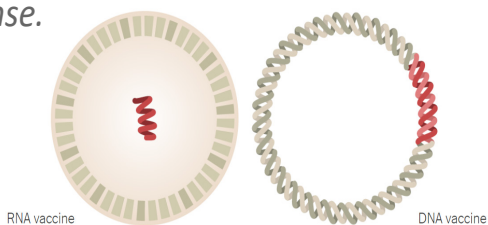
APPROVAL: Regulators review the complete trial results and plans for a vaccine's manufacturing, and decide whether to give it full approval.

COMBINED PHASES: One way to [accelerate vaccine development](#) is to combine phases. Some vaccines are now in Phase 1/2 trials, for example, which this tracker would count as both Phase 1 and Phase 2.

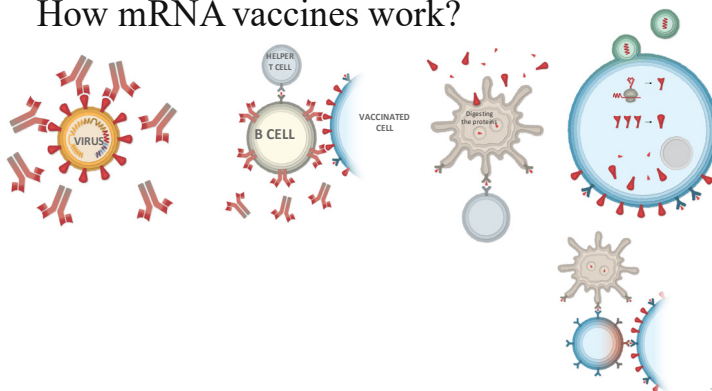
PAUSED or ABANDONED: If investigators observe worrying symptoms in volunteers, they can [pause](#) the trial. After an investigation, the trial may resume or be [abandoned](#). Trials may also be abandoned if they indicate a vaccine isn't effective against Covid-19.

Genetic Vaccines

Vaccines that deliver one or more of the coronavirus's own [genes](#) into our cells to provoke an immune response.



How mRNA vaccines work?



Coronavirus Tracker(Genetic Vaccines)

| Phase 1 | Phase 1/2 | Phase 2 | Phase 2/3 | Phase 3 | Authorized | Approved | Abandoned |
|----------------------------------|-----------------|------------------------------------|-----------------|--|----------------------------------|--------------------------------|---------------------------------|
| 15 | 00 | 01 | 01 | 04 | 03 | 02 | 04 |
| Vaccines testing safety & Dosage | Combined trials | Vaccines in expanded safety trials | Combined trials | Vaccines in large-scale efficacy tests | Vaccines in early or limited use | Vaccines approved for full use | Vaccines abandoned after trials |

Currently testing: 23
Abandoned: 4
Preclinical: 41

Genetic Vaccines01- Pfizer & Biontech Comirnaty (also known as tozinameran or BNT162b2)

PHASE 2

PHASE 3

COMBINED PHASES

APPROVED IN U.S.,

ELSEWHERE EMERGENCY USE IN OTHER COUNTRIES



VACCINE NAME: [Comirnaty](#) (also known as [tozinameran](#) or [BNT162b2](#))

EFFICACY: [91%](#)

DOSE: 2 doses, 3 weeks apart

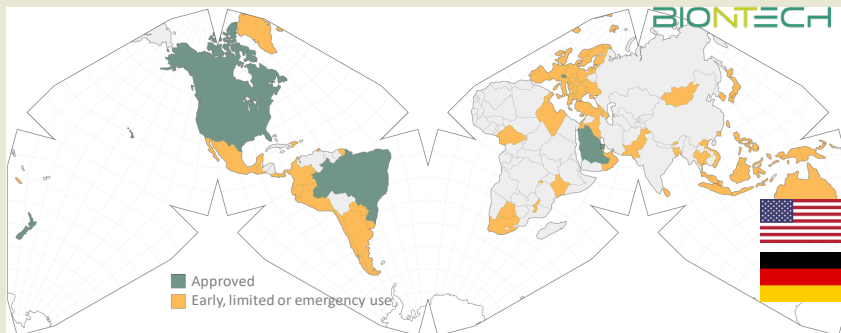
TYPE: Muscle injection

STORAGE: Freezer storage only at -13°F to 5°F (-25°C to -15°C)

5 years and older



Genetic Vaccines 01- Pfizer & Biontech



تازه های کووید

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The Comprehensive National Congress On Covid 19

Genetic Vaccines

02- Moderna & National Helath Institute

mRNA-1273 or Spikevax

moderna



PHASE 3

APPROVED IN SWITZERLAND

EMERGENCY USE IN U.S., ELSEWHERE

VACCINE NAME: [mRNA-1273](#) or [Spikevax](#)

EFFICACY: Preventing Covid-19 illness: [93.2%](#), Preventing severe disease: [98.2%](#)

DOSE: 2 doses, 4 weeks apart

TYPE: Muscle injection

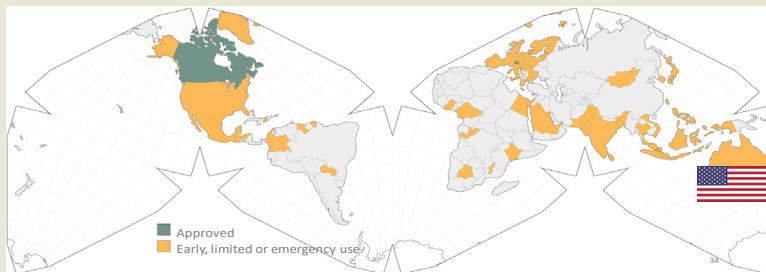
STORAGE: 30 days with refrigeration, 6 months at -4°F (-20°C)

18 years and older



Genetic Vaccines

02- Moderna & National Helath Institute



Genetic Vaccines

03- Zydus

Zydus
dedicated to life

PHASE 3

EMERGENCY USE IN INDIA

VACCINE NAME: ZyCoV-D

EFFICACY: [66.6%](#)

DOSE: 3 doses, 4 weeks apart

TYPE: Skin injection

STORAGE: [Stable at room temperature](#) for three months

12 years and older



Zydus
dedicated to life

Genetic Vaccines

03- Zydus



Genetic Vaccines04- Academy of Military Medical Sciences, Suzhou Abogen Biosciences and Walvax Biotechnology

PHASE 3

In June 2020, Chinese researchers at the **Academy of Military Medical Sciences, Suzhou Abogen Biosciences** and **Walvax Biotechnology** announced they would start their country's first safety trials on an mRNA-based vaccine, called ARCoV. Earlier studies on monkeys [reportedly](#) showed protective effects, and in the Phase 1 trial indicated it was safe in people. On Dec. 21, Xinhua reported that China was building a factory to produce [120 million doses per year](#).

Researchers launched a [Phase 2 trial](#) for the vaccine in January 2021, and [registered](#) a Phase 3 trial in April. In September, Bloomberg [reported](#) that the trial would soon be launched in Indonesia and Mexico, with results expected by the end of the year.

Updated Sept. 3

Genetic Vaccines05- Arcturus Therapeutics and Duke-NUS Medical School

PHASE 2

PHASE 3

COMBINED PHASES

The California-based company **Arcturus Therapeutics** and **Duke-NUS Medical School** in Singapore have developed an mRNA vaccine called ARCT-021. It has a "self-replicating" design that leads to a greater production of viral proteins. [Tests on animals](#) showed that it protected them against infection. In August, Arcturus [launched](#) a [Phase 1/2 trial](#) at Singapore General Hospital. On Nov. 9, the company [announced](#) that an interim analysis of the trial showed that the vaccine produced an immune response that's in the range of responses seen in people who recovered from Covid-19. On Jan. 6 Arcturus [announced](#) that they had permission to start the [Phase 2](#) portion of the trial in both Singapore and the United States. Singapore reached an agreement with Arcturus to spend up to \$175 million to acquire vaccines when they're ready.

In August, Arcturus received [approval](#) to begin testing its next-generation mRNA vaccine in Vietnam. The company [registered](#) a Phase 2/3 trial of the vaccine, called ARCT-154. The researchers [registered](#) a Phase 1/2 trial evaluating the two vaccines head-to-head with another candidate, called ARCT-165, on Sept. 8. Arcturus said it plans to file a [request for emergency use authorization](#) by the end of 2021.

Updated Oct. 12

Genetic Vaccines06- Genexine

Genexine

PHASE 2

PHASE 3

COMBINED PHASES

The South Korean company **Genexine** started testing the safety of a DNA-based vaccine in June 2020. In December, the Korea Biomedical Review [reported](#) that Genexine got disappointing results from their initial formulation and decided to restart their trials with a modified vaccine. On Jan. 20, 2021, the company [registered](#) a Phase 1/2 trial, and in June they registered a [Phase 1 trial](#) for elderly volunteers.

The Indonesian pharmaceutical company Kalbe Farma [pledged](#) in April to buy 10 million doses of Genexine's vaccine if it is proven to be safe and effective. In July, Indonesian regulators gave [the green light](#) for a late-stage clinical trial. Genexine registered [a Phase 2/3 clinical trial](#) in October to test their vaccine as a booster for other vaccines.

Updated Oct. 7



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Genetic Vaccines

07- Inovio



PHASE 2

VACCINE NAME: INO-4800

EFFICACY: Unknown

DOSE: To be determined

TYPE: Skin injection

STORAGE: Over a year at room temperature



Genetic Vaccines

08- Providence Therapeutics



PHASE 2

Canada's **Providence Therapeutics** specializes in messenger RNA vaccines to treat cancer. In response to the pandemic, they developed an mRNA vaccine against the coronavirus. They launched a [Phase 1 study](#) of an RNA vaccine in late January 2021, and in May [announced](#) that the vaccine appeared safe and produced promising levels of antibodies. In August, Providence Therapeutics launched a [Phase 2 trial](#).

In June, the company reached an [agreement](#) with the Indian vaccine maker Biological E to carry out further trials in India. Biological E agreed to purchase up to 30 million doses and planned to scale their production of the vaccine to as many as a billion doses in 2022. In September, Providence also [reached](#) an agreement with Everest Medicines to produce and market the vaccine in China.

Updated Sept. 13

Genetic Vaccines09- AnGes,Osaka University and Takara BioAG0302-COVID19

PHASE 1

PHASE 2

COMBINED PHASES

VACCINE NAME: AG0302-COVID19

EFFICACY: Unknown

DOSE: 2 doses, 2 weeks apart

TYPE: Skin injection

STORAGE: Over a year at room temperature



Genetic Vaccines10- Gennova Biopharmaceuticals and HDT Bio

PHASE 1
PHASE 2
COMBINED PHASES



Gennova Biopharmaceuticals in India and Seattle-based **HDT Bio** partnered to develop a vaccine based on self-amplifying RNA. The vaccine, known as [HGC019](#), was able to safely provoke animals to make antibodies to the coronavirus, leading India to [grant the companies approval](#) in December 2020 to start [Phase 1/2 trials](#). On May 4, 2021 HDT [announced](#) the trial was underway in India. HDT announced on Aug. 16 that it also forged a partnership with South Korean biotech company **Quratis** to develop its vaccine. The Indian Ministry of Science and Technology [announced](#) on Aug. 24 that [promising results](#) from the Phase 1 trial cleared the way for further Phase 2 and Phase 3 trials.

Updated Aug. 26

Genetic Vaccines11- GeneOne Life Science

PHASE 1
PHASE 2
COMBINED PHASES



진원생명과학(주)
GeneOne Life Science

GeneOne Life Science, a South Korean biotech company, developed a DNA-based vaccine that encodes two proteins from the coronavirus. In December 2020, they launched a [Phase 1/2 trial](#) with 345 participants. After receiving positive interim results from the trial, GeneOne [announced](#) on July 8, 2021 that it would begin Phase 2.

GeneOne is also experimenting with different vaccine delivery techniques. On Oct. 20, the company registered a [Phase 1 trial](#) to gauge how well their candidate works when injected into a patient's arm and delivered as a nasal spray. In the study, the researchers will also see if a skin suction device will improve outcomes.

Updated Oct. 23

Genetic Vaccines12- Takis Biotech and Rottapharm Biotech

PHASE 1
PHASE 2
COMBINED PHASES



Takis Biotech and **Rottapharm Biotech**, two vaccine companies in Italy, developed a vaccine called COVID-eVax. A special device uses a tiny electric pulse to deliver DNA through the skin. The DNA enters cells, which use the genetic instructions to make spike protein fragments. In February 2021, Takis and Rottapharm [launched a Phase 1/2 trial](#) in Italy. COVID-eVax can remain stable at room temperature. In September, the companies issued a [press release](#) stating that the Phase 1 trial delivered promising results. By then, Italy's vaccination rate had climbed so far that the companies said it would be difficult to recruit enough volunteers to move to the Phase 2 trial.

Updated Oct. 4

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Genetic Vaccines13- Daiichi Sankyo and University of Tokyo

PHASE 1
PHASE 2
COMBINED PHASES



Japan-based researchers at **Daiichi Sankyo** have developed an mRNA vaccine against the coronavirus in collaboration with the **University of Tokyo**. They [launched](#) a Phase 1/2 trial of the vaccine, named DS-5670, on March 22, 2021. In an Oct. 21 [press release](#), Daiichi Sankyo said that the vaccine produced no relevant safety concerns in the trial, and that it plans to move to Phase 2 in November.

Updated Oct. 23

Genetic Vaccines 14- Elixigen Therapeutics

PHASE 1
PHASE 2
COMBINED PHASES



Researchers at Baltimore-based **Elixigen Therapeutics** have created an RNA vaccine, named EXG-5003, that targets a small part of the coronavirus spike protein. In May 2021 they [launched](#) a [Phase 1/2 trial](#) of the vaccine in Japan. On Oct. 8, Elixigen [announced](#) that it has licensed its vaccine to an undisclosed company for worldwide marketing, excluding Japan.

Updated Oct. 8

Genetic Vaccines 15- Eyegene

PHASE 1
PHASE 2
COMBINED PHASES



Researchers at Korean biotechnology company **Eyegene** have developed an mRNA vaccine that uses a delivery system slightly different from other genetic vaccines. Instead of using a lipid nanoparticle, their vaccine uses liposomes — tiny fat bubbles — to bring the genetic material to the cell. Korean regulators [approved](#) a Phase 1/2 trial in August 2021 for the vaccine, called EG-COVID. Eyegene's C.E.O., Wonil Yoo, [told](#) a Korean television station that the trial began in September, and that results could come by the end of the year.

Updated Sept. 30

Genetic Vaccines16- Vaccibody

PHASE 1
PHASE 2
COMBINED PHASES



Norwegian biopharmaceutical company **Vaccibody** have developed [two DNA vaccine candidates](#) to protect against coronavirus variants. On Oct. 6, the researchers registered a [Phase 1/2 trial](#). They will test the two vaccines head-to-head in the first part of the study and then select one for further trials.

Updated Oct. 6

Genetic Vaccines

17- Chulalongkorn University and Chula Vaccine Research Center

PHASE 1



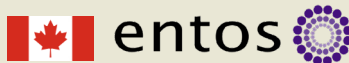
Researchers at Thailand's **Chulalongkorn University** have been developing several potential vaccines for the coronavirus. The furthest along is an mRNA-based vaccine known as ChulaCov19. In September 2020, the **Chula Vaccine Research Center** registered a [Phase 1 trial](#) to test it in humans. Delays in funding and manufacturing slowed the study's launch until [June 2021](#). In an [interview](#) with the Bangkok Post, the leader of the project said that up to 30 million doses might be produced for Thailand and six other Asian countries if the vaccine proved to be safe and effective. Citing positive preliminary results, the researchers [said](#) in August that the vaccine would soon advance to the next phase of clinical trials.

Updated Oct. 4

Genetic Vaccines

18- Entos Pharmaceuticals

PHASE 1



The Canadian company **Entos Pharmaceuticals** has created a DNA vaccine for the coronavirus. Most other genetic vaccines carry the gene for the spike protein on the surface of the virus. Entos instead chose the gene for nucleocapsid, a protein that sits inside the virus's membrane. They are betting it can offer long-lasting immunity. In October 2020, Entos [launched](#) a Phase 1 trial in Canada for their vaccine, called Covigenix VAX-001. They [began](#) dosing participants on April 15. Entos C.E.O. John Lewis [told](#) Canadian media on Aug. 4 that the vaccine produced a sufficient immune response without adverse reactions. He also said that a Phase 2 trial would take place outside of Canada. Entos later said that the trial would [take place](#) in South Africa.

Updated Oct. 4

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Genetic Vaccines

19- Symvivo



PHASE 1

On Nov. 2, 2020, the Canadian company **Symvivo** [announced](#) they had administered a DNA vaccine to their first volunteer in a [Phase 1 trial](#). The DNA is inserted into [harmless bacteria](#), which volunteers swallow in a frozen liquid (the company is working on putting the bacteria into a pill). When the bacteria reach the intestines, the DNA slips into cells in the gut lining, which then make viral proteins. Symvivo [announced](#) on July 19 that it received nearly \$5 million in funding from the National Research Council of Canada's Industrial Research Assistance Program to continue developing its vaccine.

Updated July 26

Genetic Vaccines

20- BioNet-Asia and Technovalia



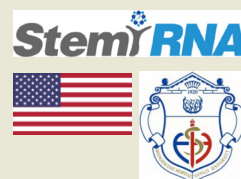
PHASE 1

Using a delivery system from [PharmaJet](#), researchers at **BioNet-Asia** and Australia-based **Technovalia** have developed a DNA vaccine called COVIGEN that can be pushed through the skin without a needle. Instead, the dose is loaded into a handheld device and shot directly into cell tissue through a jet spray of fluid. Vaccines for the flu already use the device, which PharmaJet says is a [safer alternative](#) to needle injections. The researchers [registered a Phase 1 trial](#) in Australia on Feb. 8, 2021.

Updated March 4

Genetic Vaccines

21- Stemirna Therapeutics and Shanghai East Hospital



PHASE 1

Chinese researchers at **Stemirna Therapeutics** have developed an mRNA vaccine in collaboration with **Shanghai East Hospital**. They registered a [Phase 1 trial](#) on May 1, 2021.

Updated May 20

Genetic Vaccines

22- Scancell



PHASE 1

Scancell, a British company that develops treatments for cancer, has created two DNA vaccine candidates against the coronavirus. Their first vaccine, called SCOV1, targets the original virus and its early variants. SCOV2 is intended to act as a booster shot. Scancell is using a [needle-free injection technology](#) made by Colorado-based PharmaJet to administer the vaccines into the skin through a concentrated jet of fluid. On Sept. 17, Scancell [registered](#) a Phase 1 trial in South Africa. Participants will receive two doses of SCOV1 four weeks apart, and then two doses of SCOV2 after 12 weeks.

Updated Sept. 21

Genetic Vaccines

23- University of Hong Kong



香港大學

THE UNIVERSITY OF HONG KONG



PHASE 1

Researchers at the **University of Hong Kong** are testing a DNA vaccine against the coronavirus. In a Phase 1 trial, which was [registered](#) on Nov. 1., the researchers plan to deliver a dose into the participants' muscles and then use high-voltage electric shocks to induce cells into receiving the vaccine. They wrote in the trial record that this strategy could improve vaccine uptake.

Updated Nov. 2

Genetic Vaccines

24- Imperial College London and Morningside Ventures



Imperial College
London

MORNINGSIDE

Abandoned

In early 2020, **Imperial College London** researchers developed a ["self-amplifying" RNA vaccine](#) for Covid-19, which boosted production of a viral protein to stimulate the immune system. They began Phase 1/2 trials on June 15, partnering with **Morningside Ventures** to manufacture and distribute the vaccine through a new company called VacEquity Global Health. On Dec. 18, the researchers [announced](#) a collaboration with Enesi Pharma to formulate a solid version of the vaccine that can be implanted in the skin without a needle.

On Jan. 27, 2021, Robin Shattuck, the leader of the project, [announced](#) that "it is not the right time to start a new efficacy trial for a further vaccine in the U.K." Instead of competing with authorized vaccines, they are turning their efforts to making candidates that will work well against emerging variants of the coronavirus.

Updated March 20

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Genetic Vaccines

25- Sanofi and Translate Bio



Abandoned

The French pharmaceutical company **Sanofi** collaborated with Massachusetts-based **Translate Bio** to develop an mRNA vaccine for Covid-19. In 2020, they reported that the vaccine, MRT5500, produced [a strong antibody response](#) in mice and monkeys, and [protected hamsters](#) against coronavirus infections. They followed up on that research with a Phase 1/2 trial in March 2021. Over the summer, Sanofi acquired Translate Bio for \$3 billion. On Sept. 28, the company [announced](#) that the trial had yielded encouraging results. By then, however, Pfizer-BioNTech and Moderna vaccines were widely available, and so Sanofi decided to [pull the plug](#) on its own mRNA Covid-19 vaccine program. Meanwhile, it is continuing a Phase 3 trial on a protein-based vaccine that could serve as a booster against Covid-19.

Updated Sept. 28

Genetic Vaccines

26- CureVac



Abandoned

VACCINE NAME: CVnCoV

EFFICACY: [48%](#)

DOSE: 2 doses, 4 weeks apart

TYPE: Muscle injection

STORAGE: Stable at least 3 months at 36–46°F (2–8°C)

Genetic Vaccines

27- OncoSec Immunotherapies



Abandoned

New Jersey-based **OncoSec Immunotherapies** has developed experimental cancer treatments that deliver genes into tumors. There, the injected genes produce a natural signalling molecule called IL-12, which attracts the attention of immune cells that attack the cancer. In the spring of 2020, OncoSec began adapting their technology to make a vaccine for the coronavirus. The vaccine, called CORVax12, consists of a loop of DNA that encodes both the spike protein and IL-12. Causing the body to make extra IL-12 could potentially enhance the immune system's ability to make antibodies to the spike protein. On Jan. 27, 2021, the company [began](#) dosing participants in its [Phase 1 trial](#) to test the safety of CORVax12. In November, a spokeswoman said that OncoSec was no longer investigating the vaccine.

Updated Nov. 4

Genetic Vaccines

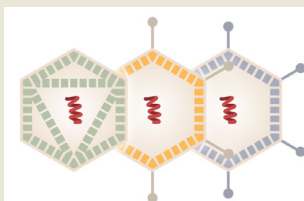
Preclinical

Other genetic vaccines in active preclinical development include vaccines from: Batavia Biosciences and RocketVax; CureVac and GSK; Defence Therapeutics; DIOSynVax; Doherty Institute and Monash University; ETheRNA; EyeGene; Globe Biotech; Greenlight Biosciences; HIPRA and Hospital Clínic de Barcelona; Infectious Disease Research Institute and Amyrus; Inovio; National Research Centre, **Egypt**; National Health Research Institutes, Taiwan; the OPENCORONA Consortia; the Spanish National Center for Biotechnology and the Spanish National Research Council.

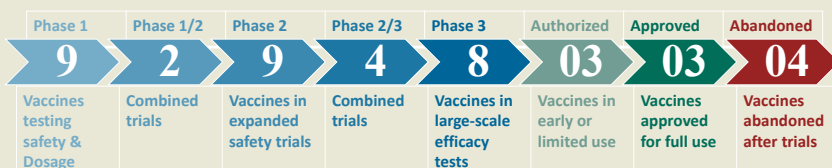
Updated Nov. 10

Viral Vector Vaccines

Vaccines that contain viruses engineered to carry coronavirus genes. Some viral vector vaccines enter cells and cause them to make viral proteins. Other viral vectors slowly replicate, carrying coronavirus proteins on their surface.



Coronavirus Vaccine Tracker (Viral Vector Vaccines)



Currently testing: 20

Abandoned: 04

Preclinical: 13

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Viral Vector Vaccines

01- Gamaleya Research Institute Sputnik V (also known as Gam-Covid-Vac)

PHASE 3

EMERGENCY USE IN RUSSIA, IRAN



МИНИСТЕРСТВО
ЗДРАВООХРАНЕНИЯ
РОССИЙСКОЙ ФЕДЕРАЦИИ



VACCINE NAME: Sputnik V (also known as Gam-Covid-Vac)

EFFICACY: [91.6%](#)

DOSE: 2 doses, 3 weeks apart

TYPE: Muscle injection

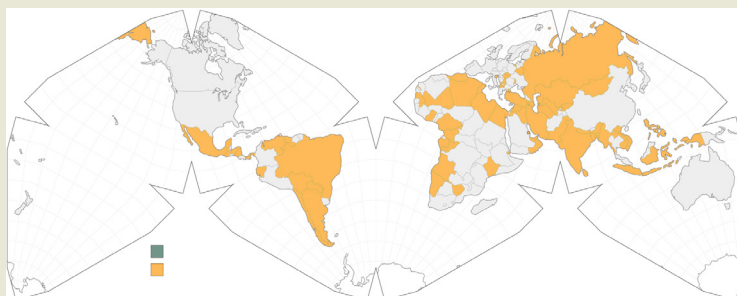
STORAGE: Freezer storage. Developing an alternative formulation that can be refrigerated.

Viral Vector Vaccines

01- Gamaleya Research Institute



МИНИСТЕРСТВО
ЗДРАВООХРАНЕНИЯ
РОССИЙСКОЙ ФЕДЕРАЦИИ



Viral Vector Vaccines 02- the University of Oxford and AstraZeneca Vaxzevria (also known as AZD1222, or Covishield in India)

PHASE 2

PHASE 3

COMBINED PHASES

APPROVED IN BRAZIL

EMERGENCY USE IN E.U., ELSEWHERE



UNIVERSITY OF
OXFORD



AstraZeneca

VACCINE NAME: Vaxzevria (also known as AZD1222, or **Covishield** in India)

EFFICACY: [74%](#) against symptomatic Covid-19; [100%](#) against severe or critical Covid-19.

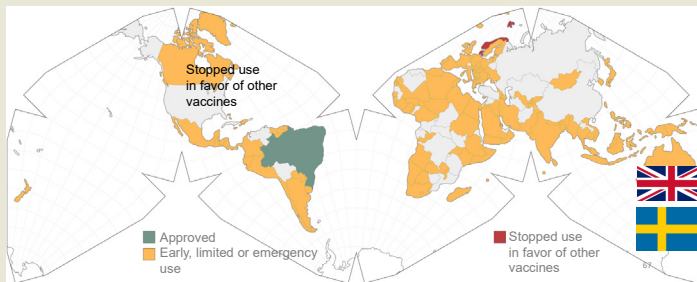
DOSE: 2 doses

TYPE: Muscle injection

STORAGE: Stable in refrigerator for at least 6 months

Viral Vector Vaccines

02- the University of Oxford and AstraZeneca



Viral Vector Vaccines

03- CanSino Biologics and Academy of Military Medical Sciences.

PHASE 3

APPROVED IN CHINA

EMERGENCY USE IN OTHER COUNTRIES



VACCINE NAME: Convidecia (also known as Ad5-nCoV)

EFFICACY: 63.7%

DOSE: Single dose

TYPE: Muscle injection

STORAGE: Refrigerated



Viral Vector Vaccines04- Beth Israel Deaconess Medical Center and Johnson & Johnson

PHASE 3

APPROVED IN CANADA

EMERGENCY USE IN U.S., ELSEWHERE



Beth Israel Lahey Health
Beth Israel Deaconess Medical Center



VACCINE NAME: Ad26.COV2.S

EFFICACY: 72% in United States, 68% in Brazil and 64% in South Africa

DOSE: 1 dose

TYPE: Muscle injection

STORAGE: Up to two years frozen at -4°F (-20°C), and up to 6 months refrigerated at $36-46^{\circ}\text{F}$ ($2-8^{\circ}\text{C}$).



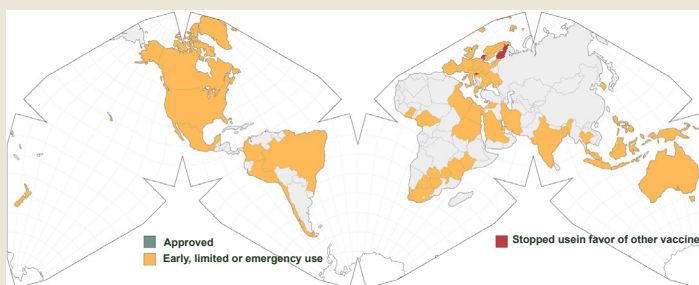
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Viral Vector Vaccines04- Beth Israel Deaconess Medical Center and Johnson & Johnson



Viral Vector Vaccines05- University of Hong Kong and Xiamen University and Beijing Wantai Biological Pharmacy

PHASE 3

In 2019, researchers at the **University of Hong Kong** and **Xiamen University** [created](#) a nasal-spray vaccine for the flu based on a genetically weakened form of the influenza virus. In early 2020, they engineered the vaccine to produce part of the coronavirus spike protein as well. On Sept. 9, they received [approval](#) to start clinical trials in partnership with **Beijing Wantai Biological Pharmacy**. They [registered](#) a Phase 1 trial on March 22, 2021. At a June 11 press conference, a researcher for the Chinese Center for Disease Control and Prevention said that this vaccine has [completed Phase 2 trials](#). And on Sept. 22, the researchers registered a [Phase 3 trial](#). The researchers are receiving [\\$5.4 million in support](#) from CEPI, the Coalition for Epidemic Preparedness Innovations.

Updated Oct. 13



Viral Vector Vaccines

06- ReiThera & Lazzaro Spallanzani National Institute for Infectious Diseases

PHASE 2

PHASE 3

COMBINED PHASES

The Italian biotechnology company **ReiThera** has developed a Covid-19 vaccine, called GRAD-COV2, that is based on an adenovirus that infects gorillas. Working in collaboration with the **Lazzaro Spallanzani National Institute for Infectious Diseases** in Rome, they found that it produced strong levels of antibodies in [mice and monkeys](#). In July 2020, they launched a [Phase 1 clinical trial](#). In November, they [announced](#) that the vaccine was well tolerated and produced antibodies, and [released a report](#) on the trial.

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In March 2021, researchers launched a [Phase 2 trial](#) of the vaccine, which delivered [encouraging results](#) in July. But it remained unclear if ReiThera would be able to advance to a final Phase 3 trial.

In May, Reuters reported, a court in Italy [struck down](#) the government's plan to fund the Phase 3 trial. The government later said it was [ready](#) to support the vaccine trial, but has yet to offer up the funds.

Updated Oct. 30

Viral Vector Vaccines07- Israel Institute for Biological Research

PHASE 2

PHASE 3

COMBINED PHASES



In the spring of 2020, the [Israel Institute for Biological Research](#) started [work](#) on a coronavirus vaccine based on vesicular stomatitis viruses. They engineered the viruses to carry the gene for the coronavirus spike protein. On Oct. 25, the Israeli government [announced](#) that the vaccine, called [Brilife](#), would be going into a Phase 1 trial. In January 2021, the vaccine moved on to a [Phase 2 trial](#). In July, Israel formed a [partnership](#) with the American company NRx Pharmaceuticals to advance research on Brilife in studies to be conducted in Israel, Georgia, and the Ukraine. The following month, NRx registered a [Phase 2/3 trial](#), with plans to recruit 550 volunteers.

Updated Sept. 7

Viral Vector Vaccines08- Washington University & Bharat Biotech

PHASE 2

PHASE 3

COMBINED PHASES



Researchers at **Washington University** designed a nasal spray vaccine that can produce high levels of coronavirus antibodies in mice [with just a single dose](#). It contains a chimpanzee adenovirus engineered to carry the spike protein gene. The Indian drug maker **Bharat Biotech** licensed the technology, and in February 2021 they won [approval](#) to launch a [Phase 1 trial](#) of a vaccine, which they named BBV154. On Sept. 21, the chairman of Bharat [announced](#) that the Phase 2/3 trial was set to begin in a matter of days. Government officials [announced](#) on Aug. 11 that they will allow Bharat to perform a trial that mixes BBV154 with Covaxin.

Updated Sept. 22

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Covid 19

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Viral Vector Vaccines08- Washington University & Bharat Biotech

PHASE 2



Researchers at **City of Hope**, a California biomedical research institute, created a [vaccine](#) based on a weakened form of a virus called Modified Vaccinia Ankara, or MVA for short. They added two coronavirus genes to the MVA virus — one for the spike protein, and one for another protein called nucleocapsid. They are testing the vaccine specifically for people with immune systems impaired by cancer and other disorders. Many of them do not produce a strong immune response to authorized vaccines based on mRNA. The City of Hope researchers hope their MVA vaccine works better. On Nov. 24, 2020, City of Hope [announced](#) the start of a [Phase 1 trial](#). In September 2021, researchers launched a [Phase 2 trial, giving the vaccine to volunteers](#) with blood cancer who have received a bone marrow transplant or a form of immunotherapy called [CAR-T](#).

Updated Sept. 17

Viral Vector Vaccines10- Icahn School of Medicine at Mount SinaiMahidol University & Government Pharmaceutical Organization & Avi-Mex



Viral Vector Vaccines 11- Vaxart



PHASE 2



While many vaccines are given as injections, some vaccines can be taken as a pill. Oral vaccines have been [approved](#) for diseases including polio, cholera, and typhoid fever. The small San Francisco company **Vaxart** specializes in developing oral vaccines. They have created and tested pills for [influenza](#) and other diseases. Last spring Vaxart began work on an oral vaccine for Covid-19. It contains an adenovirus called Ad5 (the same viral vector in CanSinoBio's vaccine and in Russia's Sputnik V).

When Vaxart gave the pill to [mice](#), they produced antibodies against the coronavirus. Mice don't suffer symptoms of Covid-19, however, so the researchers then switched to hamsters, which do. In [an unpublished study](#), they found that the vaccine pill not only [dramatically reduced](#) the amount of coronavirus in sick hamsters, but also protected them from two important symptoms of the disease: weight loss and swollen lungs.

Updated Oct. 26

Viral Vector Vaccines 12- Cellid & LG Chem

PHASE 1
PHASE 2
COMBINED PHASES



In April 2020, the South Korean biotech company **Cellid** began to [develop](#) a vaccine for Covid-19. The vaccine, called AdCLD-CoV19, was based on a combination of two strains of adenoviruses, called Ad5 and Ad35. After [testing](#) the vaccine on monkeys, Cellid entered into a [partnership](#) with the South Korean chemical manufacturer **LG Chem** to manufacture the vaccine.

In December 2020, Cellid registered a [Phase 1 trial](#) for AdCLD-CoV19, and a Phase 2 trial launched in June 2021. But the [results](#) were disappointing, leading the company to reformulate [a new version](#) of the vaccine, called AdCLD-CoV19-1. Cellid expects to finish the Phase 1 trial of the updated vaccine in October 2021 and plans on getting final safety and efficacy results in the second quarter of 2022. The company plans to run the Phase 3 trial as a comparison between Cellid's vaccine and Johnson & Johnson's, but it is having [difficulty](#) securing enough J&J doses to run the study.

Updated Oct. 4

Viral Vector Vaccines13- BIOCAD

PHASE 1
PHASE 2
COMBINED PHASES

BIOCAD

Russian biotechnology company **BIOCAD** has developed a vaccine that uses a type of virus known as an adenovirus-associated virus as a vector. The virus, called AAV-5, carries a gene encoding part of the spike protein from the coronavirus. They [registered](#) a Phase 1/2 trial for the vaccine, called BCD-250, on Sept. 8, 2021.

Updated Sept. 13



Viral Vector Vaccines13- BIOCAD

PHASE 1



Three decades ago, the **German Center for Infection Research** developed a smallpox vaccine from a harmless virus called Modified Vaccinia Ankara, or MVA for short. In recent years, they adapted it to create a vaccine for MERS, a disease caused by another coronavirus.

In the spring of 2020, they made an MVA-based vaccine for SARS-CoV-2, the coronavirus that is causing the Covid-19 pandemic. It carries the gene for the spike protein, which is produced inside cells that it invades. On Sept. 29, the center and a consortium of German universities registered a [Phase 1 trial](#). In January 2021, the center [announced](#) that their initial formulation provided disappointing results and are postponing the trial until they update it. They said that they [resumed](#) the trial with an updated version of the vaccine on July 16, 2021.

Updated Aug. 4



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Viral Vector Vaccines15- ImmunityBio

PHASE 1



The California-based company **ImmunityBio** created a vaccine using the Ad5 adenovirus, the same one used by CanSinoBio and the Gamaleya Institute in Russia. ImmunityBio [engineered](#) the Ad5 virus to carry genes for two genes from the coronavirus. In addition to the spike protein, it also carries the gene for a protein called nucleocapsid. The company hopes that this combination will provoke a strong immune response.

The company found that the vaccine protects monkeys from the coronavirus. ImmunityBio launched a [Phase 1 trial](#) of a Covid-19 vaccine in October 2020 in the United States and [another](#) in South Africa in January. In February 2021, the company [registered](#) a Phase 1 trial of an [oral version](#) of the vaccine.

On May 25, the company [announced](#) that it would study how well their candidate works as a booster shot for those who already received other vaccines. They are also testing a nasal spray version. They said on July 14 that trials of the booster shot [would begin](#) in South Africa later this year.

The chairman, C.E.O. and Global Chief Scientific and Medical Officer of ImmunityBio is billionaire [Patrick Soon-Shiong](#), the owner of the Los Angeles Times.

Updated Aug. 20

Viral Vector Vaccines16- Gritstone bio &National Institute of Allergy and Infectious Diseases

PHASE 1

In a [Phase 1 trial](#) launched in March 2021, the **National Institute of Allergy and Infectious Diseases** is testing how well these two vaccines work together, with the chimpanzee adenovirus serving as the first dose and the self-amplifying mRNA as the second. The researchers hope that this combination will produce a better immune response than two doses of either vaccine. On Sept. 20, Gritstone [dosed](#) the first volunteer in a Phase 1 trial to gauge the effectiveness of the mRNA vaccine as a booster shot in older adults who have already received the Astrazeneca vaccine.

Updated Sept. 21



Viral Vector Vaccines17- Meissa Vaccines

PHASE 1

Meissa Vaccines has developed a vaccine that can be delivered as a spray or drops into the nose. To make the vaccine, researchers started off with another virus, called respiratory syncytial virus (RSV for short). The researchers introduced mutations into the RSV virus's genes so that it replicated too slowly to cause disease. Then they added a gene for the



Meissa Vaccines

coronavirus spike protein, so that the weakened RSV viruses could present it to the immune system. [A study on monkeys](#) released in July 2021 showed that the vaccine could produce antibodies in the noses of the animals and protect them from Covid-19. The initial data from [a Phase 1 trial](#), announced [Oct. 28](#), indicate that the vaccine can also produce high levels of antibodies against the coronavirus in people's noses. The full results of the trial will be released in 2022.

Updated Oct. 30

Viral Vector Vaccines18- Tetherex Pharmaceuticals

PHASE 1



Researchers at Oklahoma-based **Tetherex Pharmaceuticals** have created a vaccine that uses genetically engineered viruses to develop immunity. They registered a [Phase 1 trial](#) in Australia on April 9, 2021. Mayo Clinic [announced](#) a deal to develop and market the vaccine technology worldwide on July 6.

Updated July 6

Viral Vector Vaccines19- CyanVac

PHASE 1



Scientists at the **University of Georgia** and the **University of Iowa** have developed a vaccine based on canine parainfluenza virus, which has never been found to cause disease in humans. They engineered it to carry proteins from the coronavirus. The vaccine, called CVXGA1, is administered as a nasal spray. In July 2021, the researchers published a [study](#) showing that a single dose of the vaccine could protect mice and ferrets against Covid-19. A spin-off company called **CyanVac** took the intranasal vaccine, called CVXGA1, to [Phase 1 trials](#) the same month, and [enrolled](#) the first participant in late September.

Updated Sept. 27

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Viral Vector Vaccines 20- EnGeneIC

PHASE 1

ENGENEIC 

Researchers at Australian biotechnology company **EnGeneIC** have modified their cancer treatment platform to carry a molecular payload that targets the coronavirus. They are producing the vaccine, known as COVID-19-EDV, primarily for people with compromised immune systems. On Sept. 7, EnGeneIC [announced](#) that it had begun a Phase 1 trial in Australia.

Updated Sept. 13



Viral Vector Vaccines 21 McMaster University

PHASE 1

McMaster University 

Canadian researchers at **McMaster University** are testing the effectiveness of two viral vector vaccines as a booster in adults who have already received two doses of an mRNA vaccine. They plan to administer the candidates into the lungs using a nebulizer. On Oct. 26, the researchers registered a [Phase 1 trial](#).

Updated Nov. 26



Viral Vector Vaccines 22- Merck & Themis Bioscience & Institut Pasteur

ABANDONED

 MERCK

The American company **Merck** acquired the Austrian firm **Themis Bioscience** in June to develop their vaccine, which had been originally developed at **Institut Pasteur**. The vaccine used a weakened measles virus that carries a gene for the coronavirus spike protein.

Researchers [launched](#) a Phase 1 trial in August 2020. On Jan. 25, Merck [announced](#) it was abandoning the effort, because the vaccine provoked a response that was weaker than a natural infection. In March they entered into a partnership with Johnson & Johnson to help produce their vaccine instead.

Updated March 4



 INSTITUT PASTEUR



Viral Vector Vaccines 23- Merck & IAVI

ABANDONED

In addition to its project with Themis, **Merck** partnered with **IAVI** on a second viral vector vaccine. It was based on vesicular stomatitis viruses, the same approach Merck successfully used to produce the [first approved vaccine for Ebola](#). They designed their coronavirus vaccine as a pill, which could have made it easier to distribute than syringes for injections. Merck and IAVI received [\\$38 million](#) from the United States government to support their research, and on September 30, 2020, they registered a [Phase 1 trial](#). But on Jan. 25, they [announced](#) they were abandoning the effort because the vaccine failed to trigger an immune system comparable to what happens in a natural infection of Covid-19.

Updated Jan. 25



Viral Vector Vaccines 24- AltimuneAdCOVID

ABANDONED

VACCINE NAME: AdCOVID
EFFICACY: Unknown
DOSE: 1 dose
TYPE: Nasal spray
STORAGE: Refrigerated

Updated June 30



Viral Vector Vaccines 24- Altimune

ABANDONED

Maryland-based **Altimune** is a biopharmaceutical company that focuses on developing vaccines delivered by nasal spray. They developed a nasal spray vaccine for Covid-19, delivering the Ad5 adenovirus to the airway. Studies on the immune system suggests that a nasal spray [could be more effective](#) for blocking the transmission of the virus than vaccines given by injection. In a study on mice, Altimune researchers found that a single dose of the vaccine gave [complete protection](#) from a lethal infection of coronaviruses. On Dec. 22, 2020, the company [registered](#) a Phase 1 clinical trial of a single dose of the vaccine.



But on June 29, 2021, Altimmune [announced](#) they were abandoning their Covid-19 vaccine. In their Phase 1 trial, they gave the spray to 80 volunteers and found that they produced substantially lower levels of antibodies than produced by Covid-19 vaccines that have already been authorized.

Updated June 30

Viral Vector Vaccines

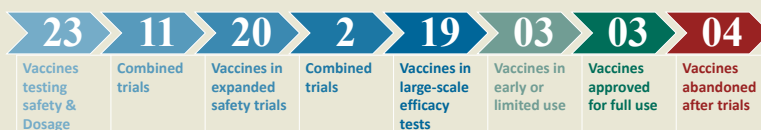
PRECLINICAL

Other viral vector vaccines in active preclinical development include vaccines from: 01- ID Pharma; 02- KU Leuven and Batavia Biosciences; 03- Smorodintsev Flu Research Institute; 04- the Spanish National Center for Biotechnology and the Spanish National Research Council; 05- Thomas Jefferson University and Bharat Biotech; 06- Tonix Pharmaceuticals; 07- University of Helsinki, University of Eastern Finland, and Rokote Laboratories Finland; 08- University of Pittsburgh; 09- University of Western Ontario; 10- Valo Therapeutics and University of Helsinki; 11- Vivaldi Biosciences; 12- Walvax Biotechnology, Tsinghua University, and Tianjin Medical University; 13- Zydus Cadila.

Updated Sept. 3

Protein-based Vaccines

Vaccines that contain coronavirus proteins but no genetic material. Some vaccines contain whole proteins, and some contain fragments of them. Some pack many of these molecules on nanoparticles.



Currently testing: 50

Abandoned: 02

Preclinical: 42



Protein-Based Vaccines 01- Vector InstituteEpi-VacCorona, Aurora-CoV

PHASE 3

APPROVED IN TURKMENISTAN

EARLY USE IN RUSSIA

VACCINE NAME: EpiVacCorona, Aurora-CoV
 EFFICACY: Unknown
 DOSE: 2 doses, 3 weeks apart
 TYPE: Muscle injection
 STORAGE: Stable in refrigerator for up to two years

Protein-Based Vaccines 01- Vector Institute



Protein-Based Vaccines 02- Anhui Zhifei Long-com Institute of Medical Biology at the Chinese Academy of Medical Sciences

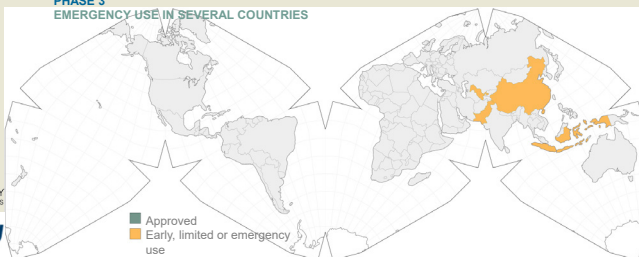
PHASE 3
 EMERGENCY USE IN SEVERAL COUNTRIES

VACCINE NAME: ZF2001,
 Zifivax
 EFFICACY: [81.76%](#)
 DOSE: 3 doses, 4 weeks apart
 TYPE: Muscle injection



Protein-Based Vaccines 02- Anhui Zhifei Long-com Institute of Medical Biology at the Chinese Academy of Medical Sciences

PHASE 3
 EMERGENCY USE IN SEVERAL COUNTRIES



Protein-Based Vaccines03- Finlay Vaccine Institute Soberana 2, or PastoCoVac (in Iran)

PHASE 3
EMERGENCY USE IN IRAN, CUBA

VACCINE NAME: Soberana 2, or PastoCoVac (in Iran)
EFFICACY: [71% with two doses, 92.4 % with Soberana Plus booster](#)



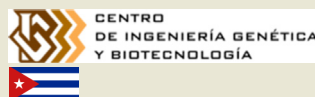
Protein-Based Vaccines03- Finlay Vaccine Institute



Protein-Based Vaccines04- Center for Genetic Engineering and Biotechnology of Cuba Abdala

PHASE 3
EMERGENCY USE IN CUBA

VACCINE NAME: Abdala
EFFICACY: [92.28%](#)



Protein-Based Vaccines04- Center for Genetic Engineering and Biotechnology of Cuba



Protein-Based Vaccines

05- Dynavax & Medigen



PHASE 3 EMERGENCY USE IN TAIWAN

Taiwan-based vaccine maker **Medigen** created a vaccine containing a combination of spike proteins and an adjuvant from **Dynavax**. After a series of promising experiments on animals, they began injecting volunteers for a [Phase 1 trial](#) in [early October 2020](#), which showed that the vaccine [provoked](#) strong immune responses. On Dec. 30, Medigen [announced](#) that it had received permission to commence a [Phase 2 trial](#). The first volunteers in the trial [were injected](#) in late January 2021. In July, Medigen started another Phase 2 trial on [children between 12 and 18 years old](#). Medigen received [permission](#) to begin a [Phase 3 trial](#) in Paraguay on July 20. And on Oct. 15, the researchers [registered a trial](#) to assess their vaccine's effectiveness as a booster for those who have received one dose of the Moderna shot. They [registered a similar trial](#) on Oct. 27 for adults with two doses of the AstraZeneca vaccine.

Taiwan granted [emergency use authorization](#) to the vaccine on July 19. Results from the Phase 2 trial [suggested](#) that volunteers were producing strong levels of antibodies and did not have serious adverse reactions. Taiwan [started administering](#) Medigen's vaccine on Aug. 23. By Oct. 22, Medigen [said](#) that 1,362,524 doses had been administered.

EMERGENCY USE IN: [Taiwan](#).
Updated Nov. 1



Protein-Based Vaccines

06- Vaxine & CinnagenSpikogen

PHASE 3 EMERGENCY USE IN IRAN



VACCINE NAME: Covax-19, Spikogen
DOSE: 2 doses, 3 weeks apart

In June, 2021, Vaxine [launched](#) a [Phase 2 trial](#) in Iran, followed by a [Phase 3 trial](#), [registered Aug. 13](#). In October, Iran issued an [emergency authorization](#) for Spikogen, to be [produced](#) by the Iranian company CinnaGen. Official results of the Phase 3 trial are [expected](#) by the end of the year.



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EMERGENCY USE

Protein-Based Vaccines07- Novavax (also known as Covovax in India)

PHASE 3
EMERGENCY USE IN INDONESIA & Philippines

VACCINE NAME: NVX-CoV2373 (also known as Covovax)

EFFICACY: [89.7%](#)

DOSE: 2 doses, 3 weeks apart

TYPE: Muscle injection

STORAGE: Stable in refrigerator

In July the U.S. government awarded Novavax another [\\$1.75 billion](#) to support the vaccine's clinical trials and manufacturing.

NOVAVAX
Creating Tomorrow's Vaccines Today



Protein-Based Vaccines08- Medicago & gsk

PHASE 3

VACCINE NAME: CoVLP

EFFICACY: Unknown

DOSE: 2 doses, 3 weeks apart

TYPE: Muscle injection

STORAGE: Stable in refrigerator



Protein-Based Vaccines gsk & Sanofi10- Sano-fi & gsk

PHASE 3

In early 2020, **Sanofi** developed a Covid-19 vaccine based on viral proteins they produced with engineered viruses that grow inside insect cells. **GSK** supplemented these proteins with adjuvants that stimulate the immune system. The vaccine, called Vidprevtyn, is based on the same design Sanofi used to create [Flublok](#), an approved vaccine for influenza. The companies [launched](#) a Phase 1/2 clinical trial in September 2020.

SANOFI



Vidprevtyn was widely expected to play a major role in tackling the pandemic. In the United States, Operation Warp Speed selected it as one of six vaccines to secure in large quantities, reaching a [\\$2.1 billion agreement](#) for 100 million doses. On Sept. 18 Sanofi closed another deal [with the European Union for 300 million doses](#) for an unspecified amount, and later reached [an agreement](#) with Canada for up to 72 million doses. In addition, Sanofi agreed to provide [200 million doses](#) to COVAX, an international collaboration to deliver the vaccine equitably across the world. The company expected to move to a Phase 3 trial in December and potentially seek emergency use authorization for Vidprevtyn in the United States by spring 2021. Sanofi announced plans to make up to one billion doses in 2021.

Protein-Based Vaccines 11- West China Hospital of Sichuan University



West China School of Medicine
West China Hospital of Sichuan University



PHASE 3

In July 2020, researchers at **West China Hospital of Sichuan University** published a [study](#) in Nature describing a vaccine made from the RBD region of the spike protein that could protect mice and monkeys from the coronavirus. To make the vaccine, researchers encoded the RBD region in a gene, which they inserted into a virus. They then infected insect cells with the virus, causing them to make the molecule in huge amounts. On Aug. 24, they [launched](#) a Phase 1 trial, and on Nov. 16 they moved to [Phase 2](#) with a study on 960 volunteers. On Jan. 22, 2021, the researchers registered [another Phase 2 trial](#) with 4,000 volunteers. A [Phase 3 trial](#) began on June 1.

Updated June 1

Protein-Based Vaccines 12- Nanogen Biopharmaceutical



PHASE 3

On Dec. 10, 2020, **Nanogen Biopharmaceutical** in Vietnam [began](#) recruiting 60 volunteers for a [Phase 1 trial](#) of their protein-based vaccine Nanocovax. Vietnam news agencies [announced](#) that Nanocovax entered a Phase 2 trial in February, 2021. Nanogen researchers [reported](#) that in these early studies, the vaccine did not cause any dangerous side effects and promising levels of antibodies. In June, Nanogen [launched](#) a [Phase 3 trial](#).

Updated Oct. 19

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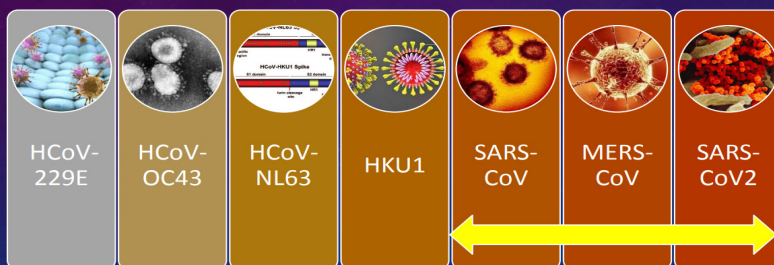


Dr Talat Mokhtari-Azad

DVM, MPH, PhD Tehran University of Medical Sciences

Review of SARS-COV 2 circulation in Iran and world

SEVEN COVS THAT CAN INFECT HUMAN AND CAUSE RESPIRATORY DISEASES



DR. MISWAR FATTAH

Nomenclature systems for virus variants...

- GISAID, WHO and Pango are established systems that name and track virus variants.
- These systems are designed to give scientists a common language in which they can discuss and investigate the evolution of SARS-CoV-2.

GISAID labelling:

- Based on marker mutations from the early split of S and L, to the further evolution of L into V and G, and later of G into GH, GR and GV, and more recently GR into GRY.
- **S:** NS8-L84S
- **L:** (Reference sequence)
- **V:** NS3-G251V
- **G:** S-D614G
- **GK:** S-D614G + S-T478K
- **GH:** S-D614G + NS3-Q57H
- **GR:** S-D614G + N-G204R
- **GV:** S-D614G + S-A222V
- **GRY:** S-D614G + S-N501Y + N-G204R

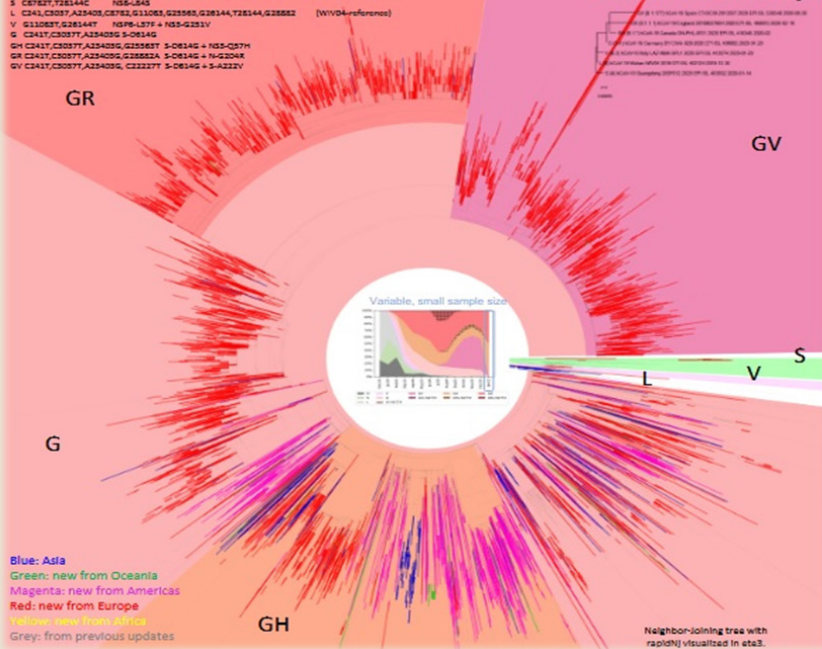
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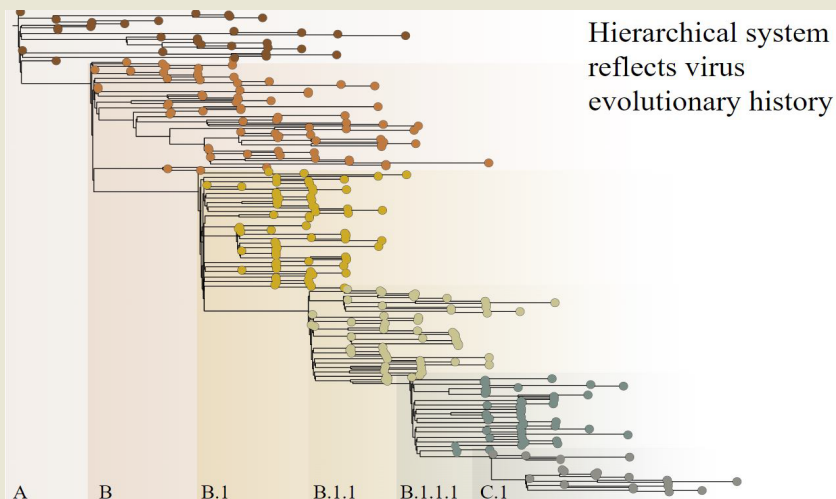
Larger clades in GISAID were named in context of marker variants relative to WIV04-reference:
 S: C87837,728144C + N50-J85
 L: C241, C207, A23409, C8783, G11083, G25563, G28144, 728144, G25562 (WIV04-reference)
 V: G110837, G28144T + N50P-137F + N50S-G2321V
 G: C2417, C20377, A23409G, S-0814G
 GH: C2417, C20377, A23409G, G25568T, S-0814G + N50S-G237H
 GR: C2417, C20377, A23409G, G25562A, S-0814G + N50S-G204K
 GV: C2417, C20377, A23409G, C23217T, S-0814G + S-A2321V

GISAID clades and PANGOLIN lineages



Pango labelling:

- The Pango dynamic nomenclature is a system for identifying SARS-CoV-2 genetic lineages of epidemiological relevance
- The Pango nomenclature is being used by researchers and public health agencies worldwide to track the transmission and spread of SARS-CoV-2, including variants of concern.
- The SARS-CoV-2 variants that first circulated were denoted as lineages A or B. As they evolved, their descendants were marked by a series of numbers. For example, B.1 includes the outbreak in Europe in early 2020.
- The variant named B.1.351, is its 351st descendant.
- If these names become too long, a new lineage begins under a different letter of the alphabet. For example, the variant that was first identified in Brazil is called P.1.



Nomenclature systems for virus variants...

- WHO system assigns SARS-CoV2 variant names that are easy to pronounce and minimizes negative effects on countries and their citizens
- WHO recommends labels using letters of the Greek alphabet,
- i.e., Alpha, Beta, Gamma,...
- Once all 24 letters have been assigned, other lists of names will be considered.

| GREEK ALPHABET | | | |
|-----------------------|---------------------|-----------------------|-----------------------|
| Α Alpha (al-fah) | Γ Gamma (gam-ah) | Ν Nu (new) | Τ Tau (taw) |
| Β Beta (bay-tah) | Η Eta (ay-tah) | Ο Omicron (om-e-cron) | Υ Upsilon (up-si-lon) |
| Χ Chi (kie) | Ι Iota (eye-o-tah) | Π Pi (pie) | Ω Omega (oh-may-gah) |
| Δ Delta (del-ta) | Κ Kappa (cap-pah) | Θ Theta (thay-tah) | Ξ Xi (zie) |
| Ε Epsilon (ep-si-lon) | Λ Lambda (lamb-dah) | Ρ Rho (roe) | Ψ Psi (sigh) |
| Φ Phi (fie) | Μ Mu (mew) | Σ Sigma (sig-ma) | Ζ Zeta (zay-tah) |

Variant of Concern (VOC)

- Transmissibility
- Severity of disease
- Effectiveness of prior SARS-CoV-2 infection
- Effectiveness of vaccines
- Effectiveness of current tests
- Effectiveness of current treatments

Currently designated variants of concern (VOCs)

| WHO label | Pango lineage* | GISAID clade | Nextstrain clade | Additional amino acid changes monitored* | Earliest documented samples | Date of designation |
|-----------|----------------|--------------|------------------|--|------------------------------|-------------------------------|
| Alpha | B.1.1.7 | GRY | 20I (V1) | +S:484K +S:452R | United Kingdom, Sep-2020 | 18-Dec-2020 |
| Beta | B.1.351 | GH/501Y.V2 | 20H (V2) | +S:L18F | South Africa, May-2020 | 18-Dec-2020 |
| Gamma | P.1 | GR/501Y.V3 | 20J (V3) | +S:681H | Brazil, Nov-2020 | 11-Jan-2021 |
| Delta | B.1.617.2 | G/478K.V1 | 21A, 21I, 21J | +S:417N +S:484K | India, Oct-2020 | VOI: 4-Apr-20 VOC: 11-May- |
| Omicron* | B.1.1.529 | GRA | 21K, 21L | +R346K | Multiple countries, Nov-2021 | VUM: 24-Nov- VOC: 26-Nov- |

Currently designated variants of concern (VOCs)

| WHO label | Pango lineage | GISAID clade | Earliest documented samples | Date of designation |
|-----------|---------------|--------------|-----------------------------|---------------------|
| Lambda | C.37 | GR/452Q.V1 | Peru, Dec-2020 | 14-Jun-2021 |
| Mu | B.1.621 | GH | Colombia, Jan-2021 | 30-Aug-2021 |

Sequencing of SARS-COV2

Selected samples are sequenced by two methods in the National Influenza Center:

- 1- Sanger sequence (partially sequencing): In this method, part of the S gene is sequenced for variant determination.
- 2- NGS(next generation sequencing) full genome sequencing) :In this method, the full length of the genome is sequenced

SARS COV-2 In IRAN (1)

- To date, Iran has experienced five waves of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic since the first detection of SARS-CoV2 on 19 February 2020 in Iran.
- As of 16 November 2021, 253640693 cases of SARS-CoV2 with 5104899 deaths were reported worldwide and in Iran 6045212 laboratory confirmed cases with 128272 deaths reported (<https://covid19.who.int/>).

SARS COV-2 In IRAN (2)

- Different lineages of SARS-CoV2 contributing to all five waves and showed that all viruses circulating during the 5th wave belonged to delta variant.
- It should be noted that for variant detection, partially sequenced S glycoprotein of more than 1000 samples with Sanger sequencer which the results were compatible with NGS results during all 5 waves (unpublished data).

SARS COV-2 In IRAN (3)

- During the 1st wave, V and L clades were detected.
- The second wave was recognized by G, GH and GR clades.
- Circulating clades during the 3rd wave were GH and GR.
- In the fourth wave GRY (alpha variant), GK (delta variant) and one GH clade (beta variant) were detected.
- All viruses in the fifth wave were in clade GK (delta variant). There were different mutations in all parts of the genomes but Spike-D614G, NSP12-P323L, N-R203K and N-G204R were the most frequent mutations in these studied viruses.

Sanger Sequencing March 2021 to 14 Dec.(Esfand- Azar 1400)

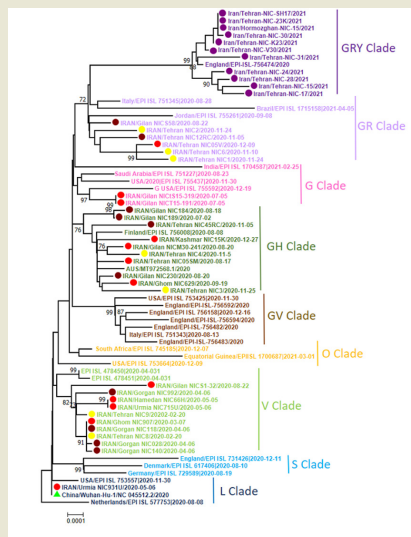
From beginning of the year 1400 , more than 700 samples have been sequenced by the Sanger method.

- Most of the samples were Alpha variants (English), which gradually were replaced by the Delta variant(Indian)
- Between June and August, 90% of the samples were the Delta variant
- The last Alpha variant were detected in 10th August 2021 (19th Mordad 1400)
- From September until now (November), 100% of the samples are delta variant.

NGS Sequencing of SARS-CoV-2 1400/2/8

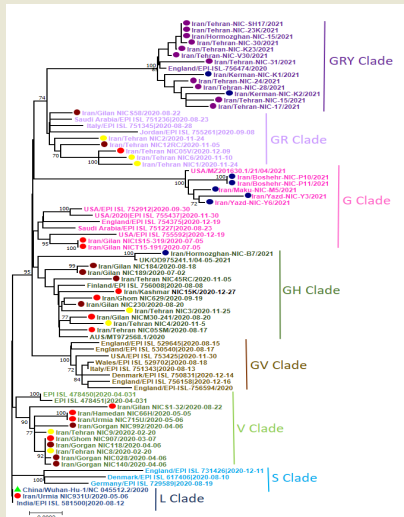
- The results of full genome sequencing of 11 SARS-CoV2 viruses during the fourth wave showed that the viruses circulating variants despite the selection of various samples including hospitalization, ICU, outpatient, return from the passenger form Turkey , Bandar Abbas and Kahrizak sanatorium, all were in Clade GRY , lineage B.1.1.7, which are known as Alpha variant (English) which was the dominant Clade in the world at that time .
- It should be noted that there were no South Africa (Beta), Brazil (Gamma) and India (Delta) variants.

NGS Sequencing of SARS-CoV-2



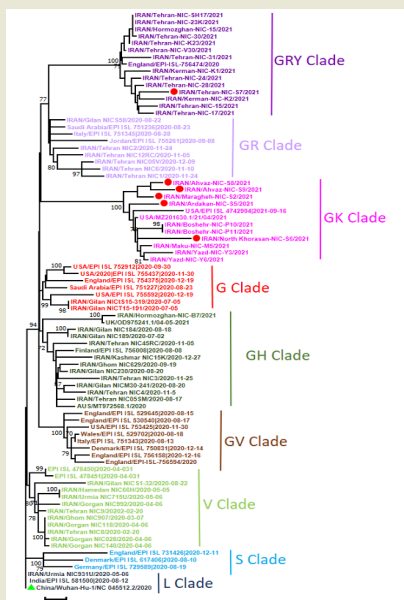
Phylogenetic tree of Iranian strains in 1400/2/8 (with yellow circle)

NGS Sequencing of SARS-CoV-2 1400/3/8



- The 8 Iranian strains that were sequenced, categorized as follows: Two strains (similar to English strains) in Clade GRY, five strains (similar to Indian strains) in Clade G and one strain (similar to African strains) in Clade GH

NGS Sequencing of SARS-CoV-2 1400/6/21



- Phylogenetic tree of Iranian strains (which are marked with a red circle). Five strains in Clade GK and one strain in Clade GRY.

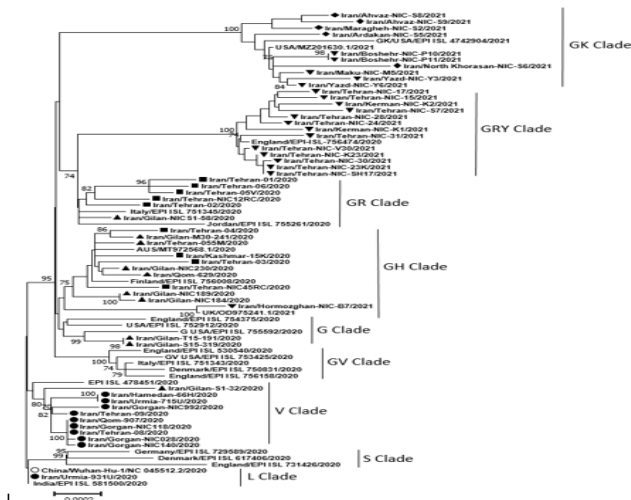


Figure 1. Phylogenetic tree of SARS-CoV2 full-length genomes constricted by MEGA 7. The Neighbor joining method was used with 1,000 bootstrap replicates. The tree contains 54 SARS-CoV2 sequences of these study compared to the reference sequence from GISAID and some other sequences from each clade. In this tree the reference sequence is marked by white circle and sequences of this study were marked as follow: The 1st wave black circle, the 2nd wave inverted black triangle, the 3rd wave with black square, the 4th wave with black triangle and the 5th wave with black diamond.

- One of the advantages of genome sequencing is identification of the circulating variants that perhaps might be useful for choosing the best compatible vaccine.
- Choosing the correct vaccine and complete vaccination will make the community safer against the disease.
- After the wide coverage of vaccination in Iran, the incidence and mortality rate is greatly decreased.
- On 26 November 2021, WHO designated the variant B.1.1.529 a variant of concern, named Omicron that has several mutations that may have an impact on how it behaves, for example, on how easily it spreads or the severity of illness it causes. Here is a summary of what is currently known.).
- The omicron variant distinguishes itself from previous variants by harboring in its genomic sequence 50 mutations (30 of which occur within the spike protein)—a jump from the 13 mutations found within the delta variant (B.1.617.2).
- More mutations does not intrinsically mean that a variant is more dangerous, but almost immediately omicron generated concern within the global health community regarding its transmissibility and ability to evade both vaccine-induced and natural immunity.

- Omicron has some deletions and more than 30 mutations, several of which (eg, 69–70del, T95I, G142D/143–145del, K417N, T478K, N501Y, N655Y, N679K, and P681H) overlap with those in the alpha, beta, gamma, or delta VoCs.⁸ These deletions and mutations are known to lead to increased transmissibility, higher viral binding affinity, and higher antibody escape.

Omicron different lineages...

The unique mix of spike amino acid changes in Omicron (clade GRA, lineage B.1.1.529 and descendants BA.1 and BA.2) is of interest as it comprises several that were previously identified to affect receptor binding and antibody escape.

Major Variants Mutation History

| Site/Type | Alpha | Delta | Omicron |
|-----------|-------|-------|---------|
| Virus | 23 | 17 | 50 |
| Spike | 9 | 7 | 32 |
| RBD | 9 | 2 | 10 |

Omicron Behavior so far

Transmissibility

- Increasing
- Epidemiology

Vaccine evasion

- Neutralization ability
- Reduction in efficacy
- T-cell response
- Transmission prevention

Virulence

- Unknown
- Seems less virulent

Incidence of SARS-CoV-2 infections by variant of concern. Note the rapid rise of Omicron

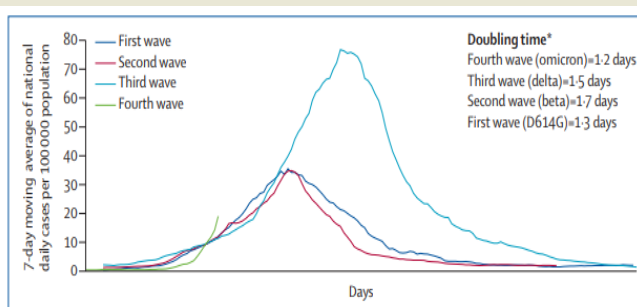
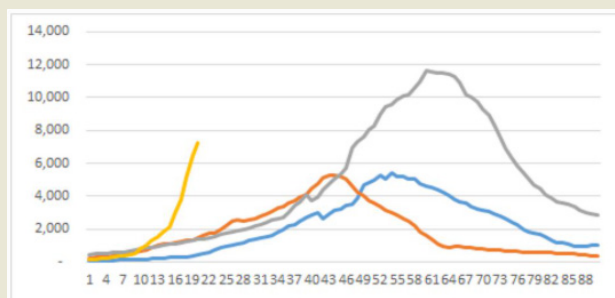


Figure: SARS-CoV-2 cases in first, second, third, and fourth waves, Gauteng Province of South Africa
 *Doubling time for the first 3 days after the wave threshold of ten cases per 100 000 population. 7-day moving average cases per 100 000 population up to Dec 1, 2021. Data are from the Department of Health, Government of South Africa.²⁰

Distribution of SARS-CoV-2 infections by major variants of concern globally and in South ... [+] STEBBING

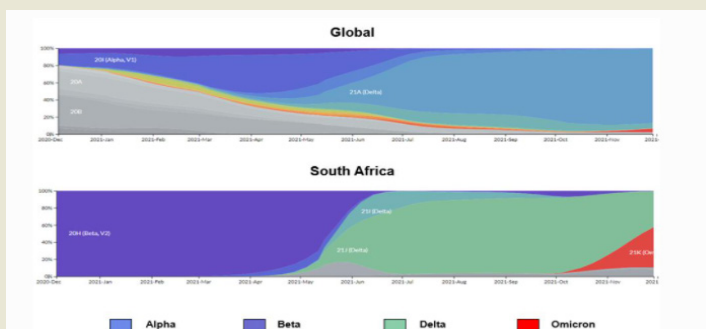
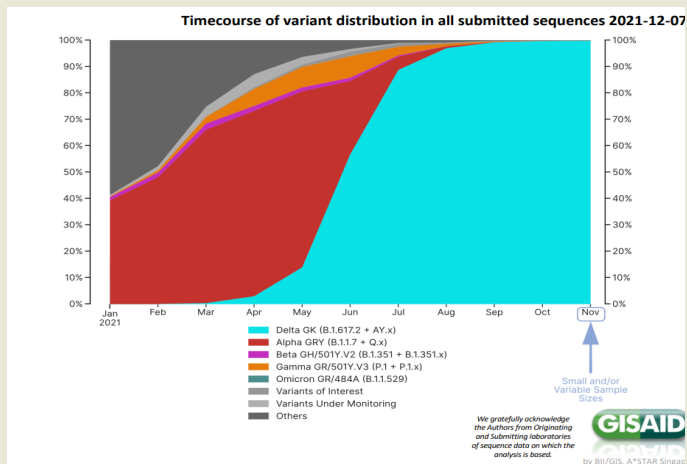
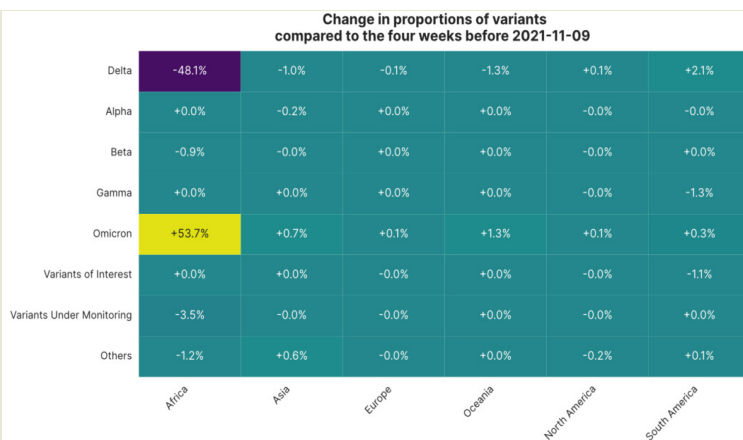


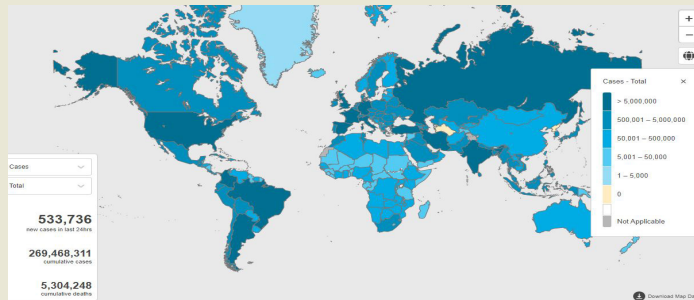
FIGURE 2: Distribution of SARS-CoV-2 infections by major variants of concern globally and in South ...
 [+] STEBBING

OMICRON variant

- Transmissibility
- Severity of disease
- Effectiveness of prior SARS-CoV-2 infection
- Effectiveness of vaccines
- Effectiveness of vaccines
- Effectiveness of current tests



WHO Coronavirus (COVID-19) Dashboard 13 December 2021



Conclusion

- We await knowledge of how this new VoC will impact clinical presentation. At this stage, the available anecdotal data from clinicians at the front lines in South Africa suggest that patients with omicron are younger people with a clinical presentation similar to that of past variants.
- Although no alarming clinical concerns have been raised thus far, this anecdotal information should be treated with caution given that severe COVID-19 cases typically present several weeks after the initial symptoms associated with mild disease.
- The report of the new variant has caused national governments to react with the reintroduction of non-pharmaceutical measures and ramped up vaccine booster programs in the hope of delaying the spread of omicron. Controversially, however, for some governments the immediate response was to issue travel bans against South Africa. The UK was the first to adopt such a proposal, and was swiftly followed by the USA, Israel, and others







Dr Jila Yavarian

MD, PhD of Virology

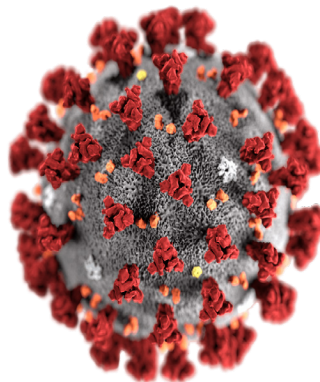
Tehran University of Medical Sciences

Outline

- Introduction
- SARS-CoV2 variants
- Diagnosis challenges

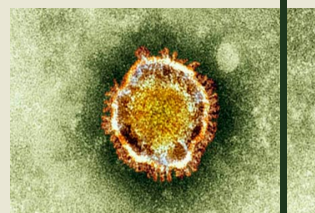
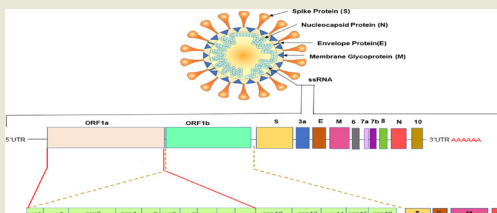
Introduction...

- Introduction
- SARS-CoV2 variants
- Diagnosis challenges



Introduction...

- Enveloped, roughly spherical
- Diameter 120-160 nm
- The spikes typically described as club-like or petal shaped
- Single stranded, positive sense RNA viruses, 26-32 kb



Introduction...

You may hear different words related to SARS-CoV2:

- Mutations
- Variants
- Strains



- Mutation an error introduced during viral replication
- Variants describes the version of the virus that has changed, through mutation, from the original virus.
- Strains is used in the same way as the word variants.

All viruses evolve over time

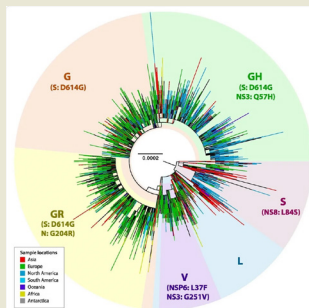
- Viruses replicate. When replicating, sometimes mistakes are made.
- Most changes have little to no impact on the viruses properties.

However some changes can lead to variants of the virus that may affect:

- Virus transmissibility
- Disease severity
- Efficacy of vaccines, therapeutics or diagnostic tools



SARS-CoV2 variants nomenclature



Nomenclature systems for virus variants...

- GISAID, WHO and Pango are established systems that name and track virus variants.
- These systems are designed to give scientists a common language in which they can discuss and investigate the evolution of SARS-CoV-2.

<https://www.gisaid.org/>
<https://cov-lineages.org/>



Nomenclature systems for virus variants...

- GISAID labelling:

Based on marker mutations from the early split of S and L, to the further evolution of L into V and G, and later of G into GH, GR and GV, and more recently GR into GRY.

S: NS8-L84S **L:** (reference sequence) **V:** NS3-G251V **G:** S-D614G **GK:** S-D614G + S-T478K **GH:** S-D614G + NS3-Q57H **GR:** S-D614G + N-G204R **GV:** S-D614G + S-A222V **GRY:** S-D614G + S-N501Y + N-G204R



Nomenclature systems for virus variants...

Pango labelling:

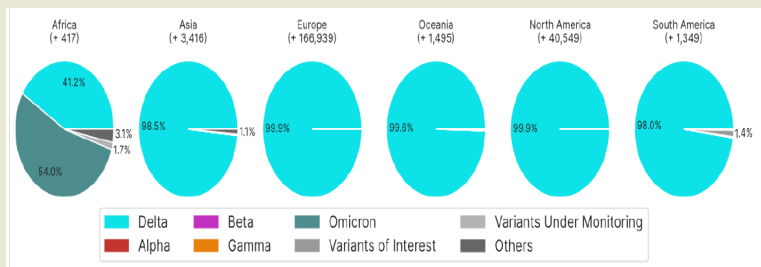
- The SARS-CoV-2 variants that first circulated were denoted as lineages A or B. As they evolved, their descendants were marked by a series of numbers. For example, B.1 includes the outbreak in Europe in early 2020.
- The variant named B.1.351, is its 351st descendant.
- If these names become too long, a new lineage begins under a different letter of the alphabet. For example, the variant that was first identified in Brazil is called P.1.

Nomenclature systems for virus variants

- WHO system assigns SARS-CoV2 variant names that are easy to pronounce and minimizes negative effects on countries and their citizens
- WHO recommends labels using letters of the Greek alphabet,
- i.e., Alpha, Beta, Gamma,...
- Once all 24 letters have been assigned, other lists of names will be considered.

| | | | | | |
|-------|---------|---------|-------|---------|-------|
| Α | Β | Γ | Δ | Ε | Ζ |
| Alpha | Beta | Gamma | Delta | Epsilon | Zeta |
| Η | Θ | Ι | Κ | Λ | Μ |
| Eta | Theta | Iota | Kappa | Lambda | Mu |
| Ν | Ξ | Ο | Π | Ρ | Σ |
| Nu | Xi | Omicron | Pi | Rho | Sigma |
| Τ | Υ | Φ | Χ | Ψ | Ω |
| Tau | Upsilon | Phi | Chi | Psi | Omega |

SARS-CoV2 variants



Variant of Concern (VOC)...

- A variant which has been associated with at least one of the following:
- Increase in transmissibility or detrimental change in COVID-19 epidemiology
- Increase in virulence or change in clinical disease presentation
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics

Variant of Concern (VOC)

| WHO label | Pango lineage | GISAID clade | Earliest documented samples | Date of designation |
|-----------|---------------|--------------|------------------------------|--------------------------------------|
| Alpha | B.1.1.7 | GRY | United Kingdom, Sep-2020 | 18-Dec-2020 |
| Beta | B.1.351 | GH/501Y.V2 | South Africa, May-2020 | 18-Dec-2020 |
| Gamma | P.1 | GR/501Y.V3 | Brazil, Nov-2020 | 11-Jan-2021 |
| Delta | B.1.617.2 | G/478K.V1 | India, Oct-2020 | VOI: 4-Apr-2021 VOC: 11-May-2021 |
| Omicron | B.1.1.529 | GR/484A | Multiple countries, Nov-2021 | VUM: 24-Nov-2021 VOC: 26-Nov-2021 |

Variant of Interest (VOI)...

- A variant which is both:
- Phenotypically changed compared to a reference isolate or has a genome with mutations that lead to amino acid changes associated with established or suspected phenotypic implications (including epidemiology, antigenicity, or virulence or changes that have or potentially have a negative impact on available diagnostics, vaccines, therapeutics or public health and social measures)
- Has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries
- Also called Variant Under Investigation (VUI)

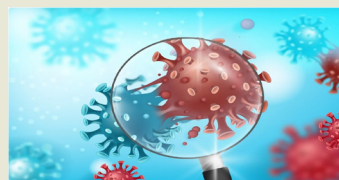
Variant of Concern (VOC)

| WHO label | Pango lineage | GISAID clade | Earliest documented samples | Date of designation |
|-----------|---------------|--------------|-----------------------------|---------------------|
| Lambda | C.37 | GR/452Q.V1 | Peru, Dec-2020 | 14-Jun-2021 |
| Mu | B.1.621 | GH | Colombia, Jan-2021 | 30-Aug-2021 |

Variant under Monitoring (VUM)...

- A variant which is being monitored by a public health agency to detect if it meets the conditions of a Variant of Concern or Interest.

- It may also be used for variants which have previously been designated as VOCs or VOIs but have been downgraded by the public health agencies based on recent data.



Variant under Monitoring (VUM)

| WHO label | Pango lineage | GISAID clade | Earliest documented samples | Date of designation |
|-----------|---------------|--------------|------------------------------------|--------------------------------------|
| - | AZ.5 | GR | Multiple countries, Jan-2021 | VUM: 02-Jun-2021 |
| - | C.1.2 | GR | South Africa, May 2021 | 01-Sep-2021 |
| Kappa | B.1.617.1 | G/452R.V3 | India, Oct-2020 | VOI: 4-Apr-2021 VUM: 20-Sep-2021 |
| Lota | B.1.526 | GH/253G.V1 | United States of America, Nov-2020 | VOI: 24-Mar-2021 VUM: 20-Sep-2021 |
| Eta | B.1.525 | G/484K.V3 | Multiple countries, Dec-2020 | VOI: 17-Mar-2021 VUM: 20-Sep-2021 |
| - | B.1.630 | GH | Dominican Republic, Mar-2021 | 12-Oct-2021 |
| - | B.1.640 | GH/490R | Republic of Congo, Sep-2021 | 22-Nov-2021 |

De-escalated Variants

- These former VOCs and/or VOIs have been de-escalated by public health agencies based on at least one the following criteria:

- (1) the variant is no longer circulating
- (2) the variant has been circulating for a long time without any impact on the overall epidemiological situation
- (3) scientific evidence demonstrates that the variant is not associated with any concerning properties

- Epsilon/B.1.427 & B.1.429

- Zeta/P.2

- AV.1

Iran NIC Sequencing program...

- For variant identification during SARS-CoV2 waves in Iran, Sanger sequencing has been performing with partially sequencing of the spike glycoprotein on some selected samples referred to Iran National Influenza Centre. Meanwhile NGS has been performing on some selected samples during each wave.

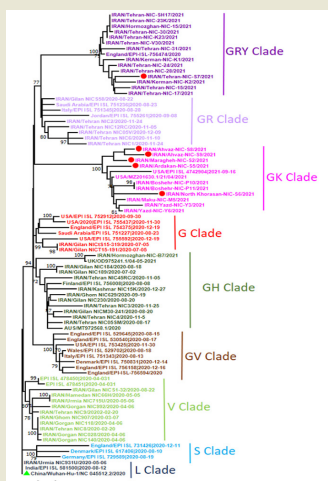
- Sample selection:
- Different cities all over the country
- Special cases with unusual co-morbidities
- Suspected imported cases
- Special cases with unusual death

Iran NIC Sequencing program...

- Last Alpha variant samples were:
- 2 samples from Maragheh/ 3 August 2021
- 1 sample from Tehran- Airport/ 8 August 2021
- 1 sample from Urmia/ 10 August 2021

Iran NIC NGS program

- Phylogenetic tree of all 61 complete genome sequencing of SARS-CoV2 variants in Iran. 6 marked strains were for the 5th wave.



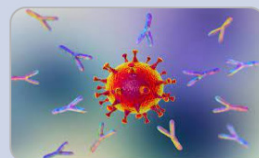
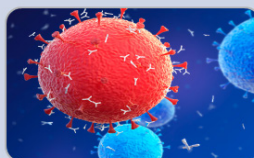
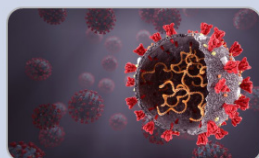
تازه های کووید

Covid 19

The Comprehensive National Congress On Covid 19

Common problems in SARS-CoV2 diagnosis

SARS-CoV2 laboratory testing



RNA
E gene
RdRp gene
N gene
S gene
rRT-PCR

Antigen
N protein
S protein

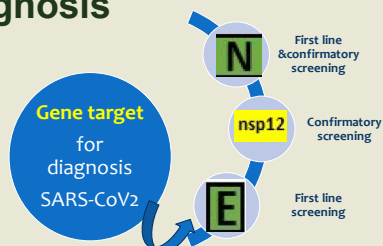
ELISA

Antibody
IgM
IgG
IgA

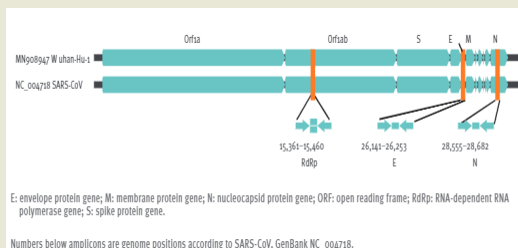
ELISA

Gold standard for diagnosis

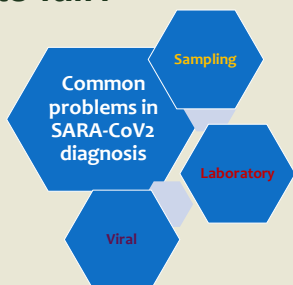
- Real time reverse transcription polymerase chain reaction (rRT-PCR) is the current gold standard for diagnosing suspected cases of COVID-19.



Relative positions of amplicon targets on SARS-CoV2 genome



Why might COVID-19 tests fail?



Sampling issues

Sampling carried out outside of the diagnostic window

Repeat sampling

Poor handling & wrong samples

Use trained staff

Repeat training courses

Sampling issues

- RT-PCR results also depend heavily on the type of sample taken: positive sampling rates vary widely between:
 - oropharyngeal swabs (32–48%)
 - nasopharyngeal swabs (63%)
 - bronchoalveolar lavage fluid (79–93%)
 - sputum (72–76%)
 - stool (29%)

Laboratory issues

Problems with primers and probe

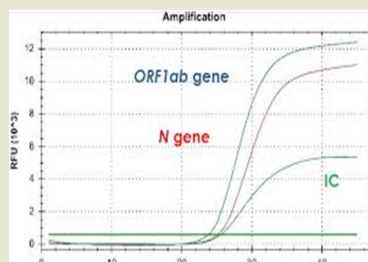
Change

Use of adequately validated assays

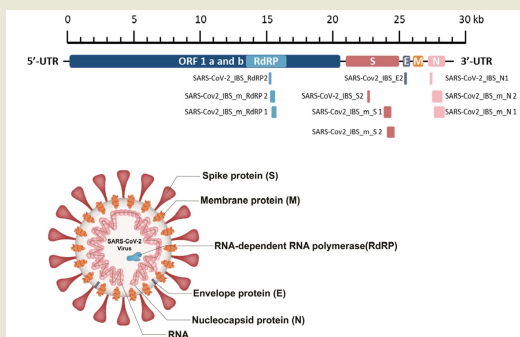
Insufficient materials

Instrument malfunctioning

Misinterpretation of the results



Virus mutations



Take home message

- Nucleic acid amplification tests may be problematic with
 - poorly timed specimen collection
 - poor-quality specimen collection
 - the requirement for trained laboratory technicians

Currently, a 'clinical diagnosis' of COVID-19 relies on a combination of sign and symptoms and RT-PCR results

- Specimen collection
 - Within 5 to 6 days of the onset of symptoms
 - Repeated testing may be particularly important if a patient has a clinical picture of viral pneumonia, a potential exposure history, and/or radiographic findings

Nucleic acid amplification test (NAAT)...

- A number of factors could lead to a negative result in an infected individual, including:
 - Poor quality of the specimen
 - The specimen was collected late in the course of the disease, or the specimen was taken from a body compartment that did not contain the virus at that given time

Nucleic acid amplification test (NAAT)

- The specimen was not handled and/or shipped appropriately
- Technical reasons inherent in the test, e.g. PCR inhibition or virus mutation.
- False positive results may occur due to technical errors and reagent contamination.





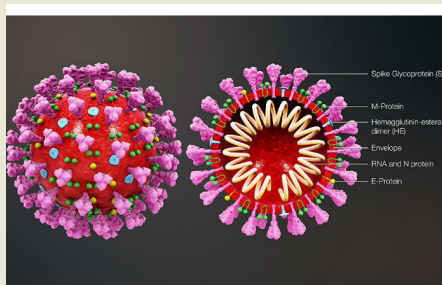
دکتر محمد وجگانی
استاد ایمنولوژی
دانشکده پزشکی دانشگاه علوم پزشکی تهران

COVID 19

Vaccines And Immunity

Virus morphology

Vaccines And Immunity



Coronavirus disease 2019 (COVID-19)

caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a serious disease that has resulted in widespread global morbidity and mortality

Most patients with COVID-19 exhibit mild to moderate symptoms

but approximately 15% progress to severe pneumonia and about 5% eventually develop acute respiratory distress syndrome (ARDS), septic shock and/or multiple organ failure.

SARS-CoV-2 infection

can activate innate and adaptive immune responses.

However, uncontrolled inflammatory innate responses and impaired adaptive immune responses may lead to harmful tissue damage, both locally and systemically.

تازه های کووید

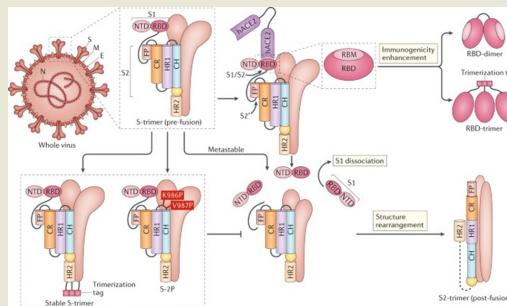
Covid 19

The Comprehensive
National Congress On Covid 19

SARS-CoV-2 contains four major structural proteins

- S proteins are responsible for recognition of the host cellular receptor to initiate virus entry.
- M proteins are embedded in the envelope and shape the virion envelope.
- E proteins are small polypeptides that are crucial for CoV infectivity.
- N proteins make up the helical nucleocapsid and bind along the viral RNA genome.

COVID 19 S antigen

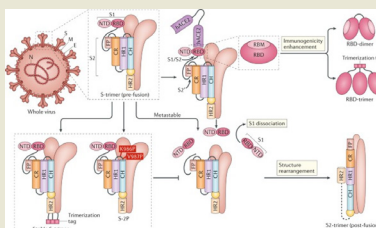


S protein

- S protein is the main protein used as a target in COVID-19 vaccines.
- S protein consists of a membrane-distal S1 subunit and a membrane-proximal S2 subunit and exists in the virus envelope as a homotrimer.
- The S1 subunit determines receptor recognition via its receptor-binding domain (RBD),
- The S2 subunit is responsible for membrane fusion, which is required for virus entry

The S protein comprises

- the S1 subunit which includes: the N-terminal domain (NTD)
- and the receptor-binding domain (RBD)
- the receptor-binding motif (RBM) within the RBD
- the S2 subunit which includes:
 - fusion peptide (FP),
 - connecting region (CR),
 - heptad repeat 1 (HR1),
 - heptad repeat 2 (HR2)
 - And central helix (CH).



The SARS-CoV-2 S protein binds to its host receptor

- the dimeric human angiotensin-converting enzyme 2 (hACE2), via the RBD and dissociates the S1 subunits Cleavage at both S1–S2
- and S2' sites allows structural rearrangement of the S2 subunit required for virus–host membrane fusion
- The RBD is an attractive vaccine target. The generation of an RBD-dimer or RBD-trimer has been shown to enhance the immunogenicity of RBD-based vaccines. A stabilized S-trimer shown with a C-terminal trimer-tag is a vaccine target

HUMORAL IMMUNE RESPONSE TO SARS-COV-2

- Current clinical reports show that antibodies against SARS-CoV-2 viral particles develop between 6 and 10 days after infection,
- with peak IgM antibody levels at 12 days, and persist for 35 days.
- In contrast, the IgG antibodies peak around 17 days and persist for up to 49 days.

Current World Health Organization guidelines

- recommend obtaining a blood sample during the first week of illness and then 3 to 4 weeks later to measure SARS-CoV-2 antibodies. 13
- Within 5 days of infection, the IgM positive rate increased from 50% to 81%,
- whereas the IgG positive rate increased from 81% to 100% in COVID-19 patients.

Vaccination

is a safe, simple, and effective way of protecting a person against COVID-19

Certain persons Including:

- pregnant women,
- breastfeeding individuals,
- autoimmune conditions and immunocompromised persons,
- diabetic patients,
- and people with respiratory and heart disease
- require special consideration for COVID-19 vaccination

At present, 184 candidate vaccines

- were being evaluated in preclinical and
- 104 in clinical stages of development.
- 41 vaccines in phase 3
- 18 COVID-19 vaccines approved,
- and are currently in use worldwide

These vaccines are in four primary groups

using various platforms:

- viral vector vaccines,
- whole virus vaccines,
- nucleic acid vaccines,
- and protein-based vaccines.

Vaccination in view of gender difference

- It has been shown that several factors, including:
 - the genetic,
 - immune system,
 - gut microbiome,
 - and steroid hormones
- are varied between men and women
- that contribute to gender - and sex-specific vaccine responses and outcomes.

Women produce more antibodies

- as a result of vaccination
- and respond more actively to infections.
- In women, a strong response of the immune system may increase the risk of autoimmune diseases
- and a good capability to fight against various infections.

A higher level of COVID-19 antibody

- has been reported in women than in men after COVID-19 infection.
- Women display more strong cellular and humoral-mediated immune responses to vaccination and infection.

Thus, the vaccine efficacy suggested for adults

- Is potentially greater for women than men.
- Men, due to high levels of testosterone, show low levels of COVID-19 vaccine effectiveness.
- In this respect, males may need more doses of the COVID-19 vaccine compared with females.

Vaccination in view of race difference

- Among those reported, the ethnic and racial distribution of the sample was not always stated, and methods are different, which may affect the results.
- Asian, Hispanic, and Black people are infected with COVID-19 more than White ethnicity, with a possible relationship of higher risk of mortality and intensive care unit (ICU) admission in Asians

COVID-19 vaccines and variants

RNA viruses such as the novel coronavirus are known for mutating and evolving quickly.

RNA replication is more error-prone compared to DNA replication, so mutations happen commonly during copying.

Sometimes the random mutation is beneficial

- for the virus, which helps it evade the host's immune system and infect new species or systems.
- A new variant of novel coronavirus emerged with a high number of mutations.

The new variants

are B.1.1.7 (Alpha), B.1.351 (Beta), P.1(Gamma), B.1.617.2 (Delta), and C.37 (Lambda).

The new variants are spread more easily, lead to severe disease, and may change the efficiency of COVID-19 vaccines

Very new variant is B1.1.529 in south Africa (1400.9.3/2022.Nov.24)

COVID-19 vaccines efficacy and immunity

No vaccine is 100% effective.

There's no report so far that the COVID-19 vaccine can prevent transmission,

but it can help protect against COVID-19 infection.

None of the approved COVID-19 vaccines

- Contain the live virus that causes COVID-19.
- This means these vaccines cannot lead to COVID-19 infection. Generally a few weeks after vaccination, the body builds immunity against COVID-19 infection.

Similar to other vaccines,

- COVID-19 vaccines can cause mild or moderate side effects within a few days after injection.
- Some side effects such as: headache, muscle pain, fatigue, fever, diarrhea, and chills have been reported, and most have happened during the first 48 h after vaccination

Some people may show a severe allergic reaction to the vaccines

- According to CDC report, 11.1 per million cases of vaccinated people reported anaphylaxis in the USA.

If the subjects report a history of anaphylaxis with previous vaccines, they are advised not to take the new vaccine.

- Polyethylene glycol (PEG) and PEG derivatives (e.g., polysorbates) are probably responsible for anaphylaxis.

It has been recommended that before vaccination

people should notify the healthcare workers about any anaphylaxis they may have had previously.

It has been proposed that all vaccinated cases remain at the vaccination site for 30 min to detect any serious side effects.

It has been reported that

the AstraZeneca and Johnson & Johnson/Janssen vaccines may have a possible link to a very rare side effect of unusual blood clots combined with low levels of platelet levels

COVID-19 vaccines dose

- The Johnson & Johnson vaccine only requires one dose,
- while the Moderna, Pfizer-BioNTech, Oxford-AstraZeneca (in a 8–12 week interval), Sputnik V (in a 3 week interval),
- Novavax (in a 3 week interval), Coronavac (in a 1 month interval) need two doses.
- The CDC documented that while there's no priority for one vaccine over another, the vaccines aren't interchangeable.

Mixing two different vaccines

can show long-lasting and strong immune responses when compared to the single vaccine.

Scientists hope that mix-and-match COVID-19 vaccination regimens (e.g. AstraZeneca and Pfizer) can trigger stronger, more robust immune responses than two doses of a single vaccine.

Mix-and-match COVID-19 vaccination is recognized by high levels of both T cells and antibodies, which kill infected cells and support other antiviral responses.

COVID-19 vaccines transport and storage

Most of the available vaccines should be stored and transported in refrigeration to freezing temperatures (e.g., the Pfizer vaccine at -70°C and Oxford-AstraZeneca $2-8^{\circ}\text{C}$).

Therefore, the storage and transport of mRNA vaccines is challenging.

Some new vaccines can be stored at -15 to -25°C for up to 14 days¹².

On the other hand, some other vaccines need ultra-cold storage (below -80°C).

Proper preparation of lyophilized form is necessary

- and powder should not be prepared until the administration.
- Liquid form loses its efficacy when kept at freezing temperatures because slow freezing leads to great stress to the colloids and increased aggregations.
- Cold chain technology is needed for the liquid form, which can be challenging for use in poor countries. Appropriate cold chain infrastructure can prevent up to 25% vaccine loss in poor countries .

COVID-19 vaccine distribution

Many people in poor and middle-income countries may not be receiving vaccines; therefore, equitable COVID-19 vaccine distribution is essential.

More than 700 million COVID-19 vaccines have been injected globally; low-income countries received only 0.2%, while wealthy countries have received more than 87%.

On average, 1 in more than 500 people in poor countries has received COVID-19 vaccines, compared with 1 in 4 people in wealthy countries

COVID-19 vaccine for children and pregnant women

- COVID-19 infection has been a more dangerous and severe disease among older people.
- Because of the high risk of severe disease in the children, elderly, immunocompromised subjects, and pregnant women, the vaccination program should be conducted with care.
- COVID-19 vaccine teams need to follow-up pregnancies long-term to recognize effects on infants and pregnancy.

The mRNA vaccines (Pfizer-BioNTech and Moderna)

- do not have the live coronavirus that leads to COVID-19 and, consequently, cannot infect.
- Moreover, the mRNA vaccines do not interact with an individual's DNA or lead to genetic alterations since the mRNA does not enter the cell's nucleus.

Some vaccinated subjects

later exposed to the coronavirus still get COVID-19.

In this context, a fully vaccinated person should continue to wear a face mask, maintain social distance, and follow health care recommendations.

Preliminary data from some countries showed that

- The viral load was 4-fold lower among those fully vaccinated with an effective vaccine.
- This finding suggests that viral transmission from fully vaccinated people is lower, as viral load has been recognized as the main factor for virus transmission.

The viral vector vaccines (J&J/Janssen vaccine)

- can be administered to pregnant women in all trimesters of pregnancy (like the Ebola vaccine).
- However, there are various types of COVID-19 vaccines, and our direct knowledge is currently limited about their effects during pregnancy.

The efficacy and safety of COVID-19 vaccines

- in lactating women, the impact of COVID-19 vaccination on the breastfed infant, and effects on milk excretion or production have not been determined.
- However, non-replicating COVID-19 vaccines pose no risk for lactating women or their babies; hence lactating women may safely be vaccinated

So far, SARS-CoV-2 has not been detected in breast milk

- and there are no recognized cases of transmission of virus to the infant through breast milk.
- However, infected women may select to breastfeed with protections to prevent transmission of the virus through respiratory droplets.
- Some newborns have shown COVID-19 shortly after birth.
- It is unknown if these newborns got the virus after, during, or before birth

COVID-19 VACCINES

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- Cold chain technology is needed for the liquid form, which can be challenging for use in poor countries. Appropriate cold chain infrastructure can prevent up to 25% vaccine loss in poor countries .

Moderna

- mRNA vaccine
- Shot in the muscle of upper arm
- Recommended for people aged 18 and older
- Most common side effects:
 - In the arm: pain, swelling, redness
 - Throughout the body: chills, tiredness, headache
- Moderna is 94.1 effective
- Allergic person don,t allowed

Pfizer - BioNtech

- mRNA
- 95% efficacy
- 2 shot, 21 day apart the upper arm
- Shot in the muscle
- Recommended for people aged 16 years and older
- Most common side effects:
 - In the arm: pain, swelling, redness
 - Throughout the body: chills. Tiredness, headache
- Allergic person don't allowed

AstraZeneca

- Adenovirus vector vaccine
- Efficacy: ½ dose + complete dose =90%
- Intra muscular administration
- Vector: Titi monkey adenovirus ECC-201
- Antigen: The spike S1 protein

Sputnik V

- Gives around 92% protection
- Vector based vaccine
- It can be stored at temperatures of between 2 and 8C degree
- Sputnik jab uses two slightly different version of the vaccine for the first and second dose-given 21 days apart
- Vectors: adenovirus 5 and 26

Sinopharm

- Has shown 86 % efficacy
- It is killed virus or inactive vaccine

Sinovac

- Has 79.34% efficacy
- It is killed virus or inactive vaccine

CovIran Barkat Vaccine

An Inactivated COVID-19 Vaccine

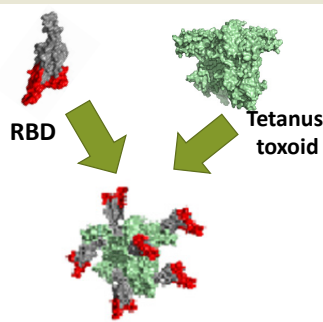
Formulation and dose of injection

- CovIran Barkat vaccine includes 5 µg inactivated whole virus particle as the immunogenic antigen and Alum adjuvant per each dose in the form of a suspension in PBS.
- 0.5mL doses of the vaccine should be injected intramuscularly, twice with a 28-day interval.

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- November 2021

سوبرانا 2/ پاستوکوک



سوبرانا 2- (پاستوکوک)، یک پروتئین نوترکیب و حاوی 25 میکروگرم بخش RBD از ژن Spike ویروس SARS-Cov-2 می-باشد. جهت حفظ پایداری این پروتئین، شش عدد منومر از بخش RBD ویروس با " توکسوئید کزاز" کنژوگه شده و برای افزایش ایمنیزایی آن، از افزونه آلومینیوم هیدروکساید استفاده شده است.

کارآزمایی بالینی فاز 1 و 2 در کودکان در کوبا

در این کار آزمایی بالینی 350 کودک 3 تا ۱۸ ساله وارد مطالعه شدند. متعاقب تزریق 2 دوز از کاندید واکسن سوبرانا 2- هیچ عارضه جدی یا شدید منتسب به واکسن مشاهده نشد. الگوی بیخطری واکسن در این گروه سنی مشابه بالغین 19 تا 29 ساله بود. بعد از دریافت 2 دوز واکسن، افزایش 4 برابری تیتراژ آنتیبادی در 99/3% کودکان 3 تا 11 سال و 92/9% کودکان 12 تا 18 سال مشاهده گردید. نتایج سایر شاخصهای ایمنولوژیک (شامل غلظت آنتیبادی IgG، مهار اتصال RBD به گیرنده ACE2 و تولید آنتیبادی نوترالیزاسیون) در این گروه سنی مشابه پاسخ ایمنولوژیک در بالغین گروه سنی 19 تا 29 سال بود.

سوبرانا پلاس/ پاستوکوک پلاس

دوز بوستر متشکل از یک پروتئین نوترکیب و حاوی 50 میکروگرم یک دایمر از بخش RBD ژن Spike ویروس SARS-Cov-2 میباشد. برای افزایش ایمنیزایی آن نیز، از افزونه آلومینیوم هیدروکساید استفاده شده است ولی کنژوگه نمی باشد. این واکسن به عنوان دوز بوستر

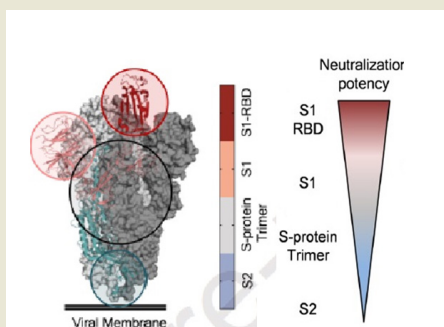
(یادآور) رژیم 2 دوزه و سایر واکسن های مورد استفاده در ایران، استفاده می شود

مشخصات واکسن های موجود از نظر انتی ژن استفاده شده در فرمولاسیون آنها:

از نظر نوع انتی ژن استفاده شده :

- آنتی ژن spike full تک ظرفیتی : اسپایکوژن
- آنتی ژن RBD بدون هیچ قسمت دیگری از آنتی ژن اسپایک: سوبرانا یا پاستوکوک
- آنتی ژن تراپمر اسپایک به تنهایی : فایزر، مدرنا ، با پایه وکتور، نوواوکس ، GSK ،
- آنتی ژن اسپایک تراپمر به همراه قطعات از انتی ژن Spike تک ظرفیتی : رازی کوو پارس

رازی کوو پارس : واکسنی که کمترین از نظر مقدار آنتی ژن و بیشترین وسعت از نظر انتی ژنسیستی را در طراحی لحاظ کرده است



A mixture of antigens

- Maximum protection against possible mutations
- Use conserved areas
- Do not use areas that pose a problem for safety

نوع آنتی ژن :
آنتی ژن اسپایک تراپمر به همراه قطعات از انتی ژن Spike تک ظرفیتی : رازی کوو پارس

رازى كوو پارس : واكسنى كه كمترين از نظر مقدار آنتى ژن و بيشترين وسعت از نظر انتى ژنسىتى را درطراحى لحاظ كرده است

مقدار استفاده :

- آنتى ژن اسپايك ترايمر S1 trimer به همراه قطعات از انتى ژن S1 and S2
تك ظرفيتى : (همگى با هم 10 ماكرو گرم)
- آنتى ژن اسپايك ترايمر : افزايش ايمنى زايى و تقليد آنتى ژن واقعى سطح
ويروس

رازى كوو پارس : واكسنى كه كمترين از نظر مقدار آنتى ژن و بيشترين وسعت از نظر انتى ژنسىتى را درطراحى لحاظ كرده است

چرا آنتى ژن S2 ؟

قسمت بى تغيير بر روى آنتى ژن اسپايك در صورتى كه ويروس جهش
بالايى هم داشته باشد به واكسن زمان ميدهد كه حداقل ايمنى زايى را بر
عليه ويروس جديد ايجاد نمايد. از طرفى اين قسمت بيشترين اپى توپ هاى
TH1 را دارد.
شكل روبرو نواحى انتخابى و مزايای آن را نشان ميدهد

نوع ادجوانت :

بايستى هر سه بازوى ايمنى را در مقابل ايمنى فعال كند مخصوصا ايمنى
سلولى ادجوانت مورد استفاده در واكسن رازى اين خصوصيات را دارد. و هيچ
پروتئينى به غير از اسپايك در آن نيست.
واكسنهاى كه در فرمولاسيون خود از كمترين مقدار آنتى ژن استفاده كرده
اند و در ادجوانت آنها ماده اكتيو ديگرى نباشد بهترين كانديدى براى استفاده
براى بوستر دوز بر روى هر پلت فرمى ميباشند
مزايای نانو ادجوات رازى در شكل روبرو مشخص است

نوع استنشاقی:

14 روز بعد از دو تزریق عضلانی ایمنی کامل در واکسن رازی همانند واکسن های دیگر ایجاد میشود:
ولی تا به امروز هیچ واکسن عضلانی نتوانسته است جلو تکثیر ویروس در قسمت بالای سیستم تنفسی بگیرد. لذا نوع استنشاقی میتواند ایمنی مخاطی را نیز تحریک کرده و قسمت بالایی سیستم تنفسی را نیز فعال میکند. با توجه به تست های انجام شده در نوع الفا ویروس فرم استنشاقی میتواند این انتقال را تا نزدیک صفر کم کند ولی با شیوع نوع دلتا این مقدار از محافظت حدود 20 درصد کم شده است ولی باز میتوان نقش مهمی در جلوگیری از انتقال ویروس داشته باشد.
رازی کوو پارس اولین واکسن تزریقی استنشاقی جهان بود که توانسته با پروتئین نوترکیب و ادجوانت نانو به این موفقیت دست یابد.

Omicron coronavirus very new variant

Mutation in:

RBD, NTD ,

NSP6,

N

AND S1/S2 furine cleavage site



references

www.thelancet.com/respiratory Published online October 21, 2021 [https://doi.org/10.1016/S2213-2600\(21\)00407-0](https://doi.org/10.1016/S2213-2600(21)00407-0)

Vaccines 2021, 9, 1223. <https://doi.org/10.3390/vaccines9111223>

The New England Journal of Medicine .org at on October 23, 2021

www.nature.com/scientificreports

Vaccines 2021, 9, 11.

Metabolism Open 12 (2021) 100124

www.thelancet.com Published online October 4, 2021

NATuRe RevleWS | MICrobiology volume 19 | July 2021 | 409

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Dr M. Boroumand M.D., ACP

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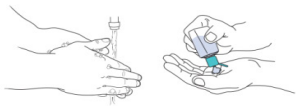
Tehran Heart Center

Tehran University of Medical Sciences

اهداف

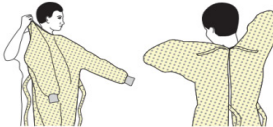
- آشنایی با کلیات نمونه گیری و روش انتقال نمونه
- آشنایی با انواع تست های آزمایشگاهی در مدیریت کووید
- آشنایی با پارامترهای عملکردی تست های تشخیصی آزمایشگاهی و اهمیت آن
- یادگیری چگونگی انتخاب روش تست تشخیصی بر اساس شرایط و سناریوهای مختلف
- یادگیری اندیکاسیون های استفاده از تست های آنتی بادی در کووید

1 Hand hygiene



Clean all surfaces of hands and wrists

2 Gown



Cover torso and wrap around back, fasten in back of neck and waist

3 Surgical/procedure mask



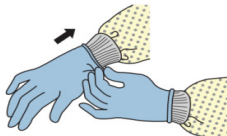
Secure ties at middle of head and neck, fit nose band to your nose and pull bottom down to completely cover chin

4 Eye protection



Place goggles or face shield over face and eyes and adjust to fit

5 Gloves



Extend to cover wrist of gown

More pieces and layers of PPE doesn't mean more protection

Wearing extra PPE may affect the fit and complicates the doffing process which may increase the risk of self-contamination.



Evidence-based guidance from international experts* **does NOT** recommend double gloving, using double or combinations of masks/respirators, head, neck or shoe covers for COVID-19 protection.

- 1 Gloves**

The outside of gloves are contaminated. Grasp palm area of one gloved hand and peel off first glove. Slide fingers of hand under other glove at wrist and peel off. Discard in regular waste bin.
- 2 Perform Hand Hygiene**

Clean all surfaces of hands and wrists.
- 3 Gown**

Unfasten ties, pull gown away from neck and shoulders, touching ONLY the inside of the gown. Turn gown inside out and roll into a bundle. Place in soiled laundry hamper (if reusable) or in regular waste bin (if disposable).
- 4 Perform Hand Hygiene**

Clean all surfaces of hands and wrists.

! If you are NOT 2 meters away from the patient, exit room now, perform hand hygiene, and finish the remaining steps.
- 5 Goggles or Face Shield**

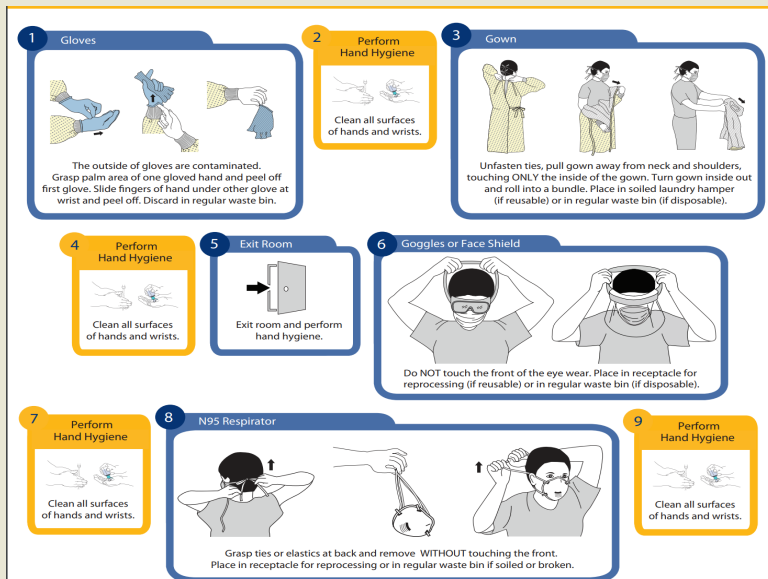
Do NOT touch the front of the eye wear. Place in receptacle for reprocessing (if reusable) or in regular waste bin (if disposable).
- 6 Perform Hand Hygiene**

Clean all surfaces of hands and wrists.
- 7 Surgical or Procedure Mask**

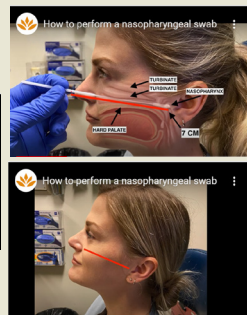
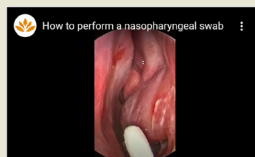
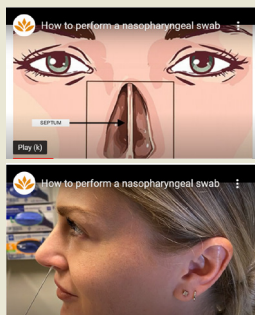
Grasp ties or elastics at back and remove WITHOUT touching the front. Place in receptacle for reprocessing or in regular waste bin.
- 8 Perform Hand Hygiene**

Clean all surfaces of hands and wrists.
- 9 Exit Room**

Exit room and perform hand hygiene.



Nasopharyngeal Swab Specimen Collection





Saline Gargle Specimen Collection

- Saline (salt water) gargle is an approved alternative to NP swab collection for outpatients who are able to follow instructions on how to swish, gargle and spit a small amount of saline
- Most people 5 years of age and older are able to provide a saline gargle sample with some guidance
- Ensure that the individual has not eaten, had anything to drink, smoked, used a vape, chewed gum or brushed their teeth for one hour before sample collection



Specimens for COVID-19 testing [4, 18, 19]

| Types of specimens | Collection devices | Transport conditions | Storage conditions | Comments |
|--|--------------------------------|----------------------|---|--|
| Upper respiratory tract specimens: NP swab ^a , OP swab ^a , and NP aspirate | Dacron or flocked swabs in VTM | 4°C | Within 5 days: 4°C Longer than 5 days: -70°C | |
| Lower respiratory tract specimen: sputum ^a | Sterile container | 4°C | Within 48 hr: 4°C Longer than 48 hr: -70°C | |
| Lower respiratory tract specimen: bronchial washing ^a | Sterile container | 4°C | Within 48 hr: 4°C Longer than 48 hr: -70°C | Pathogens might be diluted; however, the specimen can be subjected to diagnostic testing |
| Lower respiratory tract specimens: tracheal aspirate and transtracheal aspirate | Sterile container | 4°C | Within 48 hr: 4°C Longer than 48 hr: -70°C | |
| Lower respiratory tract specimen: lung biopsy | Sterile container with saline | 4°C | Within 48 hr: 4°C Longer than 48 hr: -70°C | |

| Types of specimens | Collection devices | Transport conditions | Storage conditions | Comments |
|--|--|----------------------|---|--|
| Upper respiratory tract specimens: NP swab ^a , OP swab ^a , and NP aspirate | Dacron or flocked swabs in VTM | 4°C | Within 5 days: 4°C Longer than 5 days: -70°C | |
| Lower respiratory tract specimen: sputum ^a | Sterile container | 4°C | Within 48 hr: 4°C Longer than 48 hr: -70°C | |
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| Lower respiratory tract specimen: lung biopsy | Sterile container with saline | 4°C | Within 48 hr: 4°C Longer than 48 hr: -70°C | |
| Serum ^b | Serum separation test tube (SST): adults and children, 3-5 mL; infants, 1 mL | 4°C | Within 5 days: 4°C Longer than 5 days: -70°C | For serological tests, a pair of specimens is collected Acute phase: within 7 days of symptom onset Convalescent period: 14 days after collection during acute phase Dispensing of serum into another container should be conducted in a Class II or higher BSC |

Types of COVID-19 Related Tests

☐ Diagnostic (viral) Tests

✓ *NAATs tests*

✓ *Antigen tests*

☐ Serology/Antibody and Other Adaptive Immune Response Tests

✓ *Detect antibodies (for example, IgM, IgG) to the SARS-CoV-2 virus*

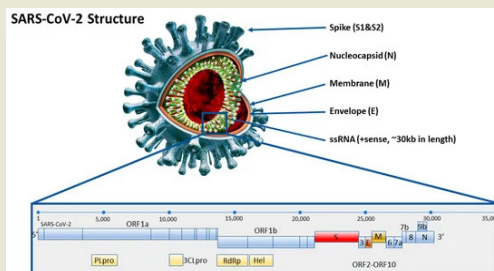
☐ Tests for Management of COVID-19 Patients

Nucleic Acid Amplification Tests (NAATs)

High-sensitivity, high-specificity tests for diagnosing SARS-CoV-2 infection

Detect one or more viral ribonucleic acid (RNA) genes

The main gene targets include the nucleocapsid (N), envelope (E), spike (S), RNA dependent RNA polymerase (RdRP) and open reading frame 1ab (ORF1ab) genes



Gene Targets in Different Products

- China (ORF1ab and N genes)
- Germany (RdRP, E and N genes)
- United States (three targets in N gene)
- France (two targets in RdRP)
- Thailand (N gene)
- Japan (pancorona and multiple targets, spike protein)
- Iran (N and RdRp)

Table 1

Target genes of various real-time RT-PCR protocols (including the reagents approved for emergency use in Korea as of March 13, 2020) [5–9]

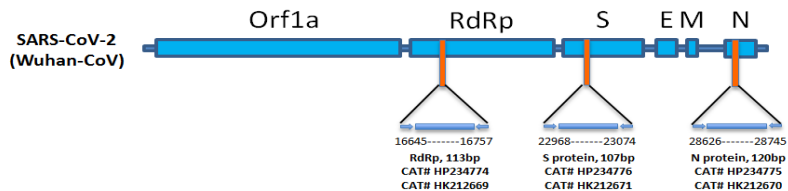
| Authors, manufacturers | Target gene | Reference |
|---|-------------------|---|
| Corman, <i>et al.</i> | <i>E, RdRp</i> | [6] |
| Chu, <i>et al.</i> | <i>orf1b, N</i> | [5] |
| Ministry of Public Health, Thailand | <i>N</i> | [7] |
| Institut Pasteur | <i>E, RdRp</i> | [8] |
| Centers for Disease Control and Prevention (USA) | <i>N</i> | [9] |
| PowerCheck 2019-nCoV* (Kogene biotech, Seoul, Korea) | <i>E, RdRp</i> | http://www.kogene.co.kr/ |
| Allplex 2019-nCoV* (Seegene, Seoul, Korea) | <i>E, RdRp, N</i> | http://www.seegene.com/ |
| nCoV Real-Time Detection* (SD biosensors, Suwon, Korea) | <i>E, RdRp</i> | http://sdbiosensor.com/ |
| DiaPlexQ 2019-nCoV*† (Solgent, Daejeon, Korea) | <i>orf1a, N</i> | http://www.solgent.com/ |
| Real-Q 2019-nCoV* (BioSewoom, Seoul, Korea) | <i>E, RdRp</i> | https://biosewoom.com |

* authorized for emergency use in Korea, as of Mar 13, 2020;

† The correct positions of the targets were not provided by the manufacturer.

Gene Targets in Different Products

- Assays for molecular diagnosis should employ a minimum of two gene targets
- While individual gene targets (namely, the S gene) in an assay may be falsely negative due to the presence of substitutions or deletions, the assay's overall sensitivity may remain unaffected



Throughput and Turnaround Times for NAATs

- Many NAATs require off-board nucleic acid extraction
- Some assays can return results in as few as 5-10 minutes, although more commonly the turnaround time is an hour or more
- Assays that require external nucleic acid extraction will be inherently slower



NAAT Laboratory Result

- All current SARS-CoV-2 RT-PCR assays with EUA approval are labeled only for the qualitative detection and are not approved for quantitative measurement
- While the Ct value can be reduced by increasing the amount of gene target in the sample, it can be influenced by many other factors as well, including the quality of the specimen collection technique, sample type (eg, NP sample vs saliva), gene target, and assay

NAATs as a Confirmatory Test

- Because laboratory-based NAATs are considered the most sensitive

tests for detecting SARS-CoV-2, they can also be used to confirm the results of lower sensitivity tests

- CDC recommends collecting and testing an upper respiratory specimen, such as nasopharyngeal, nasal mid-turbinate, or anterior nasal, when using NAATs for confirmatory testing

Vaccination & Viral Tests

Prior receipt of a COVID-19 vaccine should not affect the results of SARS-CoV-2 viral tests (nucleic acid amplification tests or antigen)



Viral Antigen Detection

- These are typically lateral-flow immunoassays intended for the qualitative detection of nucleocapsid protein antigen directly from NP and/or nasal swabs

- The presence of such antigen implies current SARS-CoV-2 infection

- Antigen tests generally have similar specificity, but are less sensitive than most NAATs

- It is best to perform this type of testing in the early stages of infection, when the viral load is generally highest



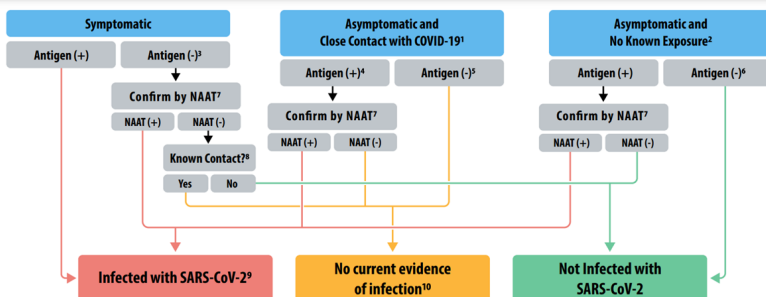
- Antigen levels in specimens collected beyond 5-7 days post symptom onset may drop below the assay's detection limit

- Although antigen detection tests are simple, easy to perform, and fairly inexpensive, one of the major concerns associated with their use is the lack of analytic and clinical sensitivity compared with RNA detection tests

- A meta-analysis of four commercially available antigen tests available outside of the United States showed that the average sensitivity was 56.2%

- In a study using HCP-collected nasal swabs in two EUA antigen tests compared with RT-PCR, one of the tests displayed a positive percent agreement (PPA) of 82.4% and a negative percent agreement (NPA) of 99.5%, in adult patients with onset of symptoms less than 7 days prior to collection

| | NAATs | Antigen Tests |
|---|--|--|
| Intended Use | Detect <i>current</i> infection | Detect <i>current</i> infection |
| Analyte Detected | Viral Ribonucleic Acid (RNA) | Viral Antigens |
| Specimen Type(s) | Nasal, Nasopharyngeal, Oropharyngeal, Sputum, Saliva | Nasal, Nasopharyngeal |
| Sensitivity | Varies by test, but generally high for laboratory-based tests and moderate-to-high for POC tests | Varies depending on the course of infection, but generally moderate-to-high at times of peak viral load* |
| Specificity | High | High |
| Test Complexity | Varies by test | Relatively easy to use |
| Authorized for Use at the Point-of-Care | Most are not, some are | Most are, some are not |
| Turnaround Time | Most 1-3 days. Some could be rapid in 15 minutes | Ranges from 15 minutes to 30 minutes |
| Cost/Test [^] | Moderate (~\$75-\$100/test) | Low (~\$5-\$50/test) |



¹ Single, multiple, or continuous known exposure to a person with COVID-19 within the last 14 days; perform NAAT first if short turnaround time is available, if person cannot be effectively and safely quarantined, or if there are barriers to possible confirmatory testing.

² No known exposure to a person with COVID-19 within the last 14 days.

³ If a symptomatic person has a low likelihood of SARS-CoV-2 infection, clinical discretion should determine if this negative antigen test result requires confirmatory testing.

⁴ In instances of higher pretest probability, such as high incidence of incidence of infection in the community, clinical discretion should determine if this positive antigen result requires confirmation.

⁵ In certain settings, serial antigen testing could be considered for those with a negative antigen test result; serial testing may not require confirmation of negative results. The role of a negative antigen test result in ending quarantine depends upon when it is performed in the quarantine period. See CDC's [Options to Reduce Quarantine](#) for guidance on use of antigen testing for this purpose and when a negative antigen test result indicates not infected with SARS-CoV-2.

⁶ If prevalence of infection is not low in the community, clinical discretion should consider whether this negative antigen result requires confirmation.

⁷ Nucleic acid amplification test; confirm within 48 hours using a NAAT, such as RT-PCR, that has been evaluated against FDA's reference panel for analytical sensitivity.

⁸ Known exposure to a person with COVID-19 within the last 14 days; if unsure, clinical discretion should determine whether isolation is necessary.

⁹ Isolation is necessary. See CDC's guidance for [Isolation](#).

¹⁰ Quarantine is necessary. See CDC's guidance for [Quarantine](#); clinical discretion should determine if and when additional testing is necessary.

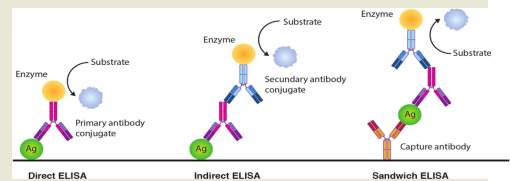
Antibody Detection

- Antibody detection tests have limited utility in the diagnosis of acute infection
- However, the use of antibody tests is viable as an aid to the diagnosis of COVID-19
- Seroconversion occurs by 2 weeks after the onset of symptoms
- Almost all patients have detectable levels of antibodies by day 28 post symptom onset
- Studies involving hospitalized patients showed the presence of all iso-types of anti-SARS-CoV-2-specific antibodies, including immunoglobulin M (IgM), IgA, and IgG

Types of antibody detection tests

Two antigens have been used as antigenic targets for the development of antibody detection assays:

- Spike (S)
- Nucleocapsid (N) proteins



Antibody Tests for SARS-CoV-2

- Can possibly be used diagnostically
- Contact tracing
- Serologic surveillance (Seroprevalence)
- Identification of those who have already had the virus (Protective Immunity)
- Identification of sources for therapeutic or prophylactic neutralizing antibodies

Emergency Use Authorizations for COVID-19 Serology Tests

Roche

Test: Elecsys Anti-SARS-CoV-2

Technology: High Throughput ECLIA

Target: Nucleocapsid

| Antibody | Performance Measure | Estimate of Performance | 95% Confidence Interval |
|----------|------------------------|-------------------------|-------------------------|
| Pan-Ig | Sensitivity (PPA) | 100% (29/29) | (88.3%; 100%) |
| Pan-Ig | Specificity (NPA) | 99.8% (5262/5272) | (99.7%; 99.9%) |
| Pan-Ig | PPV at prevalence = 5% | 96.5% | (93.9%; 98.1%) |
| Pan-Ig | NPV at prevalence = 5% | 100% | (99.4%; 100%) |

EUROIMMUN

Test: SARS-COV-2 ELISA (IgG)

Technology: ELISA

Target: Spike

| Antibody | Performance Measure | Estimate of Performance | 95% Confidence Interval |
|----------|------------------------|-------------------------|-------------------------|
| IgG | Sensitivity | 90.0% (27/30) | (74.4%; 96.5%) |
| IgG | Specificity | 100% (80/80) | (95.4%; 100%) |
| IgG | PPV at prevalence = 5% | 100% | (46.0%; 100%) |
| IgG | NPV at prevalence = 5% | 99.5% | (98.6%; 99.8%) |

Calculator for Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for individual tests and combined

| | | | | | | |
|---------------|-------|-----------------------------------|--------------------------------------|--|--------------------------------------|--|
| | | Prevalence | 5.0% | | | |
| Test 1 | | Test 1 | | | | |
| Sen1 | Sp1 | %Pos1 (Test1=pos) | PPV1 for (Test1=pos) | %Neg1 (Test1=neg) | NPV1 for (Test1=neg) | |
| 97.0% | 93.2% | 11.3% | 42.9% | 88.7% | 99.8% | |
| Test 2 | | Test 2 | | | | |
| Sen2 | Sp2 | %Pos2 (Test2=pos) | PPV2 for (Test2=pos) | %Neg2 (Test2=neg) | NPV2 for (Test2=neg) | |
| 88.0% | 96.0% | 8.2% | 53.7% | 91.8% | 99.3% | |
| | | Combined | | | | |
| | | %Pos (Test1=pos, Test2=pos) | PPV for (Test1=pos, Test2=pos) | %Discordant (Test1=pos, Test2=neg) | NPV for (Test1=pos, Test2=neg) | |
| | | 4.5% | 94.3% | 6.8% | 91.4% | |
| | | | | %Neg (Test1=neg) | NPV for (Test1=neg) | |
| | | | | 88.7% | 99.8% | |

Vaccination & Antibody Testing

- Antibody testing is not currently recommended to assess the need for vaccination in an unvaccinated person or to assess for immunity to SARS-CoV-2 following COVID-19 vaccination



Tests for Management of COVID-19 Patients

Table 1: Main characteristics of the included studies.

| Characteristics | Zhang et al. [7] | Huang et al. [8] | Chen et al. [9] | Xu et al. [10] | Liu et al. [11] | Wang et al. [12] | Chen et al. [13] | Chen et al. [14] |
|-------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-------------------------|-----------------------|-----------------------|
| Location | Wuhan, China | Wuhan, China | Wuhan, China | Zhejiang, China | Shenzhen, China | Shenzhen, China | Wuhan, China | Wuhan, China |
| No. cases | 140 (58 severe) | 41 (13 severe) | 99 (17 severe) | 62 (1 severe) | 12 (6 severe) | 34 children (no severe) | 29 cases (14 severe) | 9 pregnant |
| Age | 57 years (median) | 49 years (median) | 56 years (mean) | 41 years (median) | 54 years (mean) | 8 years (median) | 56 years (median) | 30 years (mean) |
| Women, % | 49% | 27% | 32% | 44% | 33% | 59% | 28% | 100% |
| Setting | Hospitalized patients | Hospitalized patients | Hospitalized patients | Hospitalized patients | Hospitalized patients | Hospitalized patients | Hospitalized patients | Hospitalized patients |
| Laboratory data | | | | | | | | |
| Leukocytes | ↑12%; ↓20% | ↑30%; ↓25% | ↑24%; ↓9% | ↑2%; ↓31% | ↑8% | ↑15% | ↑21%; ↓21% | ↑22% |
| Neutrophils | N/R | N/R | ↑38% | N/R | ↑17% | ↑15% | N/R | N/R |
| Lymphocytes | ↓75% | ↓63% | ↓35% | ↓58%; ↓42% | ↓55% | ↓3% | ↓69% | ↓56% |
| Eosinophils | ↓53% | N/R | N/R | N/R | N/R | N/R | N/R | N/R |
| Platelets | N/R | ↓5% | N/R | ↓5% | ↓48% | N/R | ↓17% | N/R |
| Hemoglobin | N/R | N/R | ↓50% | N/R | N/R | N/R | ↓41% | N/R |
| CRP | ↑91% | N/R | ↑86% | N/R | ↑83% | ↑3% | ↑93% | ↑75% |
| Procalcitonin | ↑35% | ↑8% | ↑6% | ↑11% | ↑8% | ↑3% | ↑6% | N/R |
| ESR | N/R | N/R | ↑85% | N/R | ↑15% | N/R | N/R | N/R |
| Albumin | N/R | N/R | ↓98% | N/R | ↓50% | N/R | ↓52% | N/R |
| ALT | N/R | N/R | ↑28% | N/R | ↑17% | N/R | ↑17% | ↑33% |
| AST | N/R | ↑37% | ↑35% | ↑16% | ↑8% | N/R | ↑24% | ↑33% |
| Bilirubin | N/R | N/R | ↑18% | N/R | ↑0% | N/R | ↑3% | N/R |
| Creatinine | N/R | ↑10% | ↑3% | ↑5% | ↑17% | N/R | ↑7% | N/R |
| CK | ↑7% | ↑33% | ↑13% | N/R | ↑17% | N/R | N/R | N/R |
| LDH | N/R | ↑73% | ↑76% | ↑27% | ↑92% | ↑29% | ↑69% | N/R |
| Myoglobin | N/R | N/R | ↑15% | N/R | ↑17% | N/R | N/R | N/R |
| Cardiac troponins | N/R | ↑12% | N/R | N/R | ↑8% | N/R | N/R | N/R |
| Ferritin | N/R | N/R | ↑63% | N/R | N/R | N/R | N/R | N/R |
| Glucose | N/R | N/R | ↓52% | N/R | N/R | N/R | N/R | N/R |
| D-dimer | ↑43% | N/R | ↑36% | N/R | ↑9% | N/R | N/R | N/R |

Laboratory data are reported as percent of patients with abnormalities defined according to the local reference ranges. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; N/R, not (clearly) reported.



Hassan Hashemi,MD

Professor of Radiology

Tehran university of medical sciences



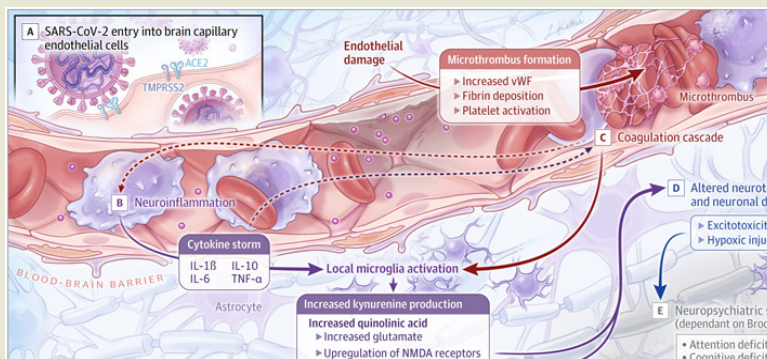
- Rhinoorbitocerebral Mucormycosis in Covid19

Covid19 complications

Respiratory and **gastrointestinal symptoms** are accompanied by short- and long-term neuropsychiatric symptoms (NPs) and **long-term brain sequelae**.

Covid-19 in vascular structures

- Microthrombosis
- Endothelial activation
- Microangiopathy,
- Vasculitis
- Extensive angiogenesis



Covid-19 and stroke

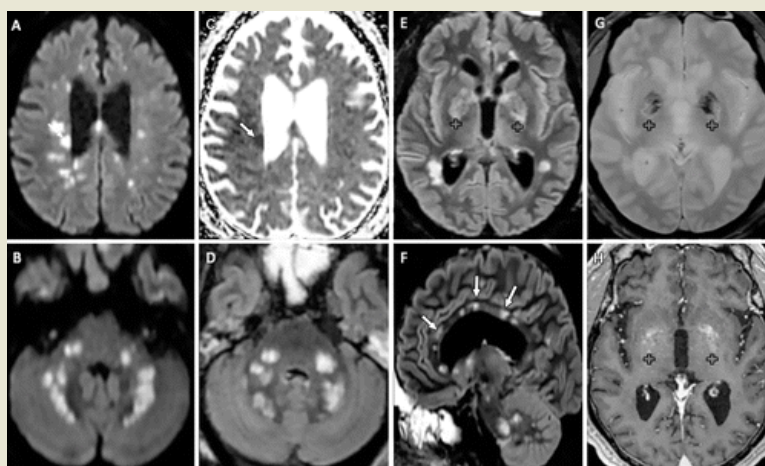
Stroke was demonstrated to be an infrequent, albeit potentially life-threatening, complication of COVID-19, affecting approximately **1–3 % of hospitalized patients**, and up to **6 % of those in the ICU**

Covid19 complications

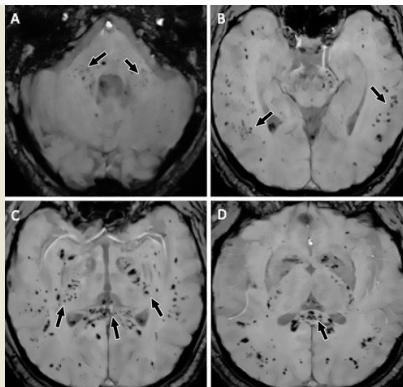
Some patients present with **anosmia**, **cognitive** and **attention deficits** , **new-onset anxiety**, **depression**, **psychosis**, **seizures**, and even **suicidal behavior**.

Covid-19 and stroke

- Ischemic stroke
- Microhemorrhage
- Hypersignal areas in temporal lobes with different enhancement



Axial susceptibility-weighted images in a 57-year-old man with abnormal wakefulness after sedation show extensive and isolated white matter microhemorrhages mainly affecting the cerebellar peduncles, subcortical white matter, internal capsule, and, corpus callosum.



Gene Targets in Different Products

- Assays for molecular diagnosis should employ a minimum of two gene targets
- While individual gene targets (namely, the S gene) in an assay may be falsely negative due to the presence of substitutions or deletions, the assay's overall sensitivity may remain unaffected

Mucor mycosis

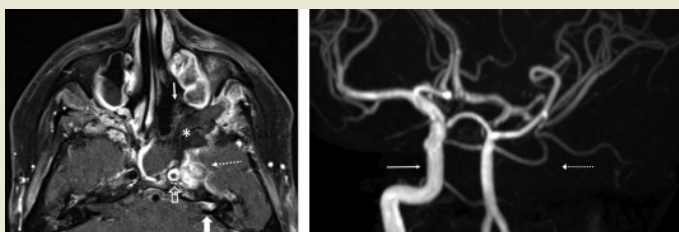
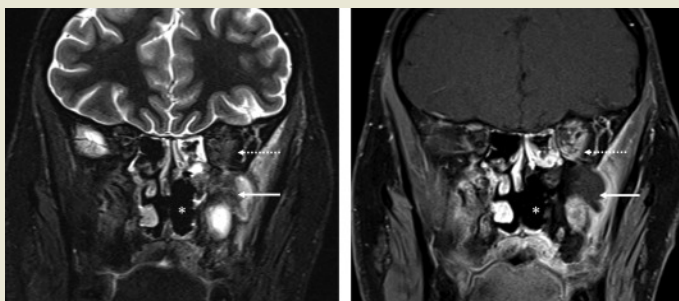
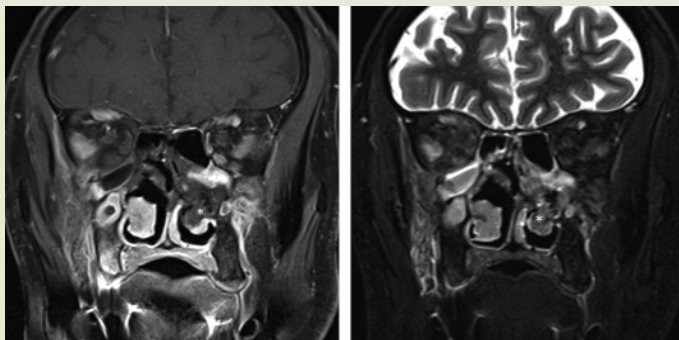
- Radiologists must have a high index of suspicion for early diagnosis. IFRS is a fulminant condition that can lead to devastating blindness, stroke, and death as early as 48 h after presentation. Early diagnosis prompts immediate institution of antifungal therapy that limits morbidity and mortality.
- Assessment of disease extent by imaging is crucial for planning extent of surgical debridement.
- Complete debridement of necrotic tissue improves survival.

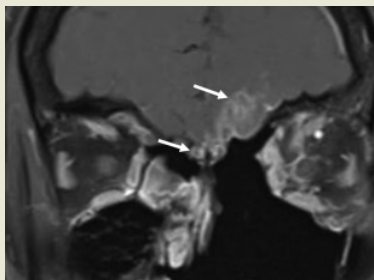
Mucor mycosis

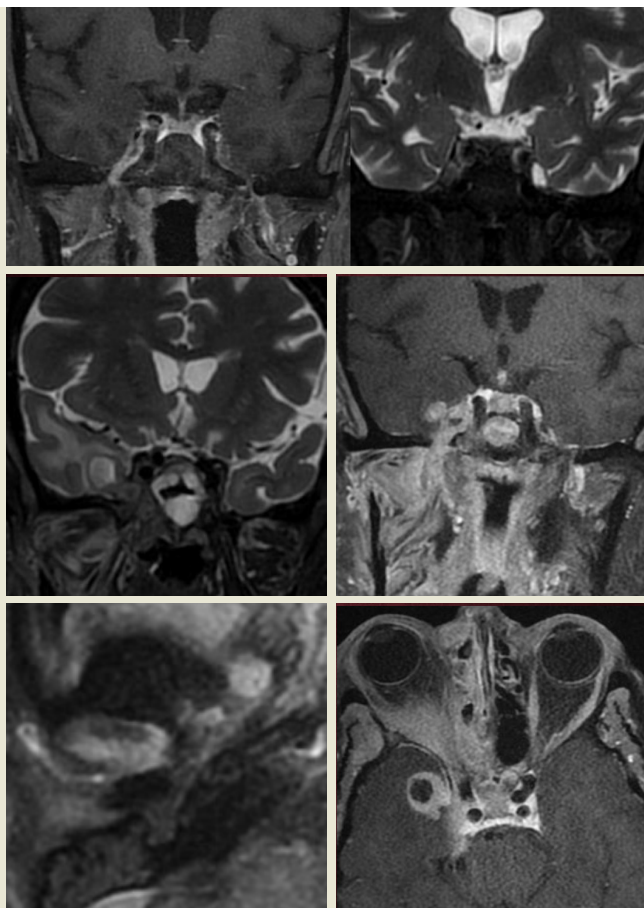
Black turbinate sign. Coronal contrast-enhanced, fat-saturated T1 and T2-STIR image show a left inferior turbinate, with lack of enhancement and relatively low T2 signal.

A 72-year-old, diabetic man with left facial pain and nasal stuffiness. Treat-

ed for COVID-19 with injectable corticosteroids and invasive ventilation. Duration between RT-PCR positivity and first maxillofacial imaging was 16 days. Patient died 12 days after first imaging from mucormycosis-related complications.









KIANI A MD

NRITLD

Post covid hemoptysis

Haemoptysis is the expectoration of blood or blood-tinged sputum from the respiratory tract.

It is considered life-threatening when it causes clinical consequences such as respiratory failure from airway obstruction, as in this case, or hypotension

- bronchiectasis
- Coagulation disorders,
- pulmonary embolism
- post-tuberculosis sequelae
- Idiopathic bleedings
- Malignancies
- vasculitis,
- arteriovenous malformations

Haemoptysis is rarely reported as a symptom of COVID- 19.

In a large case series including 1099 hospitalised patients with laboratory confirmed COVID-19 in China, haemoptysis occurred in ten patients (0.9%)

Fu and colleagues on the other hand performed a systematic review and meta-analysis of the clinical characteristics of COVID-19 involving 43 studies and showed a prevalence of 2%

Other infectious diseases have been linked with alveolar haemorrhage in immunocompetent patients including

- Influenza A (H1N1)
- Dengue, malaria
- Staphylococcus aureus infection
- Leptospirosis

+ Risk factors for predicting mortality of COVID 19 patients: A systematic review and meta analysis

Among the common symptoms of COVID-19 infections, fatigue, expectoration, **hemoptysis**, dyspnea and chest tightness were independent predictors of death

Case Report

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TANAFFOS 

Hemoptysis and Hematuria as the Initial Symptoms of COVID-19: a Case Report

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Since SARS-CoV-2 virus emerging in winter 2019 in Wuhan, Hubei, China, COVID-19 has spread among different countries. The novel corona virus has affected more than 15,000,000 people all around the world. Becoming pandemic, COVID-19 is a major concern for both people and health systems. Novel corona virus affects multiple organs such as lungs and kidneys which can lead to acute respiratory distress syndrome and acute kidney injury (AKI) ending to death. Furthermore, patients with COVID-19 may present different atypical symptoms making the diagnoses more complicated. The current patient presented to the emergency department with a 7-day history of hemoptysis and hematuria which are among the less common symptoms among patients infected with SARS-CoV-2 virus. In addition to delayed diagnosis, atypical symptoms and signs make management and treatment more difficult. Awareness of new, atypical symptoms and the effective treatment is associated with better outcome and prognosis.

Key words: COVID-19; Hemoptysis; Hematuria; Corona virus; SARS-

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doi:10.5812/ijl.10694.

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Case Report



Post-COVID-19 Massive Hemoptysis and Gastrointestinal Bleeding: A Case Report

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Abstract

Introduction: COVID-19 is a new respiratory infection caused by the coronavirus, which the World Health Organization (WHO) declared as a global epidemic in 2019. All the information obtained about this virus was different in children than in adults.

Case Presentation: The case investigated in this study was a 10-year-old boy with hemoptysis and gastrointestinal (GI) bleeding in his post-COVID-19 recovery phase.

Conclusions: COVID-19 can have a variety of presentations and complications beyond the classic respiratory symptoms and fever. This case is important and shows how COVID-19 can be life-threatening.

Keywords: COVID-19, Hemoptysis, Gastrointestinal Bleeding, Case Report

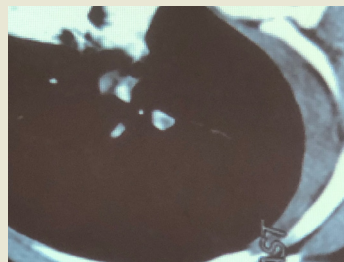
The case of a child with post-COVID-19 hemoptysis and GI bleeding shows the life-threatening effects of the COVID-19 virus

DDX of hemoptysis in covid

- Pulmonary thromboembolism
- Pulmonary mycosis
- Malignancy
- Exacerbation of pre-existing chronic bronchitis
- Pulmonary tuberculosis
- pneumonia



COVID-19 was described as causing a proinflammatory and hypercoagulable state with increased levels of lactate dehydrogenase (LDH), ferritin, CRP, D-dimer, and interleukin. Venous thromboembolism (VTE) may also accompany COVID-19 infection because of hypercoagulability. Hemoptysis may be an initial symptom of VTE.

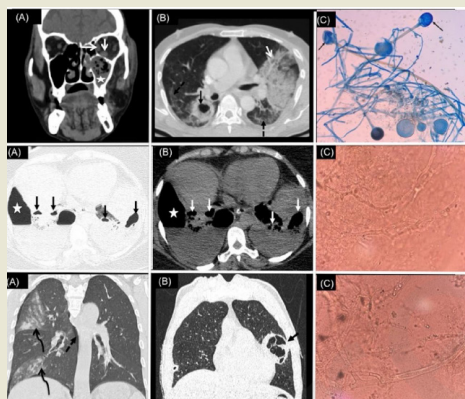


Smoking may be related to admitting with hemoptysis symptoms in COVID-19. It is known that cigarette smoke damages the alveolar epithelial cells because of oxidative stress, increases epithelial cell death, and decreases lung repair process.

- A cavity is defined as an air-filled area of the lung in the center of consolidation, mass or nodule. Cavities are present in a wide variety of infectious and non-infectious processes as a result of liquefaction of the necrotic portion of the lesion and the discharge of this necrotic material via the bronchial tree. It is uncommon for COVID-19 and other viral pneumonia infections to cause pulmonary cavitation.



A noteworthy finding is an unprecedented rise in the number of cases of the morbid fungal disease mucormycosis, which is now increasingly being associated with COVID-19.



Mucormycosis has a global incidence varying from 0.005 to 1.7 per million population. In India, however, the prevalence is estimated to be 140 per million, which is 80 times higher than the developed countries.

Individuals who have decreased immunity are specifically at high risk of being affected by this life-threatening opportunistic infection.

The susceptible groups are post-COVID recovered, immunosuppressed, those on long-term corticosteroids, chemotherapy, and iron chelation therapy.

Individuals with uncontrolled hyperglycemia irrespective of the diagnosis of diabetes mellitus, unchecked iron overload states, transplant, malignancy, burns, neutropenia, monocytopenia, tuberculosis, HIV, and chronic kidney disease are highly vulnerable

ROCM is followed by cutaneous, pulmonary, gastrointestinal, and disseminated disease . Pulmonary mucormycosis accounts for 10% of the cases . COVID-19 can worsen or even precipitate diabetes mellitus by causing glycaemic abnormalities that can persist even up to two months after recovery.

Severe COVID-19 and diabetic ketoacidosis are implicated in causing elevated ferritin and serum iron levels causing free radical damage . Acidosis has also been involved in impairing phagocyte function.

Inflammatory leukocytes in vessel walls with reactive damage to mural structures define the vasculitides. Bleeding and downstream tissue ischemia leading to necrosis present in the disease are caused by loss of vessel integrity and lumen compromise respectively

Cystic structures that meet the definition of pneumatoceles have been described during COVID-19 pneumonia, although their natural history is unknown.

The screenshot shows the EMJ website with a navigation bar including 'THERAPEUTIC AREA', 'ABOUT US', 'CONTRIBUTORS', and 'NEWSLETTERS & ALERTS'. The main content area features a case report titled 'Massive Alveolar Haemorrhage Presenting During...' with a sub-header 'Respiratory Medicine Department, Musgrave Park Hospital, Taunton and Somerset Foundation Trust, Taunton, UK'. The report includes a disclosure statement, acknowledgements, received and accepted dates, and a citation. A sidebar on the right shows the date '19 OCTOBER 2021' and the interviewer 'Sarah Walmsley'. The abstract section begins with 'The coronavirus disease (COVID-19) pandemic has challenged healthcare systems and has resulted in complex diagnostic processes for patients with non-COVID-19 pathology. Here, we demonstrate a case of massive alveolar haemorrhage secondary to antineutrophil cytoplasmic antibody-positive vasculitis, presented to a district general hospital in the UK during the first wave of the global pandemic. This case highlights some of the difficulties clinicians may face when diagnosing life-threatening antineutrophil cytoplasmic antibody-positive vasculitis amidst the COVID-19 pandemic. The authors place emphasis on the careful interpretation of chemical biomarkers such as troponin and D-dimer when assessing patients with acute respiratory distress. They also aim to highlight the importance of CT thorax imaging when seeking an alternate diagnosis to COVID-19.'

Post covid ANCA associated vasculitis

Post-Covid-19 Complications: Hemoptysis in a Middle-Aged Man

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Introduction: Sars-Cov-2 infection has been found to present differently in many patients. Patients have been found to have different degrees of response, likely having to do with variable levels of inflammation within the body. Patients who have recovered from the initial infection can develop long-term symptomatology and chronic conditions. Today, we will describe a unique case of a middle aged-healthy man who developed complications of ANCA-associated vasculitis after recovering from a mild COVID-19 infection. Case: A 51-year-old Hispanic male with no previous past medical history presented to the ED with productive sputum and hemoptysis. The patient had previously tested positive for COVID-19 one month prior, but did not require hospitalization. Physical exam findings were significant for diffuse, bilateral lower extremity palpable purpura. Initial workup was significant for CT Chest findings of diffuse patchy consolidations throughout both lungs with cavitory lesions. Additionally, the patient was found to have an acute kidney injury, with Cr 5.80 and GFR less than 10. UA revealed many red blood cells, +1 protein. Nephrology was consulted, started the patient on hemodialysis, and began workup for suspected acute glomerulonephritis (GN). Pulmonology was consulted and began workup for pulmonary renal syndrome in the setting of acute kidney injury with pulmonary disease. Infectious workup results included; a now negative COVID-19, negative Tuberculosis PCR, Respiratory culture revealing yeast. Additional workup revealed; CRP of greater than 200, D-Dimer of 6.41, Fibrinogen of 561. Notably, the patient had decreased complement C3 and C4 levels, negative Anti-GBM antibody, negative Anti-streptolysin O, positive ANCA assay, positive Proteinase antibody, and mildly positive Myeloperoxidase antibody. The patient was subsequently scheduled for renal biopsy to obtain a definitive diagnosis, but this was delayed due to increased INR. The patient's respiratory status worsened during hemodialysis. CTA at that time revealed markedly increased pulmonary infiltrates. The decision was made to intubate the patient, upon which active frank red bleeding arising from the trachea was noted. Shortly after intubation, the patient continued to hemorrhage and sustained 2 cardiac arrests; unfortunately, the patient expired. Discussion: This case is significant because it highlights a unique complication of COVID-19 leading to a possible ANCA-associated vasculitis. Much is to be learned from the Novel Sars-COV-2 virus and suspected complications and this case highlights the importance of keeping a broad differential when treating patients who have recovered from initial infection.

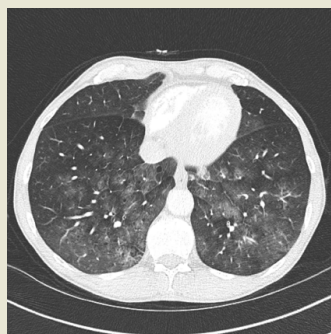
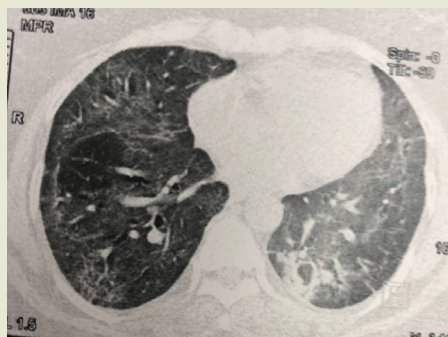
microangiopathy

In a study by Magroet al. on 5 patients with COVID-19 and respiratory ailure, lung and skin tissues were examined, and no viral cytopathic change or diffuse alveolar damage was observed n COVID-19 pneumonitis, but a capillary lesion by neutrophils. These pulmonary findings were found in small vessels with significant deposits of the complement components of C5b-9 (membrane attack complex), C4d, and lectin-dependent serine proteinase (MBL).

Similarly, a thrombogenic vasculopathy with inflammation of the pauci, with C5b-9 and C4d depositions, severely involved skin and showed a normal appearance

- A key distinguishing feature between ANCA-positive vasculitis and COVID-19 infection is the presence of haemoptysis. The literature suggests that haemoptysis is uncommon in COVID-19 and has a symptom prevalence of 2%.

- Therefore, the presence of haemoptysis is likely to indicate an alternate respiratory pathology rather than COVID-19 infection.



دکتر مصطفی قانعی

استاد دانشگاه علوم پزشکی بقیه الله (عج)
متخصص داخلی- فوق تخصص بیماری های ریه
عضو کمیته علمی ستاد ملی مقابله با کرونا
عضو کمیته ملی واکسن کرونا

درمان ضایعات ریوی بیماری کوید 19

کارکرد هر قسمت از اجزای ویروس

عملکرد بخش های مختلف ویروس

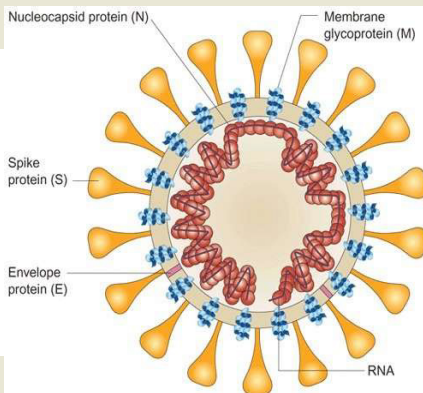
four structural proteins:

S – spikes on the outside; mediates receptor binding

M – membrane protein; assists viral assembly

N – nucleocapsid protein; regulation of viral RNA synthesis, may interact with **M** protein during virus budding

E – small envelope protein; function necessary but not fully understood



علائم ریوی کوید 19

- مرحله شدید

- مرحله متوسط

- مرحله خفیف

تشخیص افتراقی

Don't forget other LRIs:

Viral Pneumonia: Influenza (A/B), Adenovirus, Parainfluenza (Type 1-4), Respiratory syncytial virus, Human metapneumovirus, NL63

Typical bacteria CAP: Lobar – Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis; Gram neg, anaerobic if aspiration

Bacterial bronchitis or atypical CAP: Bordetella pertussis, Mycoplasma pneumoniae, and Chlamydia pneumoniae

تازه های کووید

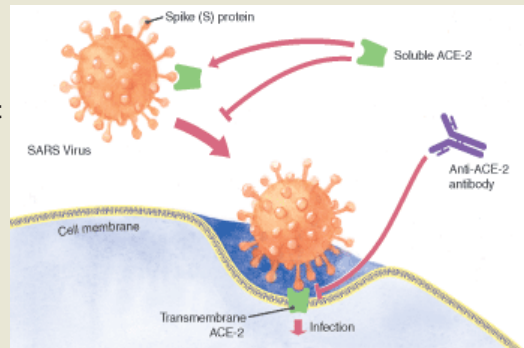
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گیرنده های کرونا ویروس تعیین کننده بیماری

ACE-2 Receptors

- Type 2 alveolar cells - highest
- Bronchial epithelia
- Tongue > buccal epithelia
- Upper Intestinal epithelia
- Myocardial cells
- Kidney proximal tubule cells
- Bladder urothelial cells



سرانجام بیماری

- **Week 1: Fever (77-98%) (intermittent or persistent), Fatigue/Malaise (11-52%), Dry cough (46-82%), dyspnea (3-31%);**

Less common: Sputum (33%), Myalgia (15%), Headache (13%), Sore throat (14%), Diarrhea (4%), Nausea/Vomiting (5%), Nasal congestion (4%), Hemoptysis (1%)

- **Week 2 (~ day 6-9 of symptoms): ~ 15-20% develop severe dyspnea due to viral pneumonia**

Hospitalization, supportive care, oxygen

- **Week 2-3: Of hospitalized patients, 1/3 ultimately need ICU care, with up to half needing intubation (i.e. ~5% of total diagnosed cases need ICU)**

Can rapidly decline (over 12-24 hrs) from mild hypoxia to frank ARDS

Cytokine Storm, Multi-organ failure

Late stage sudden cardiomyopathy/viral myocarditis, cardiac shock

عوامل خطرساز

- Age
- Diabetes
- Hep B
- COPD
- Children and pregnant women seem to do okay
- HTN
- Coronary Heart Disease
- Cerebrovascular Disease
- Cancer

عوامل خطر ساز در پیشرفت بیماری

International Immunopharmacology 98 (2021) 107894



Contents lists available at ScienceDirect

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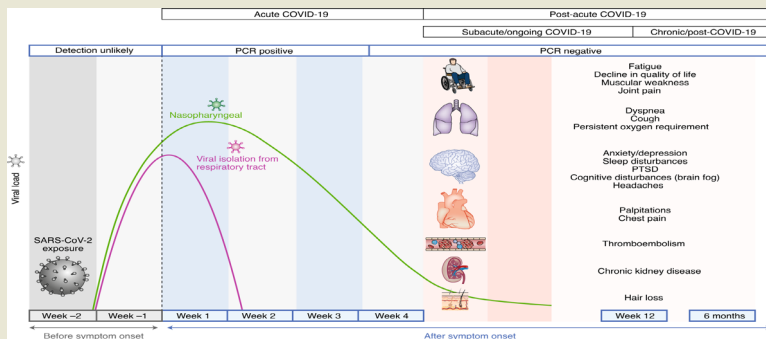
journal homepage: www.elsevier.com/locate/intimp



The risk factors and related hospitalizations for cases with positive and negative COVID-19 tests: A case-control study

Mostafa Ghanei^{a,*}, Hossein Keyvani^b, Aliakbar Haghdoust^c, Hassan Abolghasemi^{a,d}, Ghasem Janbabaie^e, Hamdi Reza Jamshidi^f, Amir Hosein Ghazale^g, Seyed Hassan Saadat^h, Mohammad Gholami Fesharakiⁱ, Mehdi Raei^j

سیر بیماری کوید 19



بیماری ویروسی با سرانجام التهابی

| | Asymptomatic or Presymptomatic | Mild illness | Moderate illness | Severe illness | Critical illness |
|-------------------------------|--|---|---|--|---|
| Features | Positive SARS-CoV-2 test; no symptoms | Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea | Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation $\geq 94\%$ | Oxygen saturation $< 94\%$; respiratory rate ≥ 30 breaths/min; lung infiltrates $> 50\%$ | Respiratory failure, shock, and multiorgan dysfunction or failure |
| Testing | Screening testing; if patient has known exposure, diagnostic testing | Diagnostic testing | Diagnostic testing | Diagnostic testing | Diagnostic testing |
| Isolation | Yes | Yes | Yes | Yes | Yes |
| Proposed Disease Pathogenesis | Viral replication | | | | |
| Potential Treatment | Antiviral therapy | | | | |
| | Antibody therapy | | Antiinflammatory therapy | | |
| Management Considerations | Monitoring for symptoms | Clinical monitoring and supportive care | Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir | Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone) | Critical care and specific therapy (dexamethasone, possibly remdesivir) |

تازه های کووید

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یافته های آزمایشگاهی

- Most Common:

WBC usually normal, Lymphopenia in 80%, Mild thrombocytopenia

Low Procal; Bacterial coinfection rare

CRP and D-Dimer elevated proportionate to severity (marker of poor prognosis); DIC over time

Increased ALT/AST to 70-100 range; Occasional increased alk phos

Mild elevation of creatinine

Generally normal troponin

- CXR (sensitivity 59%):

Bilateral patchy or reticular infiltrates, perihilar infiltrates occasionally

- CT scan (sensitivity 86%; much better than RT-PCR!)

Bilateral diffuse ground glass opacities, multifocal patchy consolidation, interstitial changes
















Changes prior to severe symptom onset!

- ECHO:

Normal EF prior to late-onset sudden cardiogenic shock with dropping to EF <10%

- Co-infection rare but possible (5%)

تشخیص افتراقی

| MEDICAL NEWS TODAY COVID-19 vs. Flu vs. Cold | | | |
|--|------------|---------------|------------------|
| | COVID-19 | Flu | Cold |
|  Incubation period | 2-14 days | 1-4 days | 1-3 days |
|  Symptom onset | Gradual | Gradual | Gradual |
|  Cough | Common | Common | Mild to moderate |
|  Shortness of breath | Common | Sometimes | Mild |
|  Fever | Common | Common | Rare |
|  Fatigue | Common | Common | Sometimes |
|  Runny nose | Sometimes | Sometimes | Common |
|  Nasal congestion | Sometimes | Sometimes | Common |
|  Diarrhea | Sometimes | Sometimes | Rare |
|  Body aches | Sometimes | Common | Slight |
|  Sore throat | Sometimes | Sometimes | Common |
|  Headache | Sometimes | Common | Rare |
|  Loss of appetite | Sometimes | Common | Sometimes |
|  Respiratory issues | Common | Sometimes | Sometimes |
|  Chills | Sometimes* | Fairly common | Uncommon |
| New loss of taste or smell | Common | Sometimes | Sometimes |

*including repeated shaking with chills

تشخیص آسیب زایی بر اساس تصاویر ریوی بیماری کوید

Hindawi
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Volume 2020, Article ID 8825761, 12 pages
<https://doi.org/10.1155/2020/8825761>



Review Article

From Radiological Manifestations to Pulmonary Pathogenesis of COVID-19: A Bench to Bedside Review

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Fatemeh Eghbal⁴, and Mostafa Ghanei¹

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In this review, we aim to assess previous radiologic studies in COVID-19 and suggest a pulmonary pathogenesis based on radiologic findings. Although radiologic features are not specific and there is heterogeneity in symptoms and radiologic and clinical manifestation, we suggest that the dominant pattern of computed tomography is consistent with limited pneumonia, followed by interstitial pneumonitis and organizing pneumonia.

یافته های تصویربرداری

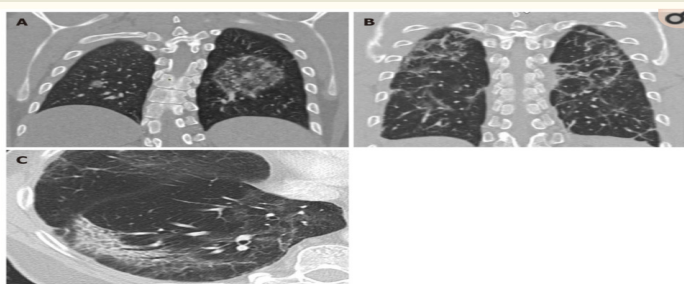


Figure 4

Computed tomography findings late stage disease. A: Reverse halo or atoll sign: Rounded opacity in the left lung with ground-glass attenuation in the center demarcated by a denser, fine ring. B: Bilateral peribronchovascular thickening and rounded opacity in the right lung; C: Peripheral, elongated, curved consolidation in the right lower lobe containing dilated bronchi.

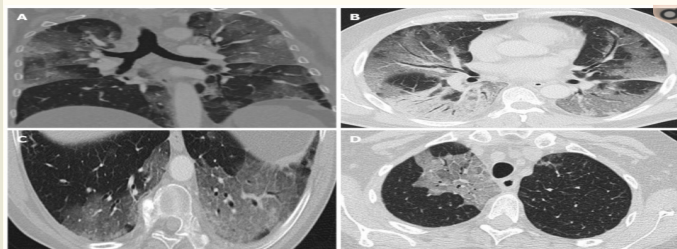


Figure 3

Computed tomography findings. A: Extensive bilateral ground-glass opacities, one with poorly-defined margins and another with clearly defined borders; B: Multilobar ground-glass opacities and consolidation with air bronchogram in the right lower lobe; C: Band of subpleural parenchyma respected in the left lung; D: Crazy-paving pattern in the right upper lobe.

درمان مرحله خفیف

- اصل اول: درمان قطعی ندارد
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- اصل سوم: درمان علامتی بهتر است باعث اختلال عملکرد ویروس شود
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- اصل پنجم: درمان بر اساس اثربخشی به هزینه و عوارض و مبتنی بر شواهد صورت گیرد
- اصل ششم: ملاک بهبودی برگشت به وضعیت قبل از بیماری است

درمان مرحله خفیف تا متوسط

- درمان علامتی بیماری کوید 19:
- دیفن هیدرامین
- مونته لوکاست
- فماتیدین
- برم هگزین
- ملاتونین
- ناپروکسن

یافته های تصویربرداری



Identification of antiviral antihistamines for COVID-19 repurposing

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آنتی هیستامین ضد ویروس

ABSTRACT

There is an urgent need to identify therapies that prevent SARS-CoV-2 infection and improve the outcome of COVID-19 patients. Although repurposed drugs with favorable safety profiles could have significant benefit, widely available prevention or treatment options for COVID-19 have yet to be identified. Efforts to identify approved drugs with *in vitro* activity against SARS-CoV-2 resulted in identification of antiviral sigma-1 receptor ligands, including antihistamines in the histamine-1 receptor binding class. We identified antihistamine candidates for repurposing by mining electronic health records of usage in population of more than 219,000 subjects tested for SARS-CoV-2. Usage of diphenhydramine, hydroxyzine and azelastine was associated with reduced incidence of SARS-CoV-2 positivity in subjects greater than age 61. We found **diphenhydramine, hydroxyzine and azelastine** to exhibit direct antiviral activity against SARS-CoV-2 *in vitro*. Although mechanisms by which specific antihistamines exert antiviral effects is not clear, hydroxyzine, and possibly azelastine, bind Angiotensin Converting Enzyme-2 (ACE2) and the sigma-1 receptor as off-targets. Clinical studies are needed to measure the effectiveness of diphenhydramine, hydroxyzine and azelastine for disease prevention, for early intervention, or as adjuvant therapy for severe COVID-19.

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درمان خلط بیمار

Study Protocol Systematic Review

Medicine®

OPEN

Evaluating the efficacy and safety of bromhexine hydrochloride tablets in treating pediatric COVID-19

A protocol for meta-analysis and systematic review

Yuying Wang, MB^a, Yinghua Zhang, MB^b, Xia Chen, MB^c, Kun Xue, MM^c, Tianjing Zhang, MD^d, Xiaohong Ren, MB^{c,e}

مهار کننده TMPRSS2

Internal and Emergency Medicine
<https://doi.org/10.1007/s11739-020-02383-3>

IM - REVIEW



Potential new treatment strategies for COVID-19: is there a role for bromhexine as add-on therapy?

Markus Depfenhart^{1,2} · Danielle de Villiers³ · Gottfried Lemperele⁴ · Markus Meyer⁵ · Salvatore Di Somma^{6,7}

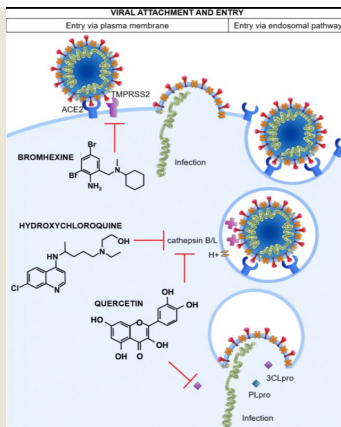
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تازه های کووید

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مکانیسم عمل برم هگزین



داروی ارزان و با احتمال تاثیر بالا و در دسترس

Study Protocol Systematic Review

Medicine

Evaluating the efficacy and safety of bromhexine hydrochloride tablets in treating pediatric COVID-19

A protocol for meta-analysis and systematic review

Yuying Wang, MB^a, Yinghua Zhang, MB^b, Xia Chen, MB^b, Kun Xue, MM^c, Tianjing Zhang, MD^d, Xiaohong Ren, MB^{e,f,g}

Abstract

Background: Bromhexine hydrochloride tablets may be effective in the treatment of Coronavirus disease 2019 (COVID-19) in children. This study will further evaluate the efficacy and safety of bromhexine hydrochloride tablets in the treatment of COVID-19 in children.

Methods: The following electronic databases will be searched, with all relevant randomized controlled trials (RCTs) up to August 2020 to be included: PubMed, Embase, Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), the Chongqing VIP China Science and Technology Database (VIP), Wanfang, the Technology Periodical Database, and the Chinese Biomedical Literature Database (CBM). As well as the above, Baidu, the International Clinical Trials Registry Platform (ICTRP), Google Scholar, and the Chinese Clinical Trial Registry (ChiCTR) will also be searched to obtain more comprehensive data. Besides, the references of the included literature will also be traced to supplement our search results and to obtain all relevant literature.

Results: This systematic review will evaluate the current status of bromhexine hydrochloride in the treatment of COVID-19 in children, to evaluate its efficacy and safety.

Conclusion: This study will provide the latest evidence for evaluating the efficacy and safety of bromhexine hydrochloride in the treatment of COVID-19 in children.

فماتیدین برای تسکین علائم گوارشی

JBC RESEARCH ARTICLE

EDITORS' PICK

Famotidine inhibits toll-like receptor 3-mediated inflammatory signaling in SARS-CoV-2 infection

Received for publication, March 8, 2021, and in revised form, June 9, 2021. Published, Papers in Press, June 30, 2021. <https://doi.org/10.1016/j.jbc.2021.100925>

Rukmini Mukherjee^{1,2}, Anshu Bhattacharya^{1,2}, Denisa Bojkova⁴, Ahmad Reza Mehdipour⁵, Donghyuk Shin^{1,2,6}, Khadija Shahed Khan⁷, Hayley Hei-Yin Cheung⁸, Kam-Bo Wong⁹, Wai-Lung Ng⁹, Jindrich Cinatl¹⁰, Paul P. Geurink¹¹, Gerbrand J. van der Heden van Noort¹², Krishnaraj Rajalingam¹³, Sandra Ciesek¹⁴, Gerhard Hummer¹⁵, and Ivan Dikic^{1,2,3,12,16}

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تازه های کووید

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۱۸۷

تسکین علائم و ضد ویروس کرونا

Review

Thieme

Famotidine Repurposing for Novel Corona Virus Disease of 2019: A Systematic Review

Authors

Santenna Chenchula^a, Avik Ray^a, Balakrishnan Sadasivam

درمان حساسیت ریوی و سرفه و مقابله با بیماری‌زایی

JOURNAL OF ASTHMA
2021, VOL. 58, NO. 10, 1348-1349
<https://doi.org/10.1080/02770903.2020.1786112>

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TREATMENT

Check for updates

Montelukast's ability to fight COVID-19 infection

Andrzej Bozek, MD, PhD^a and Janne Winterstein, MD^b

^aClinical Department of Internal Disease, Dermatology and Allergology, Medical University of Silesia, Katowice, Poland; ^bAllergy Outpatient Clinic, Munchen, Germany

ABSTRACT

Montelukast can be effective in the treatment of SARS-CoV-2 infection.

ARTICLE HISTORY

Received 29 April 2020
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KEYWORDS

Prevention; geriatric

اثر بخشی مونته لوکاست و مکانیسم تاثیر

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<https://doi.org/10.1080/02770903.2020.1786112>

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TREATMENT

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^aClinical Department of Internal Disease, Dermatology and Allergology, Medical University of Silesia, Katowice, Poland; ^bAllergy Outpatient Clinic, Munchen, Germany

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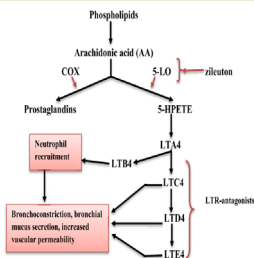


Fig. 1. Leukotriene pathway. COX: cyclooxygenase, 5-LO: 5-lipoxygenase, 5-HETE: 5-hydroperoxyoctatetraenoic acid, LTA4: leukotriene A4, LTC4: leukotriene B4, LTD4: leukotriene C4, LTE4: leukotriene D4, LTE4: leukotriene E4.

تازه های کووید

Covid 19

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ممانعت از پیشروی مسیر طوفان التهابی با مونته لوکاست

H.M. Alkuraisy et al.

European Journal of Pharmacology 904 (2021) 174196

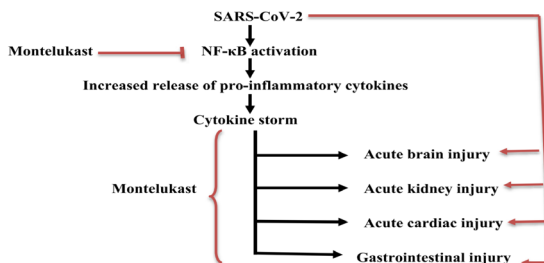


Fig. 3. Role of the Cys-LTR antagonist montelukast in the mitigation of extrapulmonary manifestations in Covid-19.

آنتی اکسیدان قوی و ضد التهاب و متعادل کننده ایمنی

AACE

Endocrine Practice

journal homepage: www.endocrinepractice.org

Review Article

Melatonin for the Early Treatment of COVID-19: A Narrative Review of Current Evidence and Possible Efficacy

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ARTICLE INFO

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Key words:
melatonin
COVID-19
viral diseases
SARS-CoV-2

ABSTRACT

Objective: To discuss the use of melatonin as an early treatment option on the first day of diagnosis for COVID-19.

Methods: Medical Subject Headings terms "COVID-19" and "viral diseases" were manually searched on PubMed, and relevant articles were included.

Results: The results showed that melatonin acts to reduce reactive oxygen species-mediated damage, cytokine-induced inflammation, and lymphopenia in viral diseases similar to COVID-19.

Conclusions: These conclusions provide evidence for potential benefits in melatonin use for COVID-19 treatment as early as the day of diagnosis.

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درمان اختلال خواب بیمار کوید 19



International Journal of
Molecular Sciences



Review

Melatonin as a Potential Adjuvant Treatment for COVID-19 beyond Sleep Disorders

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ملاتونین مانع توسعه التهاب با کمترین عارضه

Abstract: Melatonin is registered to treat circadian rhythm sleep-wake disorders and insomnia in patients aged 55 years and over. The essential role of the circadian sleep rhythm in the deterioration of sleep quality during COVID-19 confinement and the **lack of an adverse effect of melatonin** on respiratory drive indicate that melatonin has the potential to be a recommended **treatment for sleep disturbances related to COVID-19**. This review article describes the effects of melatonin additional to its sleep-related effects, which make this drug an attractive therapeutic option for treating patients with COVID-19. The preclinical data suggest that melatonin may **inhibit COVID-19 progression**. It may **lower the risk of the entrance of the SARS-CoV-2 virus into cells**, **reduce uncontrolled hyperinflammation** and the activation of immune cells, limit the damage of tissues and multiorgan failure due to the action of free radicals, and reduce ventilator-induced lung injury and the risk of disability resulting from fibrotic changes within the lungs. Melatonin may also increase the efficacy of COVID-19 vaccination. The high safety profile of melatonin and its potential anti-SARS-CoV-2 effects make this molecule a preferable drug for treating sleep disturbances in COVID-19 patients. However, randomized clinical trials are needed to verify the clinical usefulness of melatonin in the treatment of COVID-19.

درمان اختلال خواب و بهبودی بیماری

RESEARCH ARTICLE

MEDICAL VIROLOGY WILEY

Melatonin effects on sleep quality and outcomes of COVID-19 patients: An open-label, randomized, controlled trial

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بهبود اختلال خواب و ضایعه ریه با ملاتونین

Abstract

This trial aims to evaluate the effectiveness of adding melatonin to the treatment protocol of hospitalized coronavirus disease 2019 (COVID-19) patients. This was an open-label, randomized controlled clinical trial in hospitalized COVID-19 patients. Patients were randomized into a treatment arm receiving melatonin plus standard care or a control arm receiving standard care alone. The trial's primary endpoint was sleep quality examined by the Leeds Sleep Evaluation Questionnaire (LSEQ). The trial's secondary endpoints were symptoms alleviation by Day 7, intensive care unit admission, 10-day mortality, white blood cell count, lymphocyte count, C-reactive protein status, and peripheral capillary oxygen saturation. Ninety-six patients were recruited and allocated to either the melatonin arm ($n = 48$) or control arm ($n = 48$). Baseline characteristics were similar across treatment arms. There was no significant difference in symptoms on Day 7. The mean of the LSEQ scores was significantly higher in the melatonin group ($p < 0.001$). There was no significant difference in laboratory data, except for blood oxygen saturation, which has improved significantly in the melatonin group compared with the control group (95.81% vs. 93.65% respectively, $p = 0.003$). This clinical trial study showed that the combination of oral melatonin tablets and standard treatment could substantially improve sleep quality and blood oxygen saturation in hospitalized COVID-19 patients.

تازه های کووید

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درمان مناسب تب و بدن درد



molecules



Article

Antiviral Properties of the NSAID Drug Naproxen Targeting the Nucleoprotein of SARS-CoV-2 Coronavirus

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تسکین درد و کاهش تب و کاهش تکثیر ویروس

Abstract: There is an urgent need for specific antiviral treatments directed against SARS-CoV-2 to prevent the most severe forms of COVID-19. By drug repurposing, affordable therapeutics could be supplied worldwide in the present pandemic context. Targeting the nucleoprotein N of the SARS-CoV-2 coronavirus could be a strategy to impede viral replication and possibly other essential functions associated with viral N. The antiviral properties of naproxen, a non-steroidal anti-inflammatory drug (NSAID) that was previously demonstrated to be active against Influenza A virus, were evaluated against SARS-CoV-2. Intrinsic fluorescence spectroscopy, fluorescence anisotropy, and dynamic light scattering assays demonstrated naproxen binding to the nucleoprotein of SARS-CoV-2 as predicted by molecular modeling. Naproxen impeded recombinant N oligomerization and inhibited viral replication in infected cells. In VeroE6 cells and reconstituted human primary respiratory epithelium models of SARS-CoV-2 infection, naproxen specifically inhibited viral replication and protected the bronchial epithelia against SARS-CoV-2-induced damage. No inhibition of viral replication was observed with paracetamol or the COX-2 inhibitor celecoxib. Thus, among the NSAID tested, only naproxen combined antiviral and anti-inflammatory properties. Naproxen addition to the standard of care could be beneficial in a clinical setting, as tested in an ongoing clinical study.

آنچه در عمل در بیمارستانها رخ داد

Original Article

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Real Clinical Practice and Therapeutic Management Following COVID-19 Crisis in two Hospitals in Iran: A Statistical and Conceptual View

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Background: The Coronavirus disease 2019 (COVID-19) outbreak quickly has spread and became a pandemic. However, no approved therapeutics or effective treatment is available for the treatment of these patients. The present study was done to retrospectively assess the treatment strategies (e.g., pharmaceutical care services) for COVID-19 patients in selected hospitals and highlight the importance of such services in the management of a pandemic.

Materials and Methods: Data from a series of COVID-19 patients (978 patients; 658 males [66.9%] and 324 females [33.1%]) admitted to the selected hospitals in Tehran from 20 February to 19 March 2020 were retrieved retrospectively from

درمان ضد التهابی چاره نجات بیمار از مرگ

Letter to the Editor

COVID-19/SARS-CoV-2

It is time to consider an anti-inflammatory therapy based on the pathophysiology of COVID-19 infection during the right time window?

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درمان کورتیکواستروئید در مرحله بستری

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Respiratory Research

RESEARCH

Open Access

The efficacy of corticosteroids therapy in patients with moderate to severe SARS-CoV-2 infection: a multicenter, randomized, open-label trial



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درمان کورتیکواستروئید در مرحله بستری

Results: The mean LOS was significantly lower in the mITT and PP populations who received prednisolone compared with populations treated with Lopinavir/Ritonavir ($p=0.028$; $p=0.0007$). We observed no significant differences in the number of deaths, ICU admission, and need for mechanical ventilation between the Modified ITT and per-protocol populations treated with prednisolone and Lopinavir/Ritonavir, although these outcomes were better in the arm treated with prednisolone. The time to clinical recovery was similar in the modified ITT and per-protocol populations treated with prednisolone, lopinavir/ritonavir, and azithromycin ($P=0.335$; $P=0.055$; $p=0.291$; $p=0.098$).

Conclusion: The results of the present study show that therapeutic regimen (regimen I) with low dose prednisolone was superior to other regimens in shortening the length of hospital stay in patients with moderate to severe COVID-19. The steroid sparing effect may be utilized to increase the effectiveness of corticosteroids in the management of diabetic patients by decreasing the dosage.

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نتیجه درمان با فلوپیراویر در چندین بیمارستان کشور



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Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia

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ABSTRACT

Background: We examined the safety and efficacy of a treatment protocol containing Favipiravir for the treatment of SARS-CoV-2.
Methods: We did a multicenter randomized open-labeled clinical trial on moderate to severe cases infections of SARS-CoV-2. Patients with typical ground glass appearance on chest computerized tomography scan (CT scan) and oxygen saturation (SpO₂) of less than 93% were enrolled. They were randomly allocated into Favipiravir (1.6 gr loading, 1.8 gr daily) and Lopinavir/Ritonavir (800/200 mg daily) treatment regimens in addition to standard care. In-hospital mortality, ICU admission, intubation, time to clinical recovery, changes in daily SpO₂ after 5 min discontinuation of supplemental oxygen, and length of hospital stay were quantified and compared in the two groups.
Results: 380 patients were randomly allocated into Favipiravir (193) and Lopinavir/Ritonavir (187) groups in 13 centers. The number of deaths, intubations, and ICU admissions were not significantly different (26, 27, 31 and 21, 17, 25 respectively). Mean hospital stay was also not different (7.9 days (SD = 6) in the Favipiravir and 8.1 (SD = 6.5) days in Lopinavir/Ritonavir groups) (p = 0.61). Time to clinical recovery in the Favipiravir group was similar to Lopinavir/Ritonavir group (HR = 0.94, 95% CI 0.75 – 1.17) and likewise the changes in the daily SpO₂ after discontinuation of supplemental oxygen (p = 0.46).
Conclusion: Adding Favipiravir to the treatment protocol **did not reduce** the number of ICU admissions or intubations or **in-hospital mortality** compared to Lopinavir/Ritonavir regimen. It also **did not** shorten time to clinical recovery and length of hospital stay.

بهترین توصیه در وضعیت فعلی بیماری کوید 19

■ واکسیناسیون علیه کرونا ویروس



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COVID-19 and Chronic Obstructive Pulmonary Disease

COVID-19 and Chronic Obstructive Pulmonary Disease

COVID-19 & COPD

- COVID-19 pandemic has made routine management and diagnosis of COPD more difficult as a result of:
 - Reductions in face-to face consultations,
 - Difficulties in performing spirometry,
 - Limitations in traditional pulmonary rehabilitation and home care programs.
- Patients have also faced shortages of medication.

Risk of Infection with COVID-19

- The spike protein of the virus binds to ACE2 during viral attachment to host cells and that viral entry is also facilitated by TMPRSS2 (transmembrane serine protease 2) .
- Differences in the expression of ACE2 and TMPRSS2 may modulate the individual susceptibility to and clinical course of SARS-CoV-2 infection.
- ACE2 mRNA expression is increased in COPD and may be modulated by inhaled corticosteroid (ICS) use.

Risk of Infection with COVID-19

- It is not known definitively yet whether having COPD affects the risk of becoming infected with COVID-19.
- Most studies of people in the community tested for COVID-19 have not shown chronic respiratory disease as an independent risk factor for testing positive .
- COPD is an independent risk factor for hospital admission (hazard ratio, 1.55).

COPD has also been reported to independently increase the risk of severe disease or death.

Factors including:

- Prior poor adherence to therapy,
- Difficulties performing self-management,
- Limited access to care during the pandemic,
- A reduced pulmonary reserve.

Risk of Infection with COVID-19

- There are currently no peer-reviewed studies that have evaluated the effect of smoking on the risk of infection with SARSCoV- 2, but studies suggest that smoking is associated with increased severity of disease and risk of death in hospitalized patients with COVID-19.

Investigations Testing for SARS-CoV-2 Infection

- Patients with COPD presenting with respiratory symptoms, fever, or other symptoms suggesting SARS-CoV-2 infection, even if mild, should be tested for possible infection .
- Antibody testing may be used to support clinical assessment of patients who present late.

Investigations

Detection of SARS-CoV-2 does not exclude the potential for coinfection with other respiratory pathogens .

Some patients experience reactivation of long-lasting virus carriage or become reinfected, and this might be influenced by comorbidities or drugs that hamper the immune response .

Repeat testing should be performed in patients with suspected recurrence or relapse of COVID-19.

Spirometry and Pulmonary Function Testing

Performing spirometry and pulmonary function testing may lead to SARS-CoV-2 transmission as a result of coughing and droplet formation during the tests.

During periods of high prevalence of COVID-19 in the community, spirometry should be restricted to patients requiring urgent or essential tests for the diagnosis of COPD .

Whenever possible, patients should have an RT-PCR test for SARS-CoV-2 performed

Patients with a positive RT-PCR test should normally have the test delayed until negative.

Spirometry and Pulmonary Function Testing

- When routine spirometry is not available, home measurement of peak expiratory flow combined with validated patient questionnaires could be used .
- peak expiratory flow does not correlate well with the results of spirometry , has low specificity, and cannot differentiate obstructive and restrictive lung function abnormalities.

Bronchoscopy

- In some patients with COPD, diagnostic and therapeutic bronchoscopy may be required during the COVID-19 pandemic.
- Elective bronchoscopy should be delayed until patients have a negative PCR test .
- In urgent cases in which COVID-19 infection status is unknown, all cases should be managed as if positive.
- A disposable bronchoscope should be used if available , and staff should wear personal protective equipment.

Imaging

- CXR :
 - insensitive in mild or early COVID-19, not for screening in asymptomatic individuals.
 - in COPD patients with moderate-to-severe symptoms of COVID-19 and evidence of worsening respiratory status .
 - COVID-19 pneumonia changes are mostly bilateral.
 - To exclude or confirm alternative diagnoses (e.g., lobar pneumonia, pneumothorax, or pleural effusion).
- Lung ultrasound
- CT screening may show evidence of pneumonia in asymptomatic individuals infected with SARS-CoV-2 , and false negative RT-PCR tests have been reported in patients with CT findings of COVID-19 who eventually tested positive .

Risk of Infection with COVID-19

COPD Patients with COVID-19 have an increased prevalence of:

- ground-glass opacities,
- local patchy shadowing,
- interstitial abnormalities on CT scans than without COPD.

increased occurrence of DVT and PTE in COVID-19 ;
Chest CT angiography to R/O pulmonary embolism

Protective Strategies

- Wearing a tight-fitting N95 mask introduces an additional inspiratory resistance.
- RR, SPO₂, and exhaled CO₂ levels were adversely affected in patients with COPD wearing an N95 mask for 10 minutes at rest followed by 6 minutes of walking.
- Wearing a surgical mask does not appear to affect ventilation even in patients with severe airflow limitation.

Key Points for the Management of Stable COPD during the COVID-19 Pandemic

- Protective strategies

Follow basic infection control measures
face covering

- Investigations

Only essential spirometry
shielding/sheltering in place

- Pharmacotherapy

adequate supplies of medications
Continue unchanged including ICS

- Non-pharmacological therapy

Ensure annual influenza vaccination
Maintain physical activity

Differentiating COVID-19 Infection from the Daily Symptoms of COPD

- Cough and breathlessness are found in over 60% of patients with COVID-19 but are usually also accompanied by fever (over 60% of patients)
- as well as fatigue, confusion, diarrhea, nausea, vomiting, muscle aches and pains, anosmia, dysgeusia, and headaches.

Differentiating COVID-19 & COPD

- In COVID-19, symptoms may be mild at first, but rapid deterioration in lung function may occur .
- The prodrome of milder symptoms is especially problematic in patients with underlying COPD who may already have diminished lung reserve.

Differentiating COVID-19 & COPD

- The lack of recognition of the prodromal symptoms may delay early diagnosis.
- patients with COPD reporting exacerbations and suspected of having COVID-19 infection were infrequently tested for its presence.

Differentiating COVID-19 & COPD

- A high index of suspicion for COVID-19 in COPD patients who present with symptoms of an exacerbation, especially if accompanied by fever, impaired taste or smell, or gastrointestinal complaints.
- Only 65% of people returned to their previous level of health 14–21 days after testing positive for SARS-CoV-2
- Some patients continued to experience cough, fatigue, and breathlessness for weeks and a smaller proportion for months.

Maintenance Treatment for COPD during the COVID-19 Pandemic

- no conclusive data to support the alteration of maintenance COPD pharmacological treatment either to reduce the risk of developing COVID-19.
- no data on the use of long-acting bronchodilators, roflumilast, or macrolides in COPD patients and clinical outcomes or risk of SARS-CoV-2 infection.
- Thus, these patients should continue these medications required for COPD.

Maintenance Treatment for COPD during the COVID-19 Pandemic

- ICS have an overall protective effect against exacerbations in COPD
- Some laboratory data show that corticosteroids and long-acting bronchodilators can reduce the replication of SARS-CoV-2 .
- These laboratory experiments suggesting a potential protective effect of ICS against COVID-19 have not been validated by clinical studies.

Use of Nebulizers

- Aerosol therapy increases the droplet generation and risk of disease transmission.
- Although most of the aerosol emitted comes from the device, there is a risk that patients may be contaminated by aerosol and droplets produced by coughing.
- SARS-CoV-2 is viable in aerosols for up to 3 hours, and transmission to healthcare workers.
- pressurized metered-dose inhalers, dry powder inhalers, and soft mist inhalers should be used for drug delivery instead of nebulizers.

Use of Nebulizers

- The risks of nebulized therapy spreading infection can be minimized by avoiding use in the presence of other people and ensuring that the nebulizer is used near open windows or in areas of increased air circulation.
- Nebulizers may be needed in critically ill patients with COVID-19 receiving ventilatory support.

Non-pharmacological Treatment

- Annual Influenza Vaccination
- When case rates are high, center based rehabilitation is not appropriate.
- Patients should keep active at home and can be supported by home based rehabilitation programs.

Treatment of COVID-19 in Patients with COPD

- The antiviral drug remdesivir and systemic steroids for hospitalized patients with severe COVID-19.
- Importantly, there are no known drug interactions between remdesivir and inhaled COPD treatments.

Exacerbations of COPD

- Coronaviruses are among the respiratory viruses that trigger COPD exacerbations.
- Distinguishing the symptoms of a typical exacerbation from COVID-19 infection can be extremely difficult, as many of the symptoms overlap.
- If a COVID-19 infection is suspected, RT-PCR testing should be conducted .
- If COVID-19 infection is confirmed, then treatment for COVID-19 infection should be conducted regardless of the presence of COPD.

Exacerbations of COPD

-COVID-19 causes a distinct pattern of pathophysiological changes, including :

- vascular injury,
- pneumonitis associated with hypoxemia,
- high levels of systemic inflammation("cytokine storm"),
- coagulopathy,
- multiorgan involvement.

-These features are very different from typical COPD exacerbations.

Exacerbations of COPD

- COVID-19 infection resembles an exacerbation of COPD.

- Fever, anorexia, myalgias, and gastrointestinal symptoms more frequently reported in COVID-19 than in exacerbations of COPD.

- Sputum production occurs in both.

- Lymphopenia is a common finding of COVID-19

- COPD Patients with COVID-19 reported more severe fatigue, dyspnea, and diarrhea than those without COPD.

Exacerbations of COPD

- Higher risk of poor outcomes in patients with COVID-19 :

- | | |
|---------------------|-------------------------|
| - lymphopenia, | - procalcitonin, |
| - thrombocytopenia, | - creatinine kinase, |
| - elevated : | - transaminases, |
| - D-dimer, | - creatinine, |
| - CRP, | - lactate dehydrogenase |

Corticosteroids

- WHO initially recommended against the routine use of corticosteroids in COVID-19 infection at the beginning of the pandemic, except in two clinical settings:
- (ARDS)
- COPD exacerbations, in which specific indications for systemic corticosteroids were recognized .

Corticosteroids

- methylprednisolone associated with improved survival in patients with COVID-19 and ARDS .
- systemic glucocorticoids reduce mortality at 28 days in patients with COVID-19 pneumonia, especially those that are not on IMV or on pressor support .
- Systemic steroids should be used in COPD exacerbations according to the usual indications (whether or not there is evidence of a SARS-CoV-2 infection)

Antibiotics

- Antibiotic treatment for a COPD exacerbation is indicated if patients have at least two of the three cardinal symptoms, including increased sputum purulence, or if the patient requires mechanical ventilation .
- Bacterial co-infections reported infrequently in COVID-19.
- Diagnosing co-infection in patients with COVID-19 may be difficult.
- In practice, most hospitalized patients, particularly the severe ones, have been prescribed empirical antibiotic therapy .
- Antibiotics should be used in COPD exacerbations according to the usual indications whether or not there is evidence of a SARS-CoV-2 infection, particularly as patients with COPD who develop COVID-19 are reported, to more frequently develop bacterial or fungal coinfections.

Pulmonary Complication

- ARDS may be part of COVID-19 and could be considered the major pulmonary complication of COVID-19.
- Some early reports suggested that ARDS in this setting may differ from the typical ARDS.
- Subsequent studies, however, suggested that classical ARDS also presents with a large variation in lung severity , and there is considerable overlap between patients with classical ARDS and patients with COVID-19 .

Exacerbations of COPD

- Although the respiratory tract is the main target of COVID-19, extrapulmonary involvement is frequent and contributes to morbidity, disability, and mortality.
- Renal, cardiac, nervous, cutaneous, hepatic, and gastrointestinal manifestations occur.
- Concomitant respiratory comorbidities, such as COPD, may aggravate these processes.

Anticoagulation

- COVID-19 has been associated with a hypercoagulable state , and venous thromboembolism rates in both ICU and ward patients are two- to fourfold higher than expected despite thromboprophylaxis with a low-molecular-weight heparin (LMWH) or unfractionated heparin .
- Patients with COPD are already at an increased risk for venous thromboembolism , and those hospitalized with COVID-19 should receive pharmacologic thromboprophylaxis.
- In response to the high rates despite prophylactics, many institutional protocols have adopted intermediate intensity (i.e., twice-daily LMWH rather than once daily) or even a therapeutic-intensity dose strategy for thromboprophylaxis .

Ventilatory Support for Patients with COPD and COVID-19 Pneumonia

- The prevalence of hypoxic respiratory failure in patients with COVID-19 is around 19% .
- Ventilatory support has been used in up to 20% of patients who develop severe hypoxemia because of COVID-19 , and approximately 5% of patients require ICU care and advanced respiratory support .
- Patients requiring ventilatory support have a high risk of mortality , and COPD has been reported to increase the risk of respiratory failure and ICU admissions.
- HFNT significantly reduces rates of intubation and IMV.
- HFTN should be considered in preference to NIV for acute hypoxemic respiratory failure despite conventional oxygen therapy, as it may have a lower failure rate .
- Prone positioning has also been suggested for awake nonintubated patients with hypoxemia .
- NIV is the normal standard of care for patients with COPD and acute respiratory failure .
- NIV may be beneficial for the treatment of hypercapnic respiratory in patients with COPD and COVID-19 pneumonia, but it also has the potential to worsen lung injury as a result of high transpulmonary pressures and VT.
- Patients on HFNT or NIV should be monitored closely for worsening, and early intubation and IMV with adoption of a protective lung strategy, similar to that used in other forms of ARDS, should be considered .
- A PaO₂/FIO₂ ratio, 150 mm Hg may be a useful indicator for NIV failure and increased risk of mortality.
- Extracorporeal membrane oxygenation should be considered only after other strategies fail to achieve goals of oxygenation or ventilation.

Rehabilitation

- Rehabilitation should be provided to all patients with COPD and COVID-19, particularly to those that have been more severely affected or required ICU admission.
- A multinational task force has recommended early rehabilitation during.

Follow-up of Patients with COPD & COVID-19

- Approximately 30% of patients with SARS or MERS had persistent lung abnormalities that were consistent with fibrotic lung disease.
- There are not yet long-term studies on the follow-up of patients with COVID-19, nor recommendations for monitoring these patients , thus the follow up of patients with COPD who developed COVID-19 is still based on expert opinion and consensus.
- The intensity of the monitoring obviously depends on the severity of the COVID-19 episode.
- Patients who developed mild COVID-19 should be followed with the usual protocols used for patients with COPD .
- Patients who developed moderate COVID-19, including hospitalization and pneumonia but no respiratory failure, should be monitored more frequently and accurately than the usual patients with COPD, with particular attention to the need for oxygen therapy.

Conclusions

- There is little direct evidence about management of COVID-19 in people with COPD.
- Clinicians should maintain a high level of suspicion of COVID-19 in patients with COPD presenting with new or worsening respiratory symptoms, fever, and/or any other symptoms that could be COVID-19 related, even if these are mild, and should test for SARS-CoV-2.
- Patients should keep taking their oral and inhaled respiratory medications for COPD as directed, as there is no evidence that COPD medications should be changed during this COVID-19 pandemic.

KEY POINTS FOR THE MANAGEMENT OF STABLE COPD DURING COVID-19 PANDEMIC

PROTECTIVE STRATEGIES

- Follow basic infection control measures
- Wear a face covering
- Consider shielding/sheltering-in-place

INVESTIGATIONS

- Only essential spirometry

PHARMACOTHERAPY

- Ensure adequate supplies of medications
- Continue unchanged including ICS

NON-PHARMACOLOGICAL THERAPY

- Ensure annual influenza vaccination
- Maintain physical activity

KEY POINTS FOR THE MANAGEMENT OF PATIENTS WITH COPD AND SUSPECTED OR PROVEN COVID-19

SARS-CoV-2 TESTING

- Swab/Saliva PCR if new or worsening respiratory symptoms, fever, and/or any other symptoms that could be COVID related

OTHER INVESTIGATIONS

- Avoid spirometry unless essential
- Consider CT for COVID pneumonia and to exclude other diagnoses e.g. PE
- Avoid bronchoscopy unless essential
- Assess for co-infection

COPD PHARMACOTHERAPY

- Ensure adequate supplies of medication
- Continue maintenance therapy unchanged including ICS
- Use antibiotics and oral steroids in line with recommendations for exacerbations
- Avoid nebulization when possible

COPD NON-PHARMACOLOGICAL THERAPY

- Maintain physical activity as able

PROTECTIVE STRATEGIES

- Follow basic infection control measures
- Maintain physical distancing
- Wear a face covering

COVID-19 THERAPY

- Use systemic steroids and remdesivir as recommended for patients with COVID-19
- Use HFNT or NIV for respiratory failure if possible
- Use invasive mechanical ventilation if HFNT or NIV fails
- Post COVID-19 rehabilitation
- Ensure appropriate post COVID-19 follow-up



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COVID19 and Neuromuscular Disorders

COVID and Neurology

- The COVID-19 pandemic is caused by SARS-CoV-2, a member of the Coronavirinae subfamily.
- It has caused many neurological manifestations centrally and peripherally.

Central neurological manifestations of SARS-CoV-2

- A number of neurological manifestations of SARS-CoV-2 have been reported:
- Encephalitis
- Acute disseminated encephalomyelitis (ADEM)
- Encephalopathy
- Posterior reversible encephalopathy syndrome (PRES)
- Meningitis

Neuromuscular manifestations

- | | |
|--------------------------|---------------------------------|
| - Hyposmia/ageusia | - Ophthalmoparesis |
| - Facial paresis | - Guillain-Barré syndrome |
| - Symmetrical neuropathy | - Critical-illness myopathy and |
| - neuropathy | - Myalgia |
| - Myositis | - Rhabdomyolysis |

Aim of presentation

Focusing on the main neuromuscular manifestation of SARS-CoV-2 infection.

Myalgia

- In a meta-analysis:

- prevalence of myalgia: 36% (11 to 50%)

- Frequency of other symptoms:

- fever (88.5%)
- cough (68.6%)
- expectoration (28.2%)
- dyspnea (21.9%)
- Less common symptoms:
 - dizziness, diarrhea, nausea, and vomiting.
- Another meta-analysis (55 studies, 8697 patients, published between 1 January 2020 and 16 March 2020):
 - myalgia in 21.9% COVID-19 patients

Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, Zhang HY, Sun W, Wang Y. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020;92(6):577-583.

Myalgia is a common neuromuscular manifestation in COVID:>50% in some studies

Neuromuscular manifestations

- | | |
|--------------------------|---------------------------------|
| - Hyposmia/ageusia | - Ophthalmoparesis |
| - Facial paresis | - Guillain-Barré syndrome |
| - Symmetrical neuropathy | - Critical-illness myopathy and |
| - neuropathy | - Myalgia |
| - Myositis | - Rhabdomyolysis |

Myositis/Rhabdomyolysis

- Nine patients (age range 16 to 88 years, all males) with COVID-19-related myositis/rhabdomyolysis has been reported.

- Eight patients presented with generalized limb weakness.

Borku Uysal B, Ikitimur H, Yavuzer S, Islamoglu MS, Cengiz M. Case report: a COVID-19 patient presenting with mild rhabdomyolysis. Am J Trop Med Hyg. 2020;103:847–850.

Valente-Acosta B, Moreno-Sanchez F, Fueyo-Rodriguez O, Palomar-Lever A. Rhabdomyolysis as an initial presentation in a patient diagnosed with COVID-19. BMJ Case Rep. 2020;13(6):e236719.

Myositis/rhabdomyolysis

- Repetitive muscle twitching.
- Cola-colored urine
- Red blood cells in the urine
- All patients had elevated CPK levels.
- One patient who presented with cola-colored urine had most elevated CPK level of >100,000 IU/L.
- All patients had elevated levels of CRP, LDH, and serum ferritin.
- Five patients improved with conservative management.
- In addition to myositis and rhabdomyolysis, there is a report of COVID-19 - patients with critical-illness myopathy.
- All had acute flaccid quadriplegia.
- Electrophysiological tests revealed a myopathic pattern.
- They had mildly elevated CK and all patients had a good outcome.

Acute myopathic quadriplegia in patients with COVID-19 in the intensive care unit. Madia F, Merico B, Primiano G, Cutuli SL, De Pascale G, Servidei S. Neurology. 2020 Sep 15; 95(11):492-494.

Myositis/rhabdomyolysis has been reported after COVID 19 with rising CK > 100,000.

Myasthenia gravis

- There are reports of de-novo occurrence of myasthenia gravis secondary to COVID-19 and also exacerbation after the COVID.
- However, there are reports of patients (age range 42–90 years, 4 females)

تازه های کووید

Covid 19

The Comprehensive
National Congress On Covid 19

of COVID-19 infection-related exacerbation of the pre-existing myasthenia gravis.

- Both anti-AchR Ab+ and MuSK+ MG
- All patients had exacerbation of myasthenic symptoms after sore throat, fever, cough, and shortness of breath in variable combination.
- Some patients required mechanical ventilation.

Our Experience for MG

- Four myasthenia gravis (MG) patients presented following COVID-19 infection: De Novo Initiation
- The patients were between 38 and 61 years old, presenting with dysphagia, ptosis, muscle weakness, and respiratory problems with various severities.
- A high-level AchR antibody in the serum.
- All patients were treated with pyridostigmine and prednisolone.
- They had favorable outcome.
- MG is an immune-mediated disorder that can be caused by molecular mimicry by different viruses.

MG may exacerbate by COVID infection or may start as de novo.

Guillain-Barrè syndrome and Miller-Fisher syndrome

- Several previous reports have reported the association of infections, viral or bacterial, with GBS.
- >40 patients with GBS and 5 patients with MFS secondary to COVID-19 have been published.
- Most of the reports were from China, Italy, Iran and the USA.
- GBS and MFS were more frequent in elderly people.
- Time to onset of GBS/MFS ranged from 3 days to 4 weeks of onset of COVID-19 symptoms.
- Upper respiratory tract symptoms were the usual preceding symptoms.

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- Upper respiratory tract symptoms were the usual preceding symptoms.
- Hyposmia and ageusia were distinctive features seen in COVID-19 patients unlike the typical GBS where these olfactory symptoms are not seen.
- Most patients had ascending or lower limb areflexic weakness that later on progressed and involved bifacial weakness and other cranial neuropathies.
- Unlike typical GBS, respiratory failure secondary to lung involvement was common in GBS patients secondary to COVID-19.
- Majority of patients had severe demyelinating type of neuropathy.
- CSF-albumin-cytological dissociation was frequently noticed.

Guillain-Barre syndrome in patients with coronavirus disease-2019: Report of six cases and review of literature

Received: 15 June 2020
Accepted: 02 July 2020

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Our experience

- This study was performed in three referral centers of COVID-19 in Iran, and six patients with the diagnosis of GBS were enrolled.
- Patients enrolled in the study with acute progressive weakness according to the demyelinating or axonal variant of GBS.
- Four patients: axonal polyneuropathy
- Two patients: demyelinating polyneuropathy
- One patient required mechanical ventilation.
- All our patients had a favorable response to treatment.
- In one patient, the GBS symptoms recurred four months after the first episode.

Limited case reports suggest a possible association between GBS and COVID-19. - Such associations may be an incidental concurrence or a real cause-and-effect linkage.

Cranial neuropathy

- Various cranial neuropathies are described
- 3rd, and bilateral 6th nerve palsy
- painless right 6th cranial nerve palsy
- left facial palsy Glossopharyngeal, vagus, and trigeminal neuropathy

Cranial Neuropathy is reported frequently after COVID with various involvements.

-Pathomechanism of Neuromuscular Involvement

Peripheral Nerves Involvement

- Mostly thought to be immune-mediated.
- In patients with rapid evolution of GBS after the onset of COVID-19 symptoms, direct cytotoxic effects of virus on peripheral nerves is a postulated mechanism.
- The glycoproteins on the surface of the virus resemble with glycoconjugates in human nervous tissue.
- The antibodies formed against the viral surface glycoproteins acts against the glycoconjugates on the neural tissue.
- This mechanism of nerve injury is famously known as “molecular mimicry”.

Mechanism of muscle involvement

- The mechanism of myositis in COVID-19 infection is not fully understood.
- Skeletal muscles and other cells in the muscles like satellite cells, leukocytes, fibroblasts, and endothelial cells express ACE-2.
- Therefore, it is postulated that skeletal muscles are susceptible to direct muscle invasion by SARS-CoV-2.
- Other possible mechanisms suggested are
 - Immune complex deposition in muscles
 - Release of myotoxic cytokines
 - Damage due to homology between viral antigens and human muscle cells

Conclusion

- Neuromuscular manifestations are frequent after covid infection including myalgia, myositis, olfactory dysfunction, GBS, cranial neuropathy, and MG.
- The mechanism of Neuromuscular manifestations may result from
 - direct invasion
 - immunologic effects on PNS



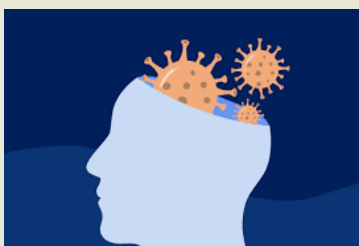
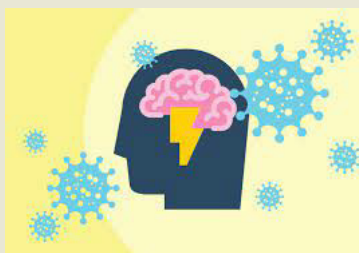
Masoud Mehrpour MD,MPH

Covid and stroke



Covid-19 and nervous system

- Neurological symptoms:
 - headache,
 - dizziness,
 - cranial nerves damage such as anosmia,
 - confusion,
 - cerebrovascular diseases,
 - encephalopathies,
- the initial presentation of COVID-19 or concur with respiratory symptoms
- Neurological involvement has been observed in up to 36% of COVID-19 patients.
 - In severe cases, cerebrovascular diseases are among the most prevalent comorbidities and are presented as an independent risk factor for poor prognosis



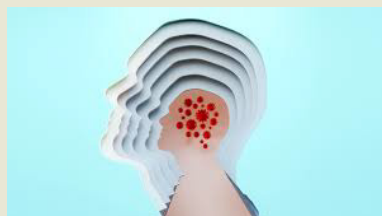
Stroke mechanism in Covid-19

- Coagulopathy and hypercoagulability as a result of systemic response to SARS-CoV-2 infection
- endothelial injury caused by direct viral invasion,
- venous stasis due to immobilization



Stroke and Covid

- generally in younger with higher admission National Institutes of Health Stroke Scale (NIHSS) score than their counterparts without COVID-19
- This could be attributed to the hypercoagulative state that predisposes COVID-19 patients to thromboembolic incidents.



Acute stroke imaging protocol

- Brain CT –
- MRI
- CTA
- CT perfusion



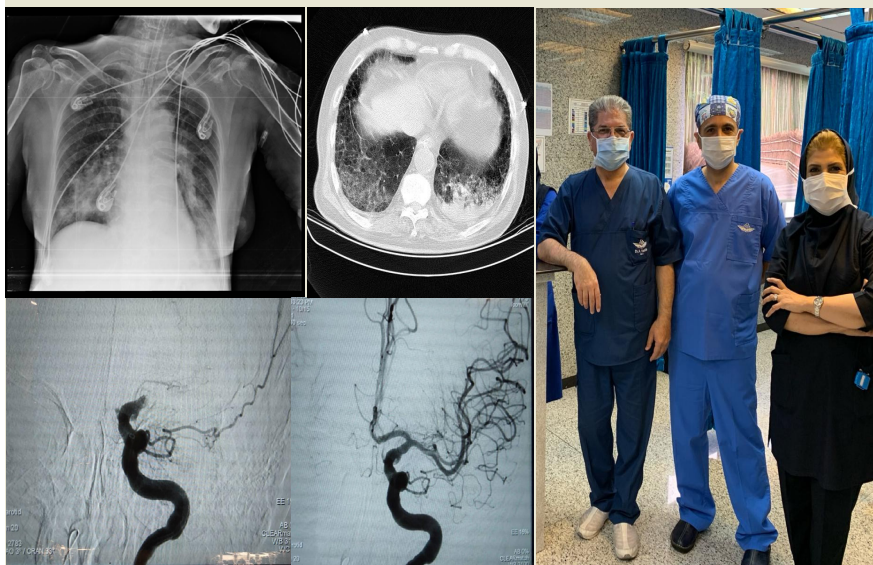
Acute stroke imaging protocol

Both COVID-19 infection and stroke carry a high probability of renal impairment
Contrast exposure required for CT angiography and perfusion images may precipitate acute kidney injury (AKI) in a highly vulnerable COVID-19 infected patient and increase risk of mortality.

Concurrent image

Concurrent chest CT scan may be obtained at the time of neurovascular imaging may identify CT chest abnormalities (consolidation, ground glass opacity and reticular opacity in the presence of architectural distortion) that may be seen in up to 82% of patients with COVID-19 infection on admission

Angio suite protection



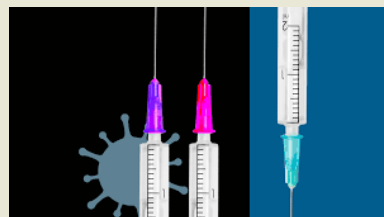
Stroke patients should be vaccinated?

having an effective vaccine is the best way to protect the most vulnerable, our friends and our families, and will save tens of thousands of lives.

the coronavirus booster and flu vaccines at the same time?

- it's perfectly ok to get the coronavirus booster and flu vaccines at the same time.

- not get them both in the same arm. So, if one-sided weakness or an atrophied muscle in one of arms, having them at different times, or having one of them in leg, which some people prefer.



Should stroke survivors take the Oxford/AstraZeneca vaccine?

- The MHRA, the European Medicines Agency (EMA), and the World Health Organisation have all said that the Oxford/AstraZeneca Vaccine is safe and that the benefits continue to outweigh the risks.

- The benefits of receiving the Oxford/AstraZeneca vaccine far outweigh any risks, even for people under the age of 40 or with underlying health conditions, which includes stroke survivors.



Are the vaccines and booster safe for stroke survivors who are taking anticoagulants?

- If taking anticoagulation medication, doctor will check that it's ok to receive the vaccination injection.

which arm to have the vaccine or booster in?

- paralysis in one arm, jab in good side, especially if the muscle in affected arm appears to be wasted.



COVID-19 related vaccine-induced immune thrombotic thrombocytopaenia (VITT) can include ischaemic stroke as well as cerebral venous thrombosis

- Reports of coagulopathy have appeared associated with COVID-19 vaccination and particularly the ChAdOx1 nCoV-19 vaccine.
- thrombocytopaenia, similar to that seen in heparin-induced thrombocytopaenia but in the absence of heparin and with antibodies to platelet factor 4. In one series of 23 patients, 13 had cerebral venous thrombosis and 5 pulmonary emboli. Median age was 46 with an age range of 21–77, and median time after vaccine was 12 days (range 6–24). Why the cerebral venous sinuses are preferentially affected remains uncertain.
- the immune-mediated coagulopathy can also cause arterial thrombosis including ischaemic stroke, although venous thrombosis and especially CVST appear more frequent.

Treating cerebral venous thrombosis and ischaemic stroke associated with vaccine-induced immune thrombotic thrombocytopaenia (VITT) presents a challenge.

- challenging
- direct oral anticoagulants (DOACs, fondaparinux, danaparoid or argatroban depending on the clinical picture
- intravenous immunoglobulin infusions,
- possibly plasma exchange.
- platelet infusions may exacerbate the condition.
- Despite optimal therapy, a high mortality has been reported and complications
- these side effects are rare and much less common than both cerebral venous thrombosis and ischaemic stroke associated with COVID-19 infection itself, as illustrated by a recent large epidemiological study.



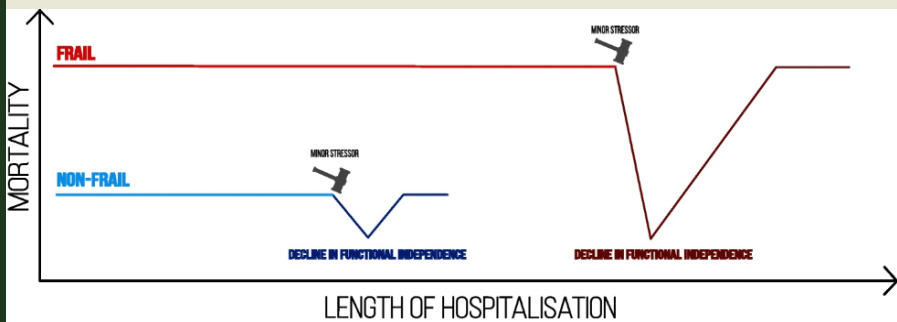
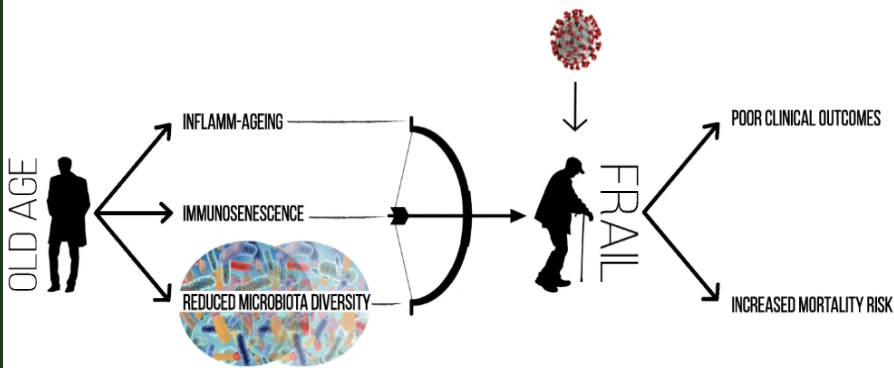
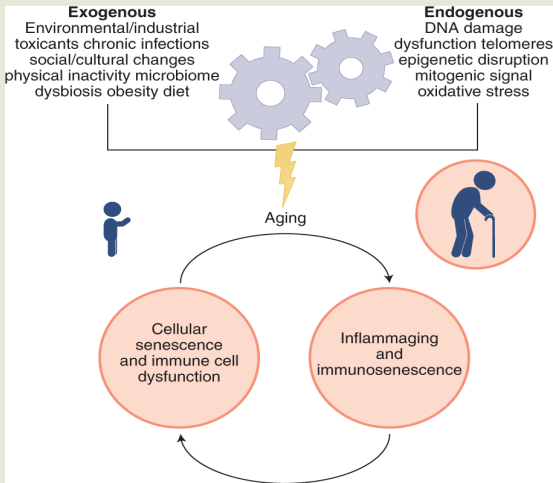
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Challenges Experienced by Older People During COVID-19
Pandemic

Challenges Experienced by Older People During COVID-19 Pandemic

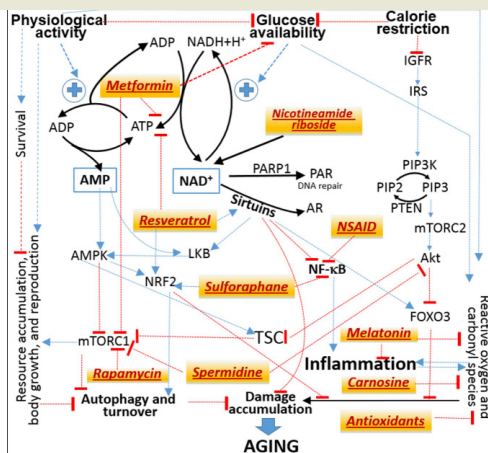


Introduction

- Human ACE2 receptor
- The ACE2 gene is highly expressed in the lungs, gastrointestinal tract, and the podocytes, and the proximal tubule segment in kidneys
- These receptors are also expressed in the cardiac myocytes

In elderly patients

- More severe and lethal
- The management of elderly patients with COVID-19 requires much more caution than younger patients



In elderly patients

Older frail adults have a pre-existing immunopathological base that puts them at a higher risk of undesired outcomes and mortality due to COVID-19 and poor response to COVID-19 vaccination. Also, their admission in ICU should depend on their degree of frailty rather than their chronological age, which is better to be screened using the CFS.

In elderly patients

- The most common symptoms in elderly patients with COVID-19 were cough (70.5%), fever (64.1%), and fatigue (44.5%).
- In the critically ill patients who needed an ICU admission, the most common symptoms were cough (67.2%), fever (62.9%), and dyspnea (61.2%).
- Some reports indicate that at first, COVID-19 may present atypical symptoms such as altered mental health in the absence of typical symptoms; thus, mental health findings related to COVID-19 should be considered
- The pneumonia severity index (PSI), multilobar involvement on chest CT scans, the prevalence of acute respiratory distress syndrome (ARDS), and the level of CRP were significantly higher.
- Lymphocytes were significantly lower.
- The rate of acute injury to the heart, kidneys, and liver and also the prevalence of secondary bacterial pneumonia were higher.

rgan systems in elderly patients with COVID-19

Pulmonary system complications

- SARS-CoV-2 interacts with the ACE2 receptor
Highly expressed in the alveoli, bronchial epithelium, and vascular endothelium
- The cytokine storm
- Senile emphysema and muscular
- Weakened respiratory/ decreased airway clearance and pulmonary reservation/ weaker immune system

Cardiovascular system complications

- The expression of ACE2 is relatively high
- Secondary to the impaired respiratory function and hypoxia
- Cardiotoxicity associated with antiviral therapies (sick sinus syndrome and Q-T interval prolongation or lead to torsade de pointes by interacting with other drugs)

Liver function impairment

- Direct effect of the virus on the hepatic cells
- Side effect of medications used in the treatment regimen
- Cytokine storm and hypoxia resulted from pneumonia
- The impaired liver function in mild cases of COVID-19 is usually transient and could be resolved without a sequela.
- Associated with impaired immune function, might cause serious consequences and increases the length of hospital stay, especially in elderly patients with multiple comorbidities.
- In the case of chronic liver disease, such as chronic hepatitis B or autoimmune disease, attention should be paid to a history of immunosuppression in patients with COVID19.
- Medications that have a hepatic mechanism (the inhibitory or activator effects)
- Polypharmacy
- Patients with a history of hepatic disease
- Drug interactions

Renal system complications

- The filtration rate is reduced by almost 10 mL/min each decade.
- Some degrees of renal dysfunction, which in turn increases the risk of drug toxicity and water and electrolyte disturbances.
- Adequate hemodynamic support and not using nephrotoxic drugs are of great importance to prevent elderly patients from renal impairment.
- The early renal replacement therapy might improve patients' prognosis in patients with renal dysfunction.
- Chloroquine and lopinavir/ritonavir, do not require dose adjustment based on the creatinine clearance.
- Some medications such as fluoroquinolone and cephalosporin require dose adjustment based on creatinine clearance.

Renal system complications

- Special attention should be paid to the polypharmacy and drug interactions.
- In patients with hypertension, due to the lack of data on the effect of calcium channel blockers on ACE2, changing ACE inhibitors to these drugs may be reasonable.

Skin disorders

- Secondary to repeated contacts with disinfectants, sanitizers, soaps, and detergents.
- This issue is more commonly referred to as contact dermatitis or exacerbation of previous xerosis and asteatotic eczema.
- In severe cases, it might lead to defects of the skin barrier and cause secondary conditions.
- Exacerbations of previous skin conditions, such as rosacea, eczema, atopic dermatitis, neurodermatitis.
- The emotional stress during the outbreak might exacerbate or result in emergence of herpes reactivation, zona, telogen effluvium, alopecia areata, and psychocutaneous disorders.
- The routine use of immunomodulators might increase the risk of developing COVID-19 or increase the risk of secondary and opportunistic infections.
- Drug reactions or interactions
- The long-term use of facial masks could also lead to facial acne and rosacea during the pandemic.

Diabetes and elderly patients with COVID-19

- In elderly patients with diabetes, regular exercise and also regular adjustment of the blood sugar, healthy eating habits, increased protein intake, and correcting the vitamins and minerals deficiencies strengthen the immune system

- Elderly patients should not be norm glycemic, but glucose should be targeted and treated based on the underlying disease, performance level, and age
- Insulin is the best controller for diabetes in bedridden patients
- Antihypertensive drugs that cause decreased water volume, such as thiazolidinediones, should be avoided.
- Attention should be paid to the hyperglycemic effects of corticosteroids.
- Special attention should also be paid to pigmentosa retinitis and the ocular side effects of hydroxychloroquine.

Special points

Long term care facilities

- Many of the facilities face many challenges, including insufficient equipment and staff, absence of standards for infection diagnosis, complex needs of residents, staff members who work at more than one facility, untrained workers, and enforcement of quarantine.
- Suspension or restriction on use of daycares
- Supplying Personal Protective Equipment
- Restricting visits
- Implementing a new detection tool
- Sites for positive cases
- Advocating hospitals on mass testing for all older people
- Putting restrictions on nursing home visitations
- The use of technologies to minimize human-to-human contact effectively prevented the spread of the virus in LTCFs
- Weekly telephone calls
- Frailty assessment using Clinical Frailty Scale (CFS), accurate morbidity and mortality reports, coordinated surveillance
- Rapid transfer of any suspected COVID-19 infection to a specialist center as soon as possible
- While waiting to be transported to the hospital, the patient should be placed in a single isolated room

- Wearing a mask (N95 or FFP2 for the patient and also the health care staff)
- Careful hand hygiene are critical preventive measures to limit the emission of the disease
- Health care personnel should also wear eye shields and use disposable gloves and gowns regularly to provide optimal levels of protection

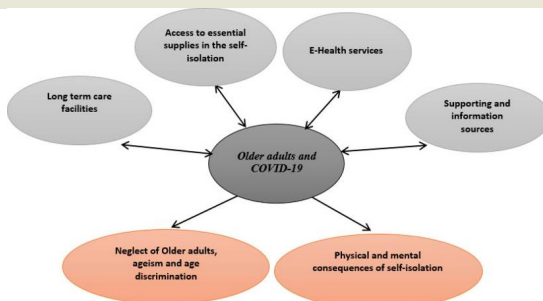
Social isolation

- Social distancing might force the elderly individuals to depression and anxiety.
- These individuals are also more vulnerable to cardiovascular problems, autoimmune diseases, neurocognitive disorders, and mental health issues.
- Elderly patients, especially those who have no close family and only rely on volunteer or social services, are more susceptible to mental isolation during the pandemic and quarantine.
- Online technologies
- Frequent phone calls by friends and relatives
- Cognitive Behavioral Therapy
- Access to essential supplies
- Increases the prevalence of loneliness, dementia, delirium and suicide, along with the changes in physical activity, drinking, and sleeping patterns.
- Fear of death is related to a weakened immune system defensive response and increased susceptibility to disease.
- Lack of access to regular medication

Neglect of Older adults, ageism and age discrimination in the COVID-19 crisis, there are a number of ways older adults who would like to assist the humanitarian efforts to fight the pandemic can participate in doing so.

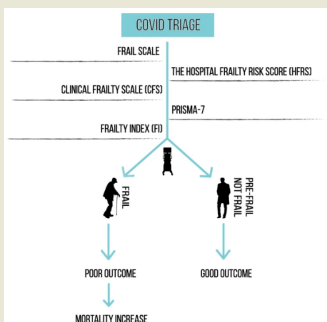
Recommendation

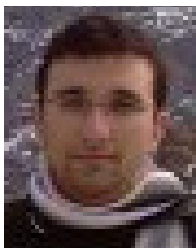
- Management of the possible comorbidities in addition to the antiviral therapy
- Prevention of drugs interaction, especially in the case of fluoroquinolones
- Precise adjustment of the dosage of the drugs based on creatinine clearance
- Prevention of the intubation or extubation as soon as possible
- Evaluation for secondary bacterial infections
- Repeated rehabilitation sessions
- Preventing the patients from delirium by mobilizing patients in the hospital as soon as possible



Frailty and COVID-19 vaccination

- Potential poor response to vaccines,
- It is predicted that older frail adults will be exposed to the same risk of infection or even, in the best case, a slightly lower risk than pre-vaccination.





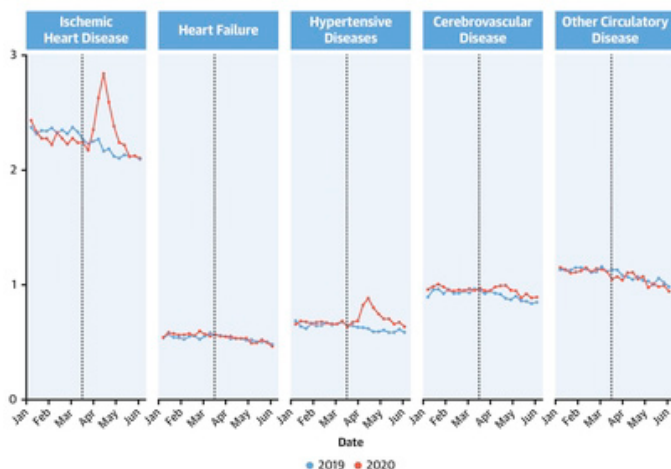
Dr. MJ Alemzadeh-Ansari

Associate professor

Rajaie Cardiovascular, Medical & Research Center

Prevalence and Mechanism

CENTRAL ILLUSTRATION: Weekly Death Rates by Cardiovascular Cause (per 100,000 Population) in the United States



Wadhera, R.K. et al. J Am Coll Cardiol. 2021;77(2):159-69.

There was an increase in deaths caused by ischemic heart disease and hypertensive diseases in some regions of the United States during the initial phase of the COVID-19 pandemic.

nature > nature reviews cardiology > review articles > article

MENU nature reviews cardiology

Review Article | Published: 20 July 2020

COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives

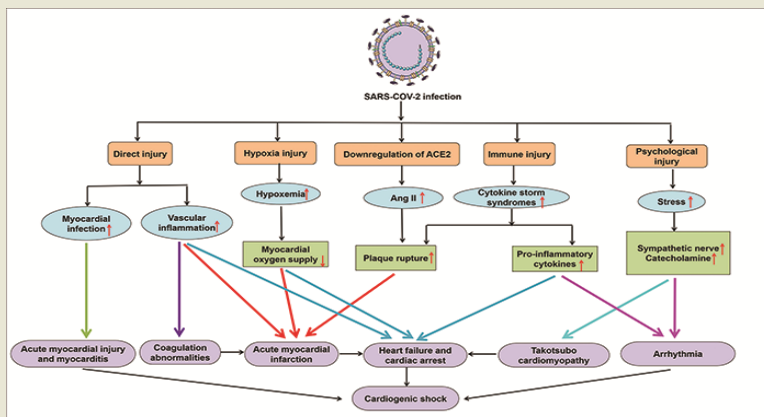
Masataka Nishiga, Dao Wen Wang, Yaling Han, David B. Lewis & Joseph C. Wu

Table 1 Prevalence of cardiovascular comorbidities in patients with COVID-19

From: COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives

| Country | Number of patients | Prevalence of comorbidity among all patients (among patients who were ventilated or in ICU) | | | | Ref. |
|---------|--------------------|---|--------------------------|--------------------------|-------------|------|
| | | Cardiovascular disease (%) | Hypertension (%) | Diabetes (%) | Obesity (%) | |
| China | 41 | 15 (23) | 15 (15) | 20 (8) | NR | 17 |
| China | 138 | 14.5 (25.0) | 31.2 (58.3) | 10.1 (22.2) | NR | 18 |
| China | 191 | 8 ^a (24) ^{a,b} | 30 (48) ^b | 19 (31) ^b | NR | 19 |
| China | 150 | 8.7 (19.1) ^b | 34.7 (42.6) ^b | 16.7 (17.8) ^b | NR | 22 |
| China | 1,099 | 2.5 ^a (5.8) ^a | 15.0 (23.7) | 7.4 (16.2) | NR | 20 |
| China | 44,672 | 4.2 (22.7) | 12.8 (39.7) | 5.3 (19.7) | NR | 21 |
| Italy | 1,591 | NR (21) | NR (49) | NR (17) | NR | 46 |
| USA | 393 | 13.7 ^a (19.2) ^a | 50.1 (53.8) | 25.2 (27.7) | 35.8 (43.4) | 47 |
| USA | 5,700 | 11.1 ^a (NR) | 56.6 (NR) | 33.8 (NR) | 41.7 (NR) | 51 |

Prevalence and Mechanism



Schematic diagram of the underlying mechanism of cardiovascular injury caused by SARS-CoV-2 infection

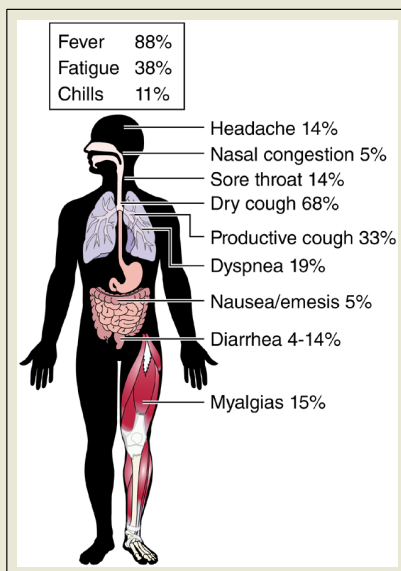
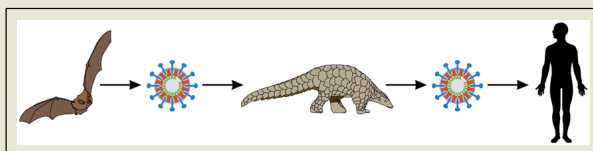


Figure 2. Symptoms of coronavirus disease 2019 (COVID-19).

Prevalence and Mechanism

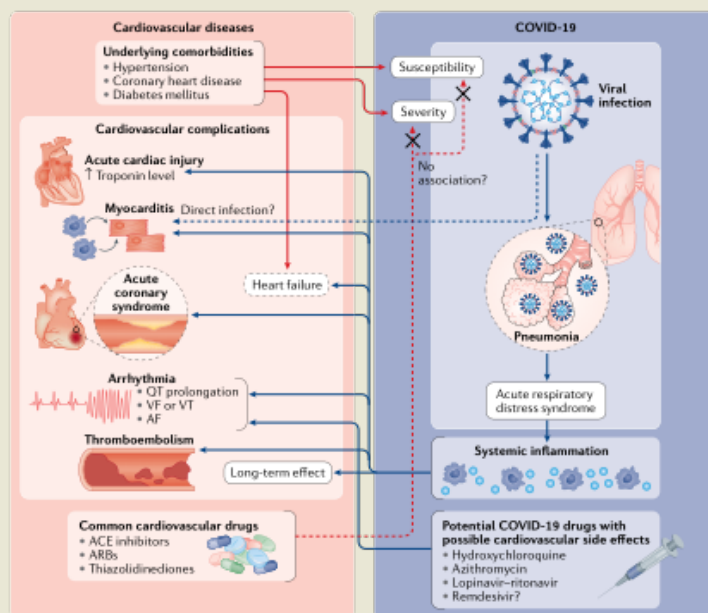


Fig. 2 | Bidirectional interaction between cardiovascular diseases and COVID-19. Cardiovascular comorbidities such

Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage

Bernhard Metzler^{1*}, Peter Siostrzonek², Ronald K. Binder³, Axel Bauer¹, and Sebastian Johannes Reinstadler¹

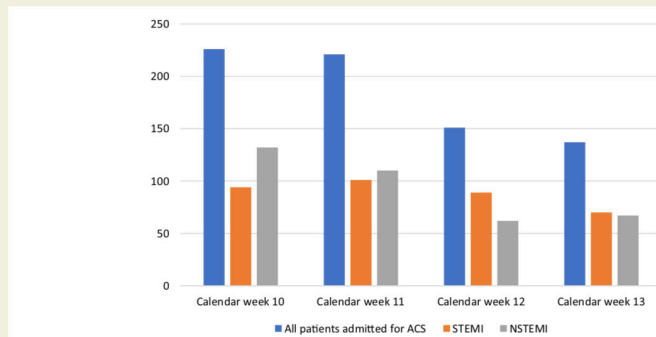


Figure 1 Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19. The absolute numbers of all ACS (blue bars), STEMI (orange bars), and NSTEMI (grey bars) admissions in Austria from calendar week 10 to calendar week 13 are shown. Abbreviations: STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction.

Comparing the first and last calendar week, there was a relative reduction of 39.4% in admissions for ACS.

Several factors might explain this important observation

- The rigorous public health measures, which are undoubtedly critical for controlling the COVID-19 pandemic, may unintentionally affect established integrated care systems.
- Amongst others, patient-related factors could mean that infarct-related symptoms such as chest discomfort and dyspnoea could be misinterpreted as being related to an acute respiratory infection.
- Moreover, the strict instructions to stay at home as well as the fear of infection in a medical facility may have further prevented patients with an ACS from going to a hospital.
- Our study does not provide data on mortality; however, considering the annual incidence of ACS in Austria ($200/100\ 000/\text{year} = 17\ 600/\text{year}$ in 8.8 million habitants)¹ and taking into consideration sudden cardiac deaths and silent infarctions (one-third), there will remain 1000 ACS cases a month.~
- The difference between the assumed number of ACS patients and the observed number in our study, i.e. 725 ACS patients in calendar weeks 10–13 is 275.

- According to these assumptions, 275 patients were not treated in March 2020.
- Based on data showing that the cardiovascular mortality of untreated ACS patients might be as high as 40% (as it was in the 1950s),
- we can theoretically estimate 110 ACS deaths during this time frame.
- Vs
- official number of COVID-related deaths in Austria was 86 on 29 March.

Clinical Research in Cardiology
<https://doi.org/10.1007/s00392-020-01705-x>

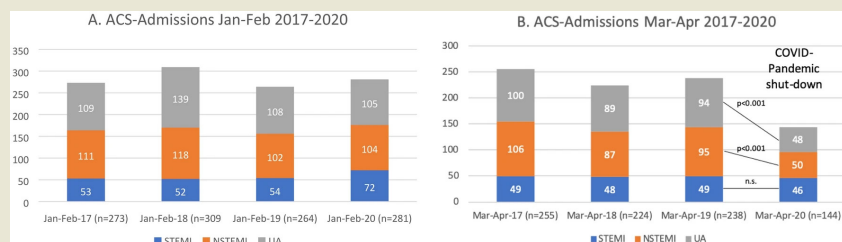
LETTER TO THE EDITORS



Collateral damage of COVID-19-lockdown in Germany: decline of NSTEMI-ACS admissions

A. K. Gitt¹ · A. K. Karcher¹ · R. Zahn¹ · U. Zeymer¹

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During the COVID-19 lockdown in Germany in March/April 2020, we observed:

- unchanged numbers for STEMI-admissions,
- but a significant 50% reduction in NSTEMI-ACS, in both UA and NSTEMI
- Possible explanations for this important observation might be system-related as well as patient-related.
- The acute presentation of STEMI with severe chest-pain probably still triggers the direct transportation to the cathlabs with no changes of admissions.
- Due to the attention to the plethora of possible symptoms of the SARS-CoV-2-infection described in the media, some patients may have mis-

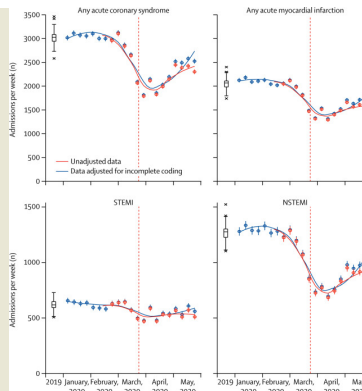
terpreted their NSTEMI-ACS symptoms such as dyspnea and chest pain as possible COVID-19-symptoms rather than as cardiovascular symptoms.

- As an early invasive treatment of NSTEMI-patients is associated with an improved outcome, we might face a higher mortality by non-treated ACS patients as a collateral damage of the COVID-19-era.

Articles

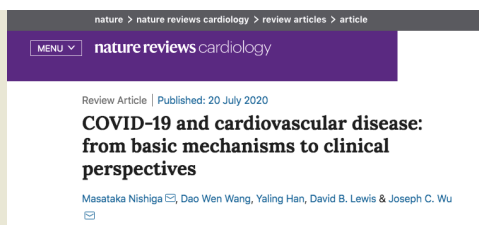
COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England

Marion A Mafham*, Enti Spata*, Raphael Goldacre*, Dominic Gair, Paula Curnow, Mark Bray, Sam Hollings, Chris Roebuck, Chris P Gale, Mamas A Mamas, John E Deanfield, Mark A de Belder, Thomas F Luescher, Tom Denwood, Martin J Landray, Jonathan R Emberson, Rory Collins, Eva J A Morris†, Barbara Casadei†, Colin Baigent†



- There was a 23% (95% CI 16–30) reduction in admissions for STEMI, and a
- reduction of 42% (38–46) in admissions for NSTEMI, from 2019 to the end of March, 2020.
- By the end of May, 2020, admission rates for acute coronary syndrome had partly recovered but remained about 16% below baseline levels.
- The partial recovery in admission rates by the end of May, 2020, suggests that the British Heart Foundation and British Cardiovascular Society publicity campaign in early April, 2020, in which people with heart attack

symptoms were encouraged to attend hospital, could have helped to allay such fears.



- Despite the potential for COVID-19 to induce ACS, the number of reported cases of ACS during the COVID-19 outbreak in Italy, Spain and the USA was actually significantly lower than during pre-COVID-19 periods, with a reported 42–48% reduction in hospitalizations for ACS and a 38–40% reduction in PCI for STEMI.

- By contrast, the incidence of out-of-hospital cardiac arrest increased during the COVID-19 outbreak in Italy, which was strongly associated with the cumulative incidence of COVID-19.

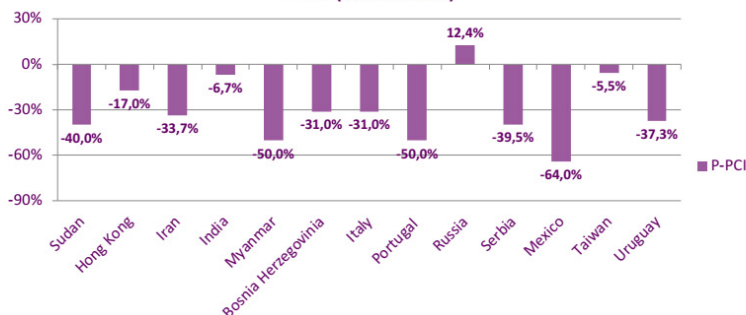
- This observation is in accordance with the finding that the number of patients with myocardial infarction seeking urgent hospital care declined by >50% during the peak of the COVID-19 outbreak, as reported in an extensive global survey by the ESC

Stent Save a Life Survey



Primary PCI

P-PCI (2020 vs 2019)



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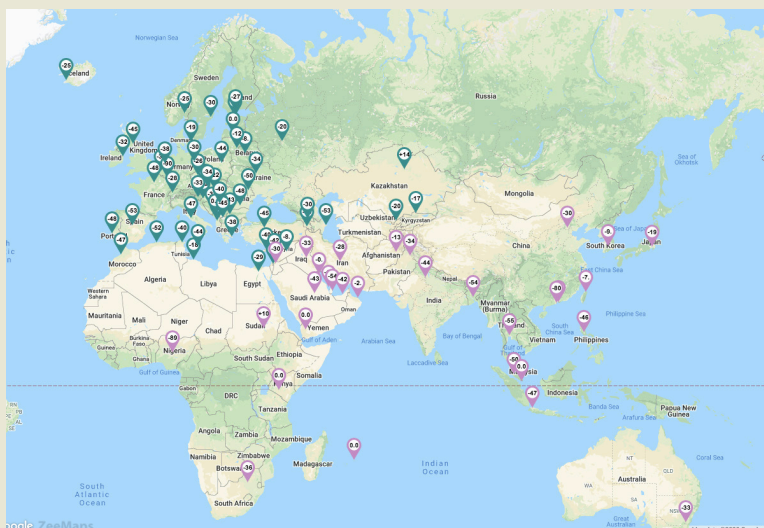
European Society of Cardiology > Education > COVID-19 and Cardiology

**COVID-19 and
Cardiology**

STEMI admissions during COVID-19

An ESC survey on ST-elevation myocardial infarction (STEMI) admissions during the pandemic

29 May 2020



STEMI Management

Management of patients with stemi during covid-19

- The maximum delay from STEMI diagnosis to reperfusion of 120 minutes should remain the goal for reperfusion therapy under the following considerations:
- Primary PCI remains the reperfusion therapy of choice if feasible within this time frame and performed in facilities approved for the treatment of COVID-19 patients in a safe manner for healthcare providers and other patients;
- Primary PCI pathways may be delayed during the pandemic (up to 60 minutes – according to multiples experiences) due to delays in the deliv-

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ery of care and the implementation of protective measures;

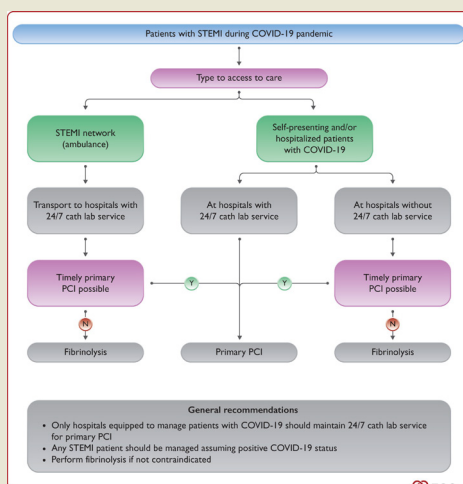
- If the target time cannot be met and fibrinolysis is not contraindicated, fibrinolysis should then become first line therapy;

- As SARS-CoV-2 test results are not immediately available in STEMI patients, any STEMI patient should be considered potentially infected;

- All STEMI patients should undergo testing for SARS-CoV-2 as soon as possible following first medical contact irrespective of reperfusion strategy, at the latest upon admission to the ICU post primary PCI. Until the result of the test is known, all precautionary measures should be taken to avoid potential infection of other patients and HCP;

- Consider immediate complete revascularization if indicated and appropriate in order to avoid staged procedures and reduce hospital stay;

All physicians involved in the management of patients with STEMI should be familiar with indications, contraindications and dosage of fibrinolysis and adhere to established administration protocols



Management of patients with stemi during covid-19

Received: 24 March 2020 | Accepted: 25 March 2020
DOI: 10.1002/ccd.28889

CORE CURRICULUM

WILEY

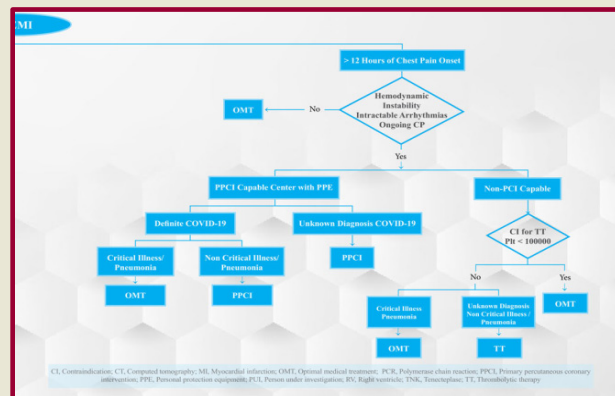
Management of ST-segment-elevation myocardial infarction during the coronavirus disease 2019 (COVID-19) outbreak: Iranian "247" National Committee's position paper on primary percutaneous coronary intervention

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- Prasugrel is not associated with significant interactions, but it predisposes patients to bleeding.

- As these patients are at higher risk of bleeding, in particular in severe cases, Clopidogrel can again be introduced as the preferred agent

- In regard to statins, Atorvastatin and Rosuvastatin need to be dose-adjusted in patients on Lopinavir/Ritonavir.

The maximum recommended dose for these agents is 20 and 10 mg, respectively

- Regarding ACEIs/ARBs, it is recommended that they be prescribed and continued in this population.

NSTE-ACS Management

Biomarker Elevation Suggesting Cardiovascular Conditions in Patients with COVID-19 Infection

- Mild elevations in cardiac troponin T/I concentrations (e.g. < 2–3 times the ULN), particularly in an older patient with pre-existing cardiac disease, do NOT require work-up or treatment for T1MI, unless strongly suggested by angina chest pain and/or ECG changes.

- Such mild elevations are in general well explained by the combination of possible pre-existing cardiac disease AND/OR the acute injury related to COVID-19.

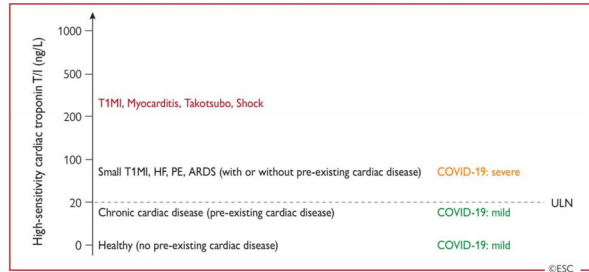
- Marked elevations in cardiac troponin T/I concentrations (e.g. > 5 times the ULN) may indicate the presence of shock as part of COVID-19, severe respiratory failure, tachycardia, systemic hypoxaemia, myocarditis, Takotsubo syndrome or T1MI triggered by COVID-19.

- In the absence of symptoms or ECG changes suggestive of T1MI, echocardiography should be considered in order to diagnose the underlying cause.

- Patients with symptoms and ECG changes suggestive of T1MI should be treated according to ESC-guidelines irrespective of COVID-19 status.

Figure 11 High-sensitivity cardiac troponin (hs-cTn) T/I concentrations should be interpreted as quantitative variables.

In non-critically-ill patients with COVID-19, mild elevations (e.g. up to 3-times the ULN) elevations are in general well explained by the combination of possible prior cardiac disease AND the acute cardiomyocyte injury related to COVID-19. Even higher concentrations indicate the presence of specific acute cardiac disease such as T1MI, myocarditis, or takotsubo syndrome. ULN denotes upper limit of normal and is assay-specific, HF denotes heart failure, PE denotes pulmonary embolism, ARDS denotes acquired respiratory distress syndrome, T1MI indicates type 1 myocardial infarction.



Potential Mechanisms Underlying the Biomarker Elevation

- The potential mechanisms underlying myocardial injury in those with COVID-19 infection are not fully understood:

- 1- Myocarditis,
- 2- septic shock,
- 3- tachycardia,
- 4- severe respiratory failure,
- 5- systemic hypoxaemia,
- 6- Takotsubo syndrome or
- 7- T1MI triggered by COVID-19

- As quantitative biomarkers of haemodynamic myocardial stress and HF, intracardiac filling pressures and end-diastolic wall stress seem to be the predominant triggers of the release of BNP/NT-proBNP

Non-Invasive Imaging

Key points:

- Do not perform routine cardiac imaging in patients with suspected or confirmed COVID-19;
- Prevent contamination from patients to other patients, to imagers and imaging equipment;

- Perform imaging studies in patients with suspected or confirmed COVID-19 only if the
- management is likely to be impacted by imaging results;
- Re-evaluate which imaging technique is best for your patients both in terms of diagnostic yield
- and infectious risk for the environment;
- The imaging protocols should be kept as short as possible.

Table 6 Non-invasive cardiovascular stress testing and imaging tests with the potential for deferral in the light of the COVID pandemic (Reproduced from Gluckman et al.¹²⁷)

- Stress testing (ECG alone or with imaging [echocardiography, radionuclide, MRI]) for suspected stable ischaemic heart disease (outpatient and inpatient)
- Cardiopulmonary exercise testing for functional assessment (outpatient and inpatient)
- Transthoracic echocardiograms (outpatient)
- Transoesophageal echocardiograms in stable patients (outpatient and inpatient)
- Cardiovascular CT (outpatient)
- Cardiovascular magnetic resonance imaging (MRI) (outpatient)
- Nuclear cardiac imaging (SPECT and PET) (outpatient and inpatient)
- Vascular imaging for asymptomatic carotid artery disease (outpatient and inpatient)
- Vascular imaging for claudication (outpatient and inpatient)
- Imaging for screening purposes (e.g., coronary calcium score, screening ultrasound to assess for an AAA or carotid disease) (outpatient and inpatient)

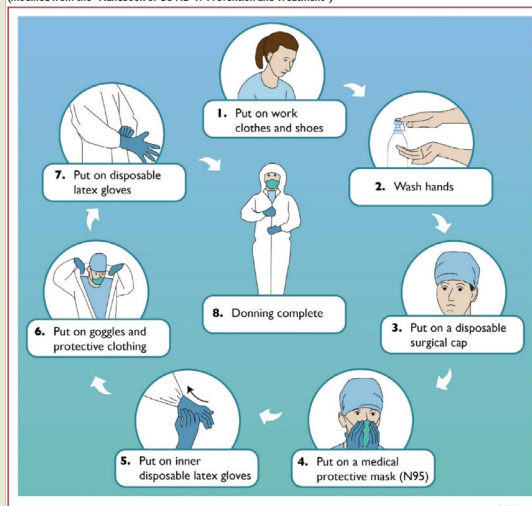
AAA = abdominal aortic aneurism; CT = computed tomography;
ECG = electrocardiogram, MRI = magnetic resonance imaging;
PET = positron emission tomography; SPECT = single photon emission computed tomography.

Transthoracic and Transesophageal Echocardiography

- Key points

- Avoid performing transthoracic, transesophageal and stress echocardiograms in patients in which test results are unlikely to change the management strategy;
 - TEE carries increased risks of spread of COVID-19 due to exposure of HCP to aerosolization of large viral load and should not be performed if an alternative imaging modality is available;
 - In COVID-19 infected patients, the echocardiogram should be performed focusing solely on the acquisition of images needed to answer the clinical question in order to reduce patient contact with the machine and the HCP performing the test;
 - POCUS, focused cardiac ultrasound study (FoCUS) and critical care echocardiography performed at bedside are effective options to screen for CV complications of COVID- 19 infection.
-
- Echocardiography can be performed bedside to screen for CV complications and guide treatment.
 - POCUS, FoCUS and critical care echocardiography are probably the preferred modalities to image patients with COVID-19.
 - Limited evidence exists for the use of lung ultrasound to differentiate ARDS (single and/or confluent vertical artefacts, small white lung regions) from HF.
 - The presence of dilated right ventricle and pulmonary hypertension may indicate contrast CT to rule out PE. In COVID-19 infected patients, echocardiography should focus solely on the acquisition of images needed to answer the clinical question in order to reduce patient contact with the machine and HCP.
 - It should not be forgotten that the risk of infection remains in the reading rooms and therefore the material used should be also frequently sanitized.

Figure 5 Guidance on donning personal protective equipment (PPE) to manage COVID-19 patients (modified from the "Handbook of COVID-19 Prevention and Treatment")



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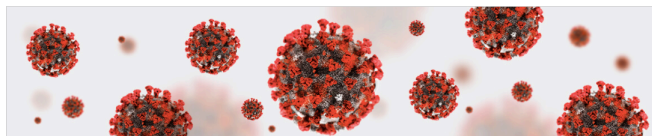
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Last updated on 22 July 2020



The ESC is a vast, diverse community. We learn from each other so that we can give our patients the best possible care. Never has this been more important than during a pandemic. This page is designed to provide you with an array of useful resources, updated regularly.

You have a mission. We're here to help.

ESC Guidance for Diagnosis and Management of CVD during the COVID-19 Pandemic *Updated*

- Patients should be categorized into 4 risk groups (i.e. very high risk, high risk, intermediate risk, and low risk) and managed accordingly.
- Patients with Troponin rise and no acute clinical signs of instability (ECG changes, recurrence of pain) might be managed with a primarily conservative approach.
- Non-invasive imaging using CCTA may speed-up risk stratification, avoid an invasive approach allowing early discharge.
- For patients at high risk, medical strategy aims at stabilization whilst planning an early (< 24 hours) invasive strategy.

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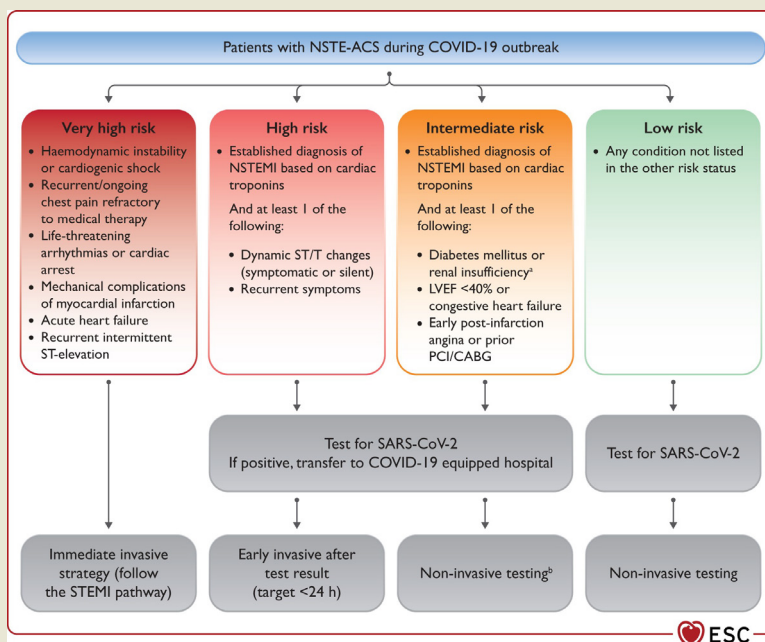
- The time of the invasive strategy may however be longer than 24 hours according to the timing of testing results.
- If feasible, a dedicated area to manage these patients while waiting for the test result should be arranged in the emergency department.
- In the case of positive SARS-CoV-2 test, patients should be transferred for invasive management to a COVID-19 hospital equipped to manage COVID-19-positive patients.

- Patients at intermediate risk should be carefully evaluated taking into consideration alternative diagnoses to T1MI, such as Type II MI, myocarditis, or myocardial injury due to respiratory distress or multiorgan failure or Takotsubo.

- In the event any of the differential diagnoses seem plausible, a non invasive strategy should be considered and CCTA should be favored, if equipment and expertise are available.

- When there is a positive SARS-CoV-2 test, patients should be transferred for invasive management to a COVID-19 hospital equipped to manage COVID-19-positive patients.

- At times of high demand on the infrastructure and reduced availability of catheterization laboratories or operators, non-invasive conservative management might be considered with early discharge from the hospital and planned clinical follow-up.

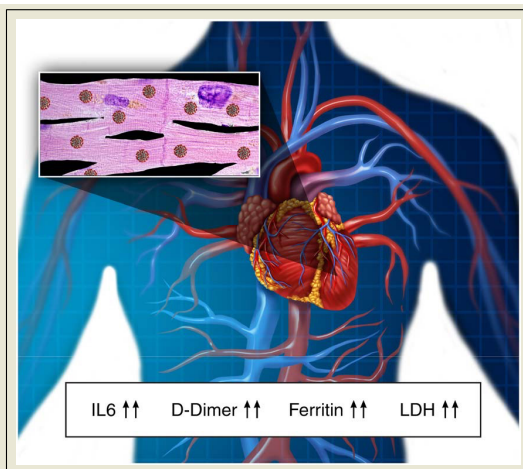


COVID-19 AND MYOCARDIAL INJURY

- Myocardial injury, evidenced by elevated cardiac biomarkers, was recognized among early cases in China.
- (elevated high-sensitivity cardiac troponin I [hs-cTnI] or new ECG or echocardiographic abnormalities) was present in 7.2% of patients overall and 22% of patients who required ICU care.
- The report from the National Health Commission of China reported that almost 12% of patients without known CVD had elevated troponin levels or cardiac arrest during hospitalization.
- Notably, hs-cTnI was >99th percentile upper reference limit in 46% of non-survivors as opposed to 1% of survivors.

2 mechanism:

- **Direct myocardial involvement mediated by ACE2.**
 - A murine model demonstrated pulmonary infection with SARS-CoV also precipitated an ACE2 - dependent myocardial infection.
 - Among humans, during the Toronto SARS outbreak, SARS-CoV viral RNA was detected in 35% of autopsied hearts.
- Other suggested mechanisms of COVID-19-related cardiac involvement include a cytokine storm, mediated by an imbalanced response among subtypes of T helper cells, and hypoxia-induced excessive intracellular calcium leading to cardiac myocyte apoptosis.



2 mechanisms:

- Myocardial injury can result from the associated cytokine storm manifested by elevated levels of interleukin-6 (IL-6), ferritin, lactate dehydro- genase (LDH), and D-dimer (stress cardiomyopathy)
- Myocardial dysfunction from the direct ef-

fect of severe acute respiratory syndrome coronavirus 2 on the heart (potentially viral myocarditis mediated by ACE2).

For example,

- 1 case recently published described a man presenting with chest pain and STEMI on his ECG, but without coronary obstruction.
- An echo: LVEF: 27%, LVEDD: 5.8 cm
- elevated cardiac biomarkers (troponin T >10 ng/mL, NT-proBNP [N-terminal pro-BNP] >21 000 pg/ mL).
- 24 After a therapeutic approach that included IVIg and steroids, ejection fraction and cardiac biomarkers normalized within 3 weeks.

For example,

- a 63-year-old man with no cardiac history
- presented with both severe respiratory manifestation and evidence of fulminant myocarditis
- with an LVE (LVEDD: 6.1 cm) and LVEF: 32%
- The patient had an elevated troponin I (>11 ng/mL) and NT-proBNP (>22 000 pg/mL).
- Given the severity of his cardiogenic shock, he was placed on:
- extracorporeal membrane oxygenation
- IVIg
- steroids,
- antiviral therapy, and
- renal replacement therapy.
- The patient ultimately showed recovery of his LVEF within 2 weeks.
- Both of these patients were treated with glucocorticoids but the impact of this therapy is unclear.
- The World Health Organization and Centers for Disease Control and Prevention do not recommend glucocorticoid use unless indicated otherwise (eg, chronic obstructive pulmonary disease or asthma exacerbation).

Heart failure and cardiac arrest

- Virus infection is an important cause of aggravating heart failure or inducing acute heart failure.
- Previous reports have suggested that SARS-CoV and MERS-CoV infection can cause or aggravate heart failure.
- the possibility of right heart failure and associated pulmonary hypertension should be considered.
- Lung involvement in patients with COVID-19 can cause ventilation-perfusion mismatch and a decrease in pulmonary vascular beds.

Then, microvascular occlusion and reduced functional residual capacity increase pulmonary vascular resistance, resulting in pulmonary hypertension and right heart failure.

- In order to reduce case fatality rate, it is necessary to attach great importance to the treatment and prevention of heart failure in patients with COVID-19.

Arrhythmia

- Arrhythmias are common cardiac manifestations described in COVID-19 patients.

Heart palpitations were also reported to be one of the initial symptoms in some patients with COVID-19.

- However, the types of arrhythmia and specific ECG changes in COVID-19 patients have not been published or presented.
- Of note, arrhythmia can occur in patients with COVID-19, but the manifestations related to arrhythmia may be masked by respiratory symptoms.
- Therefore, patients with severe COVID-19 should be closely monitored for paroxysmal tachycardia or increased pulse rate that does not match the disease status.

Takotsubo cardiomyopathy

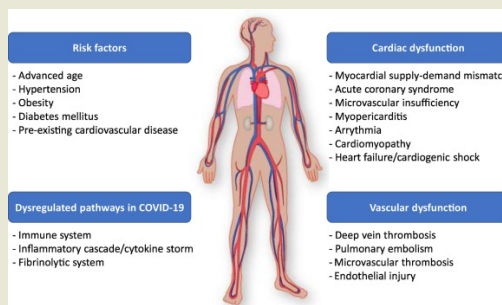
- Takotsubo cardiomyopathy, also called stress-induced cardiomyopathy, is a clinical syndrome characterized by acute and transient regional left ventricular systolic dysfunction usually triggered by physical or emotional stressors including infections.
- The COVID-19 pandemic has caused an unprecedented health crisis, leading to anxiety, distress, and fear, with emerging cardiovascular im-

plications.

- Several studies have noted the occurrence of Takotsubo cardiomyopathy in patients infected with COVID-19.
- Thus, the current pandemic scenario of COVID-19 may represent an important trigger for Takotsubo cardiomyopathy, not only due to the respiratory infection, but by the profound psychological and emotional stress caused by the isolation period resulting in an excessive release of catecholamines.

Coagulation abnormalities

- Patients with COVID-19 are more likely to have an elevated risk of arterial and venous thromboembolism due to a state of endothelial dysfunction, vascular inflammation, and hypercoagulability associated with SARS-CoV-2 infection.
- Abnormal coagulation parameters, such as prothrombin time, fibrin degradation products, activated partial thromboplastin time, and D-dimer, were noted in patients with COVID-19.
- In particular, increased levels of fibrin degradation products and D-dimer were suggested to be closely associated with poor prognosis.
- These studies suggest that a substantial proportion of patients with COVID-19 have coagulation abnormalities, which may contribute to the development of multiple cardiovascular manifestations of COVID-19.
- Pulmonary thromboembolism (PTE) is frequently observed in patients with COVID-19, mainly involving the:
 - segmental (90.2%) and
 - subsegmental arteries (61.0%) of pulmonary segments
 - affected by a consolidation pattern (67.6%).



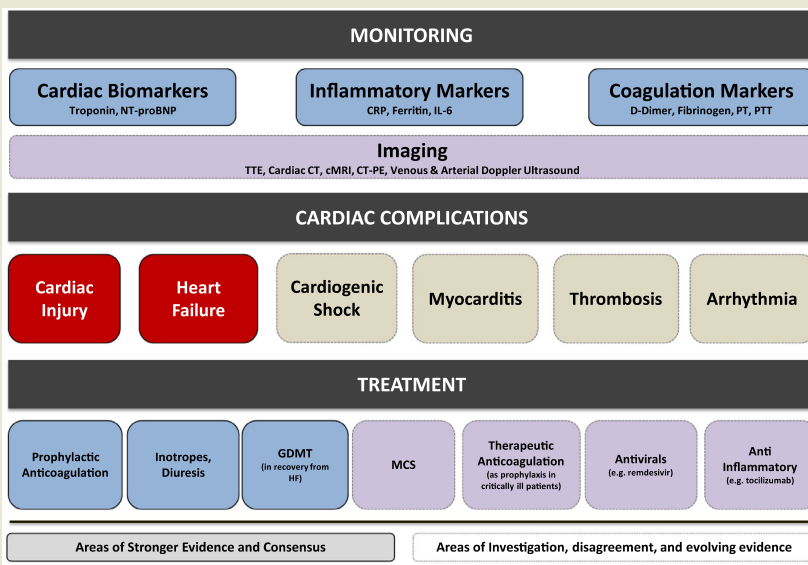


Table 7 Potential interactions of drugs to treat COVID-19^a

| Drugs used to treat COVID-19 | Interactions | Action |
|-----------------------------------|---------------------------------------|-------------------|
| Dexamethasone | Warfarin | Monitor INR |
| Methylprednisolone | Warfarin | Monitor INR |
| Antiretroviral drugs | Antiarrhythmics | Use QT prolongin |
| | NOACs | Avoid apixaban a |
| | Statins | Start with low-do |
| | Warfarin | Monitor INR |
| Colchicine | Statins | Consider reducin |
| | CYP3A4 inhibitor | Consider reducin |
| Chloroquine or hydroxychloroquine | Beta-blockers and QT prolonging drugs | Monitor ECG |

COVID-19, coronavirus disease 2019; ECG, electrocardiogram; INR, international normalized ratio; NOACs, non-vitamin K antagonist oral anticoagulants.

^a These medications will be administered during hospital admission.

Cardiovascular disease and COVID vaccine



- Patients with CV risk factors and disease are at variable risk for adverse outcomes in COVID-19 based on the severity of their comorbidities.
- Patients with more advanced CVD are at higher risk compared with those with well-controlled CV conditions.
- For example, those patients with poorly controlled hypertension, insulin-dependent diabetes, or diabetes with microvascular and/or macrovascular complications as a result of poor glycemic control should be considered higher risk compared with patients who are medically optimized.
- Similarly, patients with morbid obesity should be considered higher risk compared with patients who are overweight.
- Patients with high-risk or symptomatic ASCVD, including CAD or PAD, should be considered at higher risk compared with patients with asymptomatic or fully revascularized disease.
- In patients with a history of cardiac dysrhythmia, those with poorly controlled or poorly tolerated AF/flutter should be considered at higher risk.
- Furthermore, those patients with a history of VT or VF previously requiring ICD therapy and/or longitudinal treatment with an antiarrhythmic medication should be considered at higher risk as well.
- Among patients with heart failure, those with worse functional status (i.e., New York Heart Association class III/IV) and those requiring recent hospitalization or an urgent visit for worsening heart failure should be considered higher risk compared with those patients who are well-compensated on medical therapy and infrequently hospitalized.

- Patients with heart failure who are being considered for or are already listed for a heart transplant should be considered at especially high risk, given their advanced, decompensated disease.
- Additionally, patients with a history of a heart transplant should be considered higher risk, given their immunosuppressed status, especially those in the immediate postoperative state and at the highest intensity of immunosuppression.
- Although there are less data in the PH population, patients with moderate-severe PH should be considered higher risk, especially those who are decompensated and being considered or listed for lung transplant.
- Patients with ACHD with advanced physiological stage, indicating more advanced disease, should be prioritized.

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- Patients with ACHD with advanced physiological stage, indicating more advanced disease, should be prioritized.

Cardiovascular diseases and related conditions that can increase the risk of severe illness for COVID-19

- Any acute cardiovascular diseases that require urgent treatment in the hospital in the last 6 months.
- Pulmonary hypertension – a condition of increased blood pressure within the arteries of the lungs
- Congenital heart disease in adult patients presented with heart failure symptoms
- Coronary artery disease with uncontrolled chest pain or angina
- Advanced heart failure or patient underwent a heart transplant
- Severe obesity (with body mass index greater than 35 kg/m²)
- Patients with at least 2 comorbidities or risk factors contributing cardiovascular diseases which fall out of desired ranges, such as uncontrolled diabetes and hypertension.
- Patients with comorbidities and uncontrolled type 1 diabetes (insulin dependent diabetes)

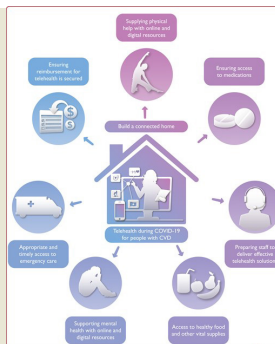
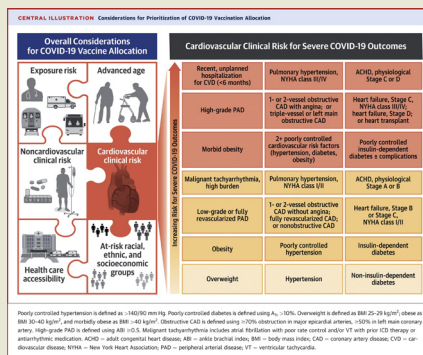
Key advantages of COVID-19 vaccines in patients with cardiovascular disease

- Patients with cardiovascular diseases should be vaccinated instantly once their symptoms are under control.
- After vaccination, the immune system is activated to produce immunity to protect the body against infections.
- Benefits of COVID-19 vaccines include:
 - Killing the virus if the immunity is boosted adequately.
 - Suppression of viral replication in the body, causing inability of the virus to continue growing and multiplying.
 - Prevention of viral integration into cells and minimizing the risk of infection.
 - Prevention of disease transmission to others since viral replication in the body can no longer continue.

- Once herd immunity is achieved, SARS-CoV-2 virus cannot further multiply. Thus, besides halting viral mutations, COVID-19 vaccination is an important tool to help ending this global pandemic.



ACC Health Policy Statement on Cardiovascular Disease Considerations for COVID-19 Vaccine Prioritization





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The Kidney and COVID-19 Infection

Hematuria

- A 10-year-old Caucasian female child, previously healthy, was admitted to the emergency department with a one-day history of fever (38°C), mild respiratory symptoms (cough and sore throat) and gross hematuria.

- Her physical examination was unremarkable.

- Urinalysis showed the presence of normally shaped red blood cells and renal ultrasound showed no abnormalities. Renal function was normal.

- All nasopharyngeal swabs specimens were positive for the detection of SARS-CoV-2 RNA and negative for all other respiratory viruses.

- Hematuria and renal injury have been commonly described in viral respiratory infections including influenza A and B, adenovirus and other pathogens.

- Cheng et al. reported hematuria in 26.7% of the patients.

- Another study involving 193 patients with COVID-19 infection has reported that, at hospital admission, 59% of the patients had proteinuria, 44% hematuria.

- Both proteinuria and hematuria are strongly associated with an increased hospital mortality.

- In particular, the authors have shown that, at univariate analysis the presence of proteinuria was associated with a 4 up to 11-fold increased risk of in-hospital death compared with COVID-19 patients without kidney damage, whereas hematuria increased the risk of death by 12 times.

- Microhematuria observed in some positive COVID-19 patients may be manifestations of renal infarction.

Proteinuria

- > 40% of cases have proteinuria at hospital admission and > 60% of cases have proteinuria during hospitalization.

- Cheng et al. have shown that among 710 consecutively hospitalized patients with COVID-19, 44% had proteinuria.

Greater incidence of proteinuria are demonstrated in patients with severe or critically ill COVID-19 pneumonia (81.2% and 85.7%, respectively, versus 43.8%).

Proteinuria (Case Report)

- We had a 65-year-old man who tested positive for SARS-COV-2 infection and onset of nephrotic syndrome, without antecedent of kidney disease and who had normal urine tests shortly before being affected by COVID-19.
- He had a moderate COVID-19 pneumonia.
- CANCA is positive. Pathological findings indicate a RPGN pattern.
- He was responded to pulse of steroid and cyclophosphamide.

KIDNEY DISEASES UKD

Newly Diagnosed Glomerulonephritis During COVID-19 Infection Undergoing Immunosuppression Therapy, a Case Report

Firouzeh Moeinzadeh,^{1,2} Majid Dezfouli,² Azar Naimi,³ Shahrzad Shahidi,^{1,2} Hazhir Moradi^{1,4}

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Keywords: COVID-19, glomerulonephritis, immunosuppression

During the COVID-19 pandemic, we had a 25 years old male case without any underlying disease or history of autoimmune disease in COVID-19 Clinic, Isfahan, Iran. He presented with arthralgia and weakness so we started COVID-19 therapeutic regimen. In his hospitalization, creatinine increases and abnormalities in random urine sediment was seen. Methylprednisolone and cyclophosphamide were prescribed due to suspected glomerulonephritis. After renal biopsy the diagnose was confirmed as crescentic proliferative glomerulonephritis. The patient also, underwent plasmapheresis and intravenous immunoglobulin injection. He was discharged healthy without development of new pulmonary symptoms despite immunosuppressive treatment.

IJKD-2020.14.239-42
www.ijkd.org

Hypokalemia

- The high prevalence of hypokalemia among patients with COVID-19 suggests the presence of disordered rennin-angiotensin system activity, which increases as a result of reduced counteractivity of angiotensin-converting enzyme 2, which is bound by severe acute respiratory syndrome coronavirus 2.

Causes of Hypokalemia

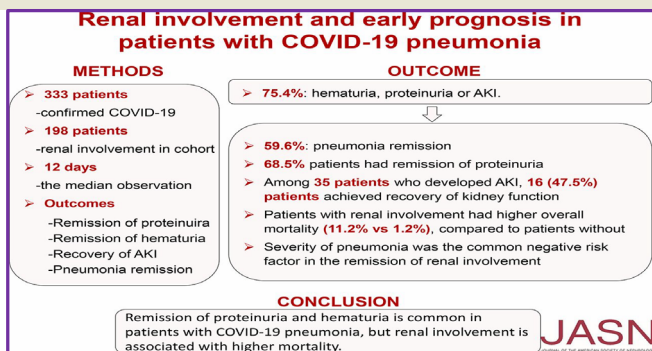
- Activation of the renin-angiotensin system (Kaliuresis)
- Loss of potassium through the gut
- Loss of appetite and poor diet due to the infection
- Kidney damage, perhaps due to direct viral cytotoxicity on tubular cells
- Drugs

Hypokalemia

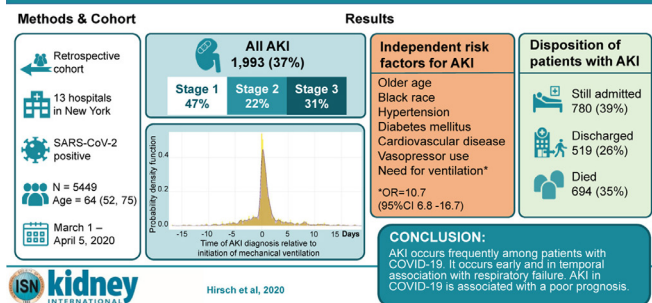
- Hypokalemia is an independent predictor of invasive mechanical ventilation requirement and seems to be a sensitive biomarker of severe progression of COVID-19.

- Increased release of ADH because of gastrointestinal fluid losses (diarrhea, vomiting) or low oral fluid intake

SIADH induced by pneumonia, respiratory insufficiency or probably as a result of the marked elevation of inflammatory cytokines (Interleukin-6).



Acute kidney injury (AKI) in patients hospitalized with COVID-19



AKI

- Acute kidney injury (AKI) is common among critically ill patients with COVID-19, affecting approximately 20–40% of patients admitted to ICU.

AKI

- Around 20% of patients admitted to an intensive care unit (ICU) with COVID-19 require renal replacement therapy (RRT) at a median of 15 days from illness onset.

AKI in 997 COVID-19 patients in Baqiyatallah Hospital

| FACTORS | STRATA | Total (N=997) N (%) | AKI - N (row %) | | p-value |
|---------------|---------------|---------------------------|----------------------|-----------------------|---------|
| | | | NO (N=712; 71.5%) | YES (N=285; 28.5%) | |
| COVID-19 | Moderate | 625 (62.7) | 483 (77.3) | 142 (22.7) | <0.001 |
| | Severe | 372 (37.3) | 229 (61.6) | 143 (38.4) | |
| LOS (days) | Mean \pm SD | 8.80 \pm 4.35 | 7.84 \pm 3.35 | 11.19 \pm 5.52 | <0.001 |
| Age (years) | Mean \pm SD | 56.6 \pm 14.7 | 55.0 \pm 14.7 | 60.8 \pm 13.9 | <0.001 |
| ICU Admission | No | 667 (66.9) | 532 (79.8) | 135 (20.2) | <0.001 |
| | Yes | 330 (33.1) | 180 (54.6) | 150 (45.5) | |
| Diabetes | No | 504 (50.6) | 415 (82.3) | 89 (17.7) | <0.001 |
| | Yes | 493 (49.5) | 297 (60.2) | 196 (39.8) | |

Table 1. Potential causes of AKI in COVID-19 patients.

| Renal | Non-renal |
|---------------------------------------|--|
| Direct renal parenchymal infection | Rhabdomyolysis-associated pigment nephropathy |
| Acute tubular injury | Cytokine release syndrome |
| Podocyte injury | Sepsis-associated multi-organ failure |
| Fibrin thrombus or fibrinoid necrosis | Nephrotoxicity related to diagnostic and therapeutic interventions |
| | Cardiorenal syndrome—heart-kidney crosstalk and lung-kidney axis |

Pathophysiology of AKI in COVID-19

Multifactorial

Predisposing factors: sepsis, hypovolemia, and nephrotoxins

Cardiorenal syndrome, particularly right ventricular failure secondary to COVID-19 pneumonia, might lead to kidney congestion and subsequent AKI.

Left ventricular dysfunction might lead to low cardiac output, arterial underfilling, and kidney hypoperfusion.

Pathophysiology of AKI in COVID-19

- SARS-CoV-2 can directly infect the renal tubular epithelium and podocytes through an angiotensin converting enzyme 2 (ACE2)-dependent pathway and cause mitochondrial dysfunction, acute tubular necrosis, the formation of protein reabsorption vacuoles, collapsing glomerulopathy, and protein leakage in Bowman's capsule.

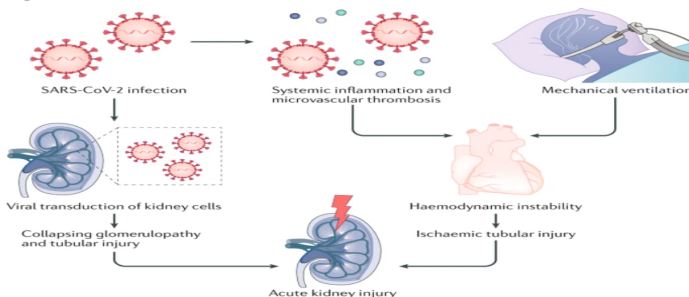
Pathophysiology of AKI in COVID-19

- Another potential mechanism of AKI involves SARS-CoV-2-related immune response dysregulation, as indicated by observed lymphopenia and cytokine release syndrome (cytokine storm).

Pathophysiology of AKI in COVID-19

- Other contributors to AKI might include rhabdomyolysis, macrophage activation syndrome, and the development of microemboli and microthrombi in the context of hypercoagulability and endotheliitis.

Fig. 1: Potential mechanisms of AKI in COVID-19.



SARS-CoV-2 may transduce podocytes, possibly leading to collapsing glomerulopathy. Alternatively, tubular epithelial transduction could lead to tubular injury and acute kidney injury (AKI). SARS-CoV-2 infection of lung parenchyma leads to systemic inflammation and microvascular thrombosis, contributing to haemodynamic instability. Peri-intubation hypotension may worsen kidney perfusion, leading to ischaemic tubular injury and AKI.

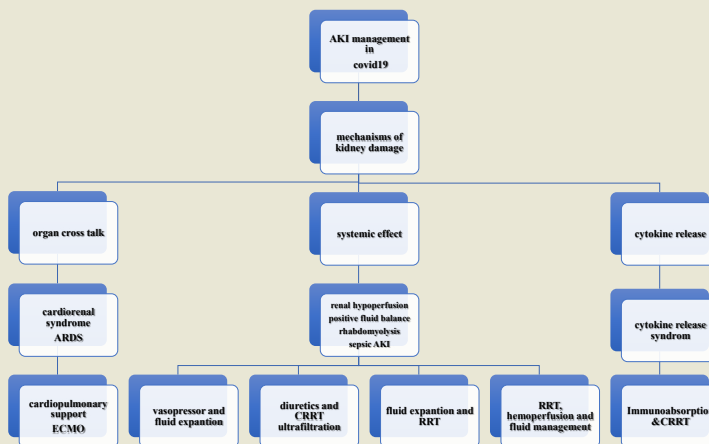
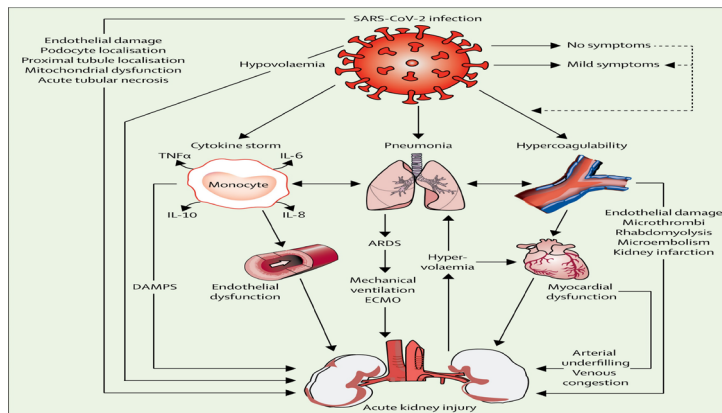


Table 2. Antiviral drugs used in COVID-19.

| Drug | Renal dose adjustment | Renal side effect | Additional feature |
|---------------------|-------------------------------|--|---|
| Azithromycin | Careful use if GFR <10 ml/min | Rarely AKI, interstitial nephritis | HD: No dose adjustment or supplemental dose necessary PD: No dose adjustment or supplemental dose necessary CRRT: No dose adjustment or supplemental dose necessary |
| Favipiravir | No valid data | No valid data | Renal clearance No valid data for HD, PD or CRRT |
| Hydroxychloroquine | None | Risk of renal insufficiency in chronic use | Cannot be removed by dialysis HD: No dose adjustment (expert opinion) PD: No dose adjustment (expert opinion) CRRT: No dose adjustment (expert opinion) |
| Lopinavir/Ritonavir | No valid data | None | Dose adjustment is not necessary in HD patients Avoid once-daily dosing in HD patients No recommendation for PD and CRRT |
| Remdesivir | Do not use GFR <30 ml/min | No valid data | HD: Do not use PD: Do not use CRRT: Do not use |
| Tocilizumab | None | Nephrolithiasis | No valid data for HD, PD or CRRT |

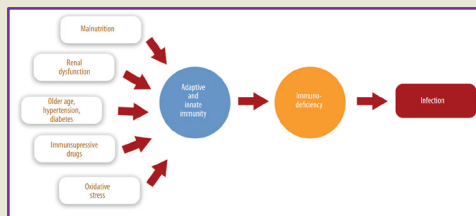
Baricitinib in COVID-19

- eGFR ≥ 60 mL/min/1.73 m²: No dose adjustment
- eGFR 30 to <60 mL/min/1.73 m²: Decrease to 2 mg/day
- eGFR 15 to <30 mL/min/1.73 m²: Decrease to 1 mg/day
- eGFR <15 mL/min/1.73 m², patients on dialysis, have end-stage renal disease, or have acute kidney injury: Not recommended

COVID 19 and kidney transplantation

- Kidney-transplant recipients appear to be at particularly high risk for critical Covid-19 illness due to chronic immunosuppression and coexisting conditions.

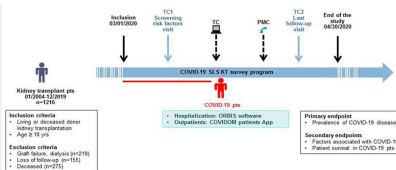
Factors affecting the disease course in kidney recipients



COVID 19 infection in kidney transplant recipients: Disease Incidence and Clinical Outcomes

METHODS

- Prospective study on 1216 patients actively followed in two transplant centers in Paris (799 at Saint-Louis Hospital, and 417 at Bichat Hospital)
- Follow-up during the peak period of COVID-19 infection
- Sixty-six (5%) patients diagnosed with COVID-19 disease.



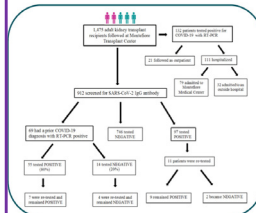
CONCLUSION

Kidney transplant recipients had an elevated risk of COVID-19 if they were non-White and had comorbidities such as obesity, diabetes, or asthma and chronic pulmonary disease; those who were diagnosed with COVID-19 had a 24% mortality rate.

JASN
JOURNAL OF AMERICAN SOCIETY OF NEPHROLOGY

doi: 10.1681/ASN.2020050639

COVID-19 INFECTION IN KIDNEY TRANSPLANT RECIPIENTS AT THE EPICENTER OF PANDEMICS



The prevalence of SARS-CoV-2 infection was 23.4% in the 975 patients tested by either RT-PCR or SARS-CoV-2 IgG. Older patients and patients with higher serum creatinine levels were more likely diagnosed by RT-PCR compared to SARS-CoV-2 IgG.

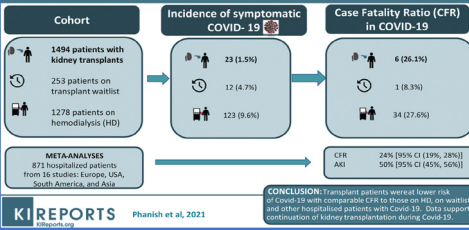
Overall mortality 20.5%
Mortality in hospitalized patients 37.8%
Older age, receipt of deceased-donor transplant, lack of influenza vaccination in the previous year and higher serum IL-6 levels were associated with mortality

CONCLUSION: 42% of kidney transplant recipients were SARS-CoV-2 IgG positive without significant symptoms and 80% of kidney patients developed an antibody response after confirmed diagnosis by RT-PCR.

ASN kidney

Azizi et al, 2020

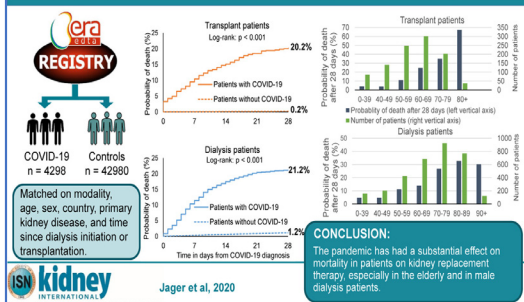
Systematic Review and Meta-analysis of COVID-19 and Kidney Transplant Recipients, the South West London Kidney Transplant Network experience



KI REPORTS

Phanish et al, 2021

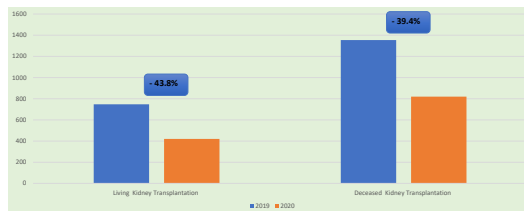
Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe.



ASN kidney

Jager et al, 2020

Living and Deceased Kidney Transplantation in Iran: 2019 vs 2020



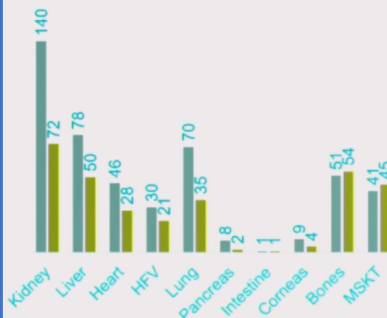
Living Transplantation in KSA: 2019 vs 2020

■ Living Kidney Transplantation ■ Living Liver Transplantation



Organ Utilization & Tissue Recovery from Deceased Donors During the COVID-19 Pandemic

■ 2019 ■ 2020



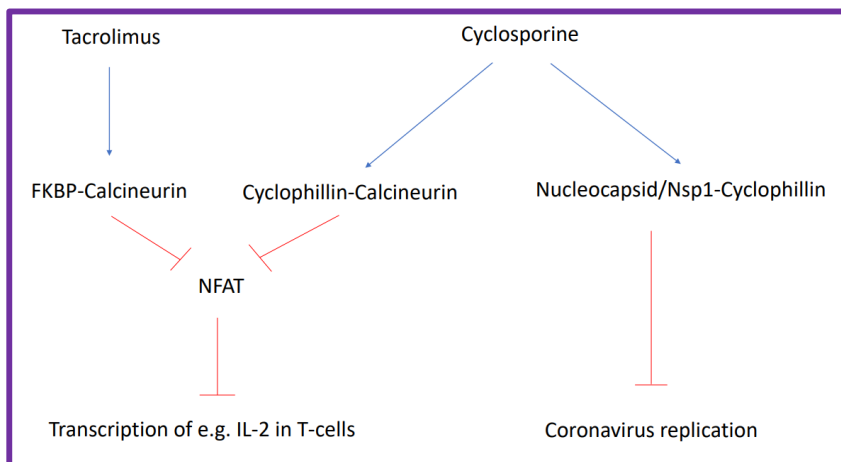
Management

- Management of acute COVID-19
- Adjusting immunosuppression
- Steroid therapy
- mTOR inhibitors
- Tocilizumab
- Several independent studies have shown that coronavirus replication and growth depend on active immunophilin pathways.
- Cyclosporine at non-cytotoxic concentrations induces a strong inhibition of the replication of several coronaviruses including SARS-CoV2.
- The cyclosporine concentration required to inhibit virus replication exceeds by far the serum concentrations that typically are well below 200 ng/mL.

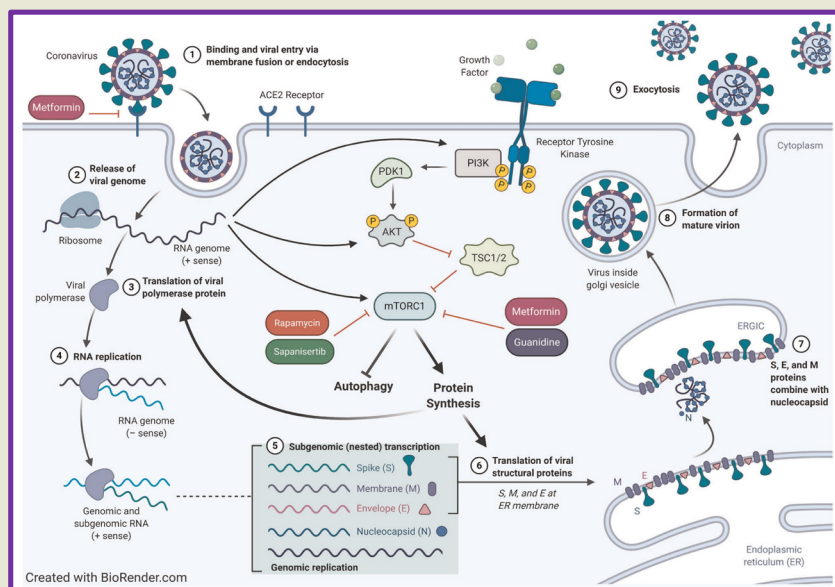
CNI could be continued to be used in kidney transplant patients for 2 different reasons.

- The ability of these agents to reduce viral replication, as demonstrated by experimental studies on SARS-CoV.
- The assumption that they may have the ability to reduce a similar

cytokine storm during the course of COVID-19, based on the effectiveness of CNI in hemophagocytic lymphohistiocytosis and capillary leak syndrome.

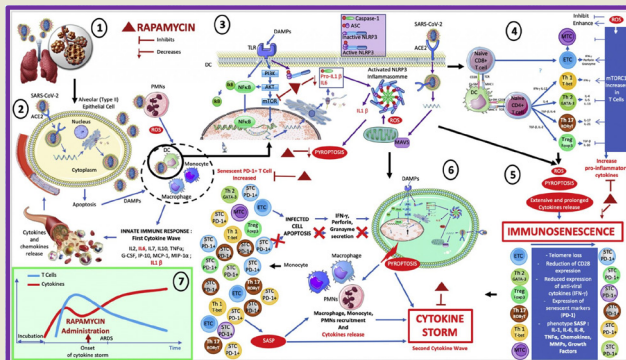


mTOR inhibitors

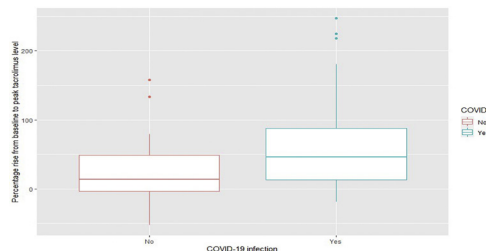


Created with BioRender.com

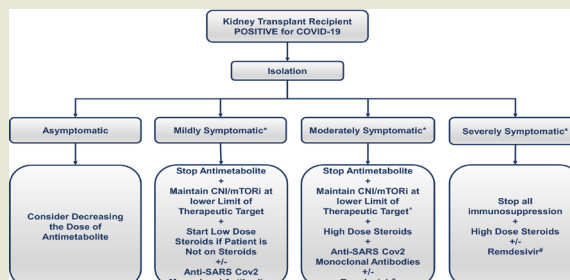
- In kidney transplant recipients using mTORi (everolimus or sirolimus), there were also higher proportions of Treg.
- Tregs suppress effector T cell induction and proliferation, which prevents cytokine storm.



CNI could be continued to be used in kidney SARS-CoV-2 and Tacrolimus Blood Concentration in Kidney Transplant Recipients



Suggested algorithm for the management of the COVID-19-positive kidney transplant recipient





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December 2021

Coronavirus Disease 2019 and theThyroid - Progress and Perspectives

Agenda

- Introduction
- Thyroidal insults In COVID-19 and their management
 - Major Sequelae**
Destructive Thyroiditis ,AIT
 - Minor Sequelae**
NTIS
- Etiologic background for thyroidal insults in COVID-19

Introduction

- Recently, evidence has been accumulated for changes in:

- Thyroid function
- Thyroid diseases associated with COVID-19.

Thyroiditis an Underestimated Manifestation of SARS-CoV-2 Infection? Insights From a Case Series. J Clin Endocrinol Metab (2020)

Alteration in thyroid functionality during SARS-COV infection

The CoVs are subdivided into four genera² such as

Alphacoronavirus

Betacoronavirus (β CoV)

Gammacoronavirus

Deltacoronavirus.

Since both SARS-CoV and SARS-CoV2 belong to the same β - Coronavirus group, sharing the key clinical manifestations in common

Immune Responses to SARS-CoV, Mers-CoV and SARS-Cov-2. Adv Exp Med Biol (2020)

تازه های کووید

Covid 19

The Comprehensive
National Congress On Covid 19

Thyroid disease in SARS

- Transient subclinical thyrotoxicosis
- Central hypothyroidism
- Primary hypothyroidism

were previously reported in patients with SARS

Hypocortisolism in Survivors of Severe Acute Respiratory Syndrome (SARS). Clin Endocrinol (Oxf.) (2005)

Thyroidal insults in COVID-19 & management

- The consequences of COVID-19 were divided into major and minor influences on the thyroid gland and its function.
- Thyroid disease process related to autoimmunity tend to occur earlier in the subjects with preexisting autoimmunity to the thyroid gland

Major Sequelae

- Damage to the thyroid per se and suppression of TSH by thyrotoxicosis together cause extremely low thyroidal uptake of radioiodine.
- Thyrotoxicosis in SAT commonly subside within 3 months

Thyroiditis. N Engl J Med (2003)348:2646–55. doi: 10.1056/NEJMra021194

Subacute Thyroiditis (SAT)

Destructive Thyroiditis / Subacute Thyroiditis (SAT)

- This is an inflammatory disorder, usually with a painful goiter, palpitation, fever and fatigue.
- Elevated CRP and ESR, together with focal hypoechogenic areas in the thyroid gland are characteristic laboratory findings of SAT

Clinical Characteristics of 852 Patients With Subacute Thyroiditis Before Treatment. Intern Med (2008)

- Viral infection such as human foamy virus (HFV), mumps, coxsackie, adenovirus, EBV, measles, chickenpox, CMV, influenza, and rubella have all been implicated as a cause of SAT

- An association of HLA and SAT was also reported

- To date, a total of 13 cases of SAT with COVID-19 have been reported.

- Most reports (7/13, 54%) were from Italy.

- Patients were distributed across all generations (18-69 years old) with overwhelming female predominance (11/13, 85%).

- The onset of SAT ranged from '7 weeks before' to '7 weeks after' the diagnosis of COVID-19.

- Fever was a common symptom in the patient with COVID-19 irrespective of the presence or absence of SAT so that it cannot be taken as a sign of SAT in this situation.

- Accordingly, thyroidal pain and tenderness are diagnostic clues for SAT with the combination of thyrotoxic signs and symptoms such as palpitations, finger tremor, hyperhidrosis, and soft stool.

- The patients usually show:

Increased FT3 and FT4

Decreased TSH.

- Izumi previously reported that: mean (SD) value for FT3 to FT4 ratio was

0.399 (0.089) in GD

0.335 (0.057) in SAT

0.304 (0.072) in PT)

- The lower FT3/FT4 in the presence of thyrotoxicosis can be a marker for thyroiditis, not Graves' hyperthyroidism .

Simple and Practical Parameters for Differentiation Between Destruction-Induced Thyrotoxicosis and Graves' Thyrotoxicosis. Clin Endocrinol (Oxf) (2002)

- A hypoechogenic area in the thyroid, either focal or diffuse, was found in the majority of them

- Echogenic evidence for increased vascularization was absent in all of the patients tested

- Thyroid autoantibodies (TSH receptor autoantibody (TR Ab), Tg Ab, and TPO Ab) were seldom positive

Atypical SAT

- Muller et al. reported a high frequency of atypical SAT in their patients with COVID-19.
- They reported that 13 out of 85 (15%) COVID-19 patients admitted to their high-intensive care units (HICU20) had overt thyrotoxicosis
- Corresponding value was 1% in the HICU patients without COVID-19 (HICU19)

2% among patients with COVID-19 in the low-intensive care units (LICU20).

Atypical Thyroiditis. Lancet Diabetes Endocrinol (2020)8:739–41. doi: 10.1016/S2213-8587(20)30266-7

Subacute Thyroiditis (SAT)

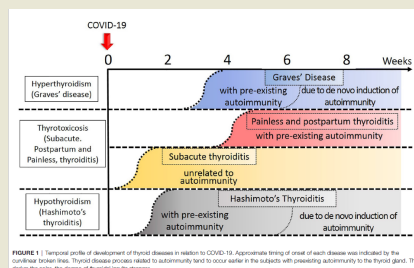
As an entire group:

- Mean (SD) FT4 in patients in HICU20 was, 18.7 (5.4) pmol/l
- LICU20 was 13.5 (4.6) pmol/l (significantly higher (P = 0.016).

Atypical SAT

- The authors named these patients 'atypical' because thyroidal pain and swelling were absent.
- Despite such 'atypical' physical findings:
 - Focal hypoechogenic areas
 - Decreased 99mTc uptake
 - Negativity of thyroid autoantibodies (except for one patient)
- were all present as in the typical subacute thyroiditis, which made them propose the new concept, 'atypical SAT'.

Temporal profile of development of thyroid disease



Thyrotoxicosis & hypothyroidism

- Lania et al. In 287 non ICU bed COVID-19 patients reported that :
- Thyrotoxicosis developed in 58 patients (20%) , possibly provoked by systemic inflammation or immune activation induced by COVID-19.
- Out of the 58 thyrotoxic patients, thyrotoxicosis was clinically overt in 31 (53%).
- Hypothyroidism in (5%) 15 out of the 287

Thyrotoxicosis in Patients With COVID-19: The THYRCOV Study. Eur J Endocrinol (2020)

Thyrotoxicosis

- In the entire group, there was a strong, inverse correlation between IL-6 and TSH (Spearman rho = -0.41, P < 0.001)
- Indirectly suggesting at least a partial contribution of inflammatory destruction of the thyroid to the elevation of thyroid hormone.
- The patients with thyrotoxicosis (TSH < 0.34 mIU/l) had significantly higher levels of the mean serum IL-6 than those without thyrotoxicosis (P < 0.05) (most of them > 10 pg/ml with the reference range < 6.4 pg/ml)
- Suggesting inflammation due to COVID-19 infection, as indexed by elevated IL-6, was a driving force for the thyroiditis
- They concluded that COVID-19 may have provoked thyrotoxicosis.
- In summary, thyrotoxicosis may occur in 10-20% of the patients with COVID-19.
- Increased IL-6 were also reported by Bartalena et al. in cases of destructive thyroiditis.

Interleukin-6 and the Thyroid. nEur J Endocrinol (1995) 132(4):386-93. doi: 10.1530/eje.0.1320386

Serum IL-6

- IL-6 has been reported to be involved with various autoimmune and inflammatory diseases .
- Serum IL-6 can predict disease severity in patients with COVID-19.

Profiling Serum Cytokines in COVID-19 Patients Reveals IL-6 and IL-10 Are Disease Severity Predictors. Emerg Microbes Infect (2020)

Management of SAT& Atypical SAT

- SAT is treated with 16-40 mg/day prednisolone followed by tapering within 4-6 weeks.
- Atypical SAT is a self-limiting disorder, and therefore can be observed without specific pharmacological treatment.

Autoimmune Thyroid Disease (AITD)

Painless Thyroiditis (PT) Painless Postpartum Thyroiditis (PPT)

- These disorders may belong to destructive thyroiditis, and also may be subtypes of autoimmune thyroid disease (AITD) ,although painless SAT may also occur if the inflammatory response is mild

Painless thyroiditis

- Majority of the patients with PT and PPT:

- 1-initially experience a mild thyrotoxic phase with elevated thyroid hormone and depressed TSH
- 2- Followed by depressed thyroid function
- 3- Recovery to normal within several months, i.e., spontaneous resolution of the thyroid dysfunction.

Painless thyroiditis

- Autoimmune associated thyroiditis with COVID-19 may preferentially be observed in the subjects who possess susceptibility to AITD
- Because the patients who experienced PT and PPT in association with COVID-19 often developed thyroid autoantibody positivity 1-1.5 months later.
- Such patients may share HLA genotypes with patients with AITD

Painless Postpartum Thyroiditis

- PPT patients who had both TPOAb and TgAb often have an increased percentage of activated T cells, such as HLA-DR+ and CD3+ cells, in the peripheral circulation.
- Thus, alteration in the T-cell population may be predisposed to or associated with the development of PPT

Painless Postpartum Thyroiditis

- Elefsiniotis et al. encountered the development of PPT in 4 out of 16 chronic HCV-infected women, proposing “viral triggered PPT” as a sub-type of the thyroiditis.
- Altered cell populations in patients with HCV infection have been considered as a reflection of Th1/Th2 imbalance

Graves' Disease (GD) and Hashimoto's Thyroiditis (HT)

AITD

- The AITD's are a constellation of thyroid-specific autoimmune diseases, and Graves' disease (GD) and Hashimoto's thyroiditis (HT) are the two major disorders included in this entity.
- GD is characterized by TSH receptor antibodies (TRAb) which stimulate the thyroid follicular cells leading to hyperthyroidism.

Hashimoto's Thyroiditis

- HT is characterized by the positivity of thyroglobulin autoantibody (TgAb) and thyroperoxidase autoantibody (TPOAb).
- Hypothyroidism in HT is due to T-cell mediated damage of thyrocytes and interstitial fibrosis.

Graves' disease

- The serum thyroid autoantibodies such as TgAb and TPOAb are often also positive in GD.
- Transitions of patient from GD to HT and vice versa are not uncommon, and a positive family history for GD often overlaps with that for HT.
- Provocation or activation of AITD by COVID-19 toward the seemingly opposite direction, to GD or HT, can be understood from these perspectives.
- The association of viral and non-viral infection and AITD has often been suggested.
- For example, serological evidence of infection with human herpesvirus-6 (HHV-6), and toxoplasma gondii, HCV was obtained from patients with AITD at, or around, the time of diagnosis of AITD.
- However, it remains to be determined whether the infection was causal for the development of the thyroid diseases or just innocent bystanders.
- The relationship between SARS and AITD also has not been described with certainty.
- Two cases of GD with COVID-19 were reported by Mateu- Salat et al:
 - 1- one case was a relapse of hyperthyroidism in a 60- year-old woman in whom GD had been in the state of drug-free remission for longer than 30 years.
 - 2- The other was the development of GD in a 53-year-old woman without a known history of thyroid disease.
- Cervical pain was absent and Graves' ophthalmopathy was equivocal in both of these cases.
- Despite such ambiguity in signs and physical findings, the serum thyroid hormone were indeed elevated and TSH suppressed, thyroid iodine scintigram uptake increased and TRAb was positive, so that they were diagnosed as GD.
- The timing of the diagnosis of GD was 1 and 2 months after the onset of COVID-19 in the former and the latter, respectively.
- A 21-year-old woman presented with tachycardia, palpitation, anxiety, and finger tremor 17 days after the diagnosis of COVID-19.
- Her mother had hypothyroidism.

- A diffuse, non-tender, moderate-sized goiter was present.
- Elevated thyroid hormone and suppressed TSH , and the positivity of TRAb indicated the diagnosis of GD.
- Graves' ophthalmopathy or dermopathy was absent.
- The three patients with GD responded to thiamazole and β blocker uneventfully.

Hashimoto's Thyroiditis

- A 45-year-old man with COVID-19 who presented with fatigue and muscle weakness was diagnosed as HT, based on the hypothyroidism with the positivity of TPOAb and successfully treated with 25 mg/day L-thyroxine.
- In the patients with AITD, depending upon the different background thyroid autoimmunity, a variety of organ-specific autoimmune abnormalities may be provoked or activated upon SARS-CoV- 2 infection.

Abnormal TFT

- Liu et al. reported that 25 out of a consecutive 191 (13%) patients with COVID-19 showed abnormal results in thyroid function tests.

Ten patients had isolated low TSH, suggestive of subclinical thyrotoxicosis: one of them was positive for TPOAb and TRAb, and two of them were positive for TRAb

Therefore, the three might have had subclinical GD.

- Apart from the ten patients, there was a patient with isolated high FT4 and another with high FT4 and low FT3, who were also positive for TRAb leaving the possibility of mild GD.

- Three patients:

The first one with isolated high FT4 with TgAb positivity

The second with isolated TSH elevation with positive TPOAb and TgAb

The third with low TSH and FT3.

Abnormal TFT

- The remaining ten patients with isolated low FT3 were compatible with non-thyroidal illness syndrome, and one patient was positive for TRAb and TPOAb .
- Overall, 14/191 (7%) had features of thyrotoxicosis, diagnosed by low TSH and/or raised FT4.
- The authors reexamined 10 of the 25 patients a median of 28 days after the initial thyroid function test and found normalization, permanent hypothyroidism, and various stages of thyroiditis in evolution, with no uniform recovery.

Management of AITD in COVID-19

- PT and PPT are self-limiting disorders, and therefore can be observed without specific pharmacological treatment.
- Regarding the management of GD, treatment of thyrotoxicosis by thionamide drugs is usually safe, but should be performed with caution.
- This is because the signs and symptoms of COVID- 19 are indistinguishable from those of anti thyroid drug-induced agranulocytosis.
- Hypothyroidism due to HT can be treated by a regular L-T4 supplement.

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Minor Sequelae

Non-Thyroidal Illness Syndrome

- A systemic disease of any kind, if it is critical, causes the nonthyroidal-illness syndrome (NTIS), characterized by low T3 levels as a result of changes in type 1 deiodinase activity.
- Patients in the ICU typically present with decreased serum T3, normal or low T4, and normal or slightly decreased TSH.

Prevalence of Non-Thyroidal Illness

- 28% (41 out of 149 patients with COVID-19) fitted the diagnosis of NTIS (FT3 levels < 2.3 pg/ml). (Zou et al.)
- FT3 were significantly lower in patients with
- Severe COVID-19 (66 out of 100: 66%) versus
- Mild COVID-19 patients (34 out of 100: 34%) (Gao et al.)

Non-Thyroidal Illness Syndrome

- In a consecutive evaluation of deceased (N = 113) and recovered (N = 161) COVID-19 patients, levels of TSH and FT3 on admission were significantly lower in the former.
- Low FT3 is commonly associated with, or predictive, of an intractable form of COVID-19.

- Another group found that total T3 levels were inversely correlated with the severity of COVID- 19.

Non-Thyroidal Illness Syndrome

- Nonetheless, the data should be interpreted carefully because a significant proportion of the patients (31/50: 62%) were taking glucocorticoid at the time of the hormone measurements .
- Somewhat differently, Khoo et al. reported that 289 out of 334 (87%) patients with COVID-19 were euthyroid.
- They recognized that patients with COVID-19 had lower TSH and FT4 compared to those who did not have COVID-19.
- They also reported that TSH and FT4 were both depressed upon admission for the treatment of COVID-19 compared to the pre-hospital baseline levels
- They also reported that patients who were admitted to the ICU had lower TSH than those treated at the non-emergency ward.
- There was a significant inverse correlation between cortisol and TSH and between CRP and TSH, and a positive correlation between CRP and FT4 levels
- The findings suggested stress-induced suppression of TSH in COVID-19.
- At least partial recovery of TSH toward the baseline was observed at the follow-up at several months later.
- Elevated serum cortisol in patients with COVID-19 were reported, and hypercortisolism has been reported to suppress TSH.
- This change in TSH may be likely due to the changes in deiodinase activity in CNS.

Management of NTIS in COVID-19

- Since NTIS is due to the systemic dysfunction by COVID-19, the treatment for COVID-19 is essential to obtain normal thyroid functional test results.

AITD Patients Response to COVID-19

- Gerwen et al identified 251 patients with hypothyroidism receiving thyroid hormone replacement among 3,703 patients with COVID-19 (251/3703, 7%)
- They concluded that hypothyroidism was not associated with an increased risk of hospitalization, mechanical ventilation, or death in patients with COVID-19.

Etiologic background for thyroidal insults in COVID-19

Hyperinflammatory Syndrome

- COVID-19, especially in its severe form, is associated with a hyperinflammatory syndrome
- Similar hypercytokinemia with multiorgan failure seen in SARS.

In COVID-19:

- Proinflammatory /Th1 cytokine production is increased
- Th2 cytokines increased
- which was a different picture from SARS .

Pathogenetic role of cytokines in development of thyroiditis and flare-up of the thyroid autoimmunity.

In COVID-19 dormant AITDs such as GD and HT become clinically overt by:

- 1- Th2-mediated autoantibody production
- 2- Th1-mediated cellular immunity
- 3- exaggerated further by Treg dysfunction.

- Significant positive correlation between serum IL-6 and the degree of thyrotoxicosis in patients with COVID-19.
- The finding suggested that elevation of IL-6 and/or cytotoxic effects of T-cells during the hyperinflammatory syndrome might be causal for thyroidal destruction of the thyroiditis in COVID-19.

Apoptosis

- The pathological findings in the three cases of COVID-19 :
- Apoptosis of follicular cells in the absence of the virus itself in thyrocytes
- Suggesting, cytokine mediated thyroid insult in SARS and COVID-19.

Hyperinflammatory Syndrome

- As a conclusion
- The hyperinflammatory syndrome in COVID-19 appears to provoke AITD such as GD, HT, PT, and PPT in some patients and activate otherwise dormant diseases into a clinically recognizable state in others.

1- SARS-CoV-2

infects systemic organs through acquired immunity (1a innate immunity (1b

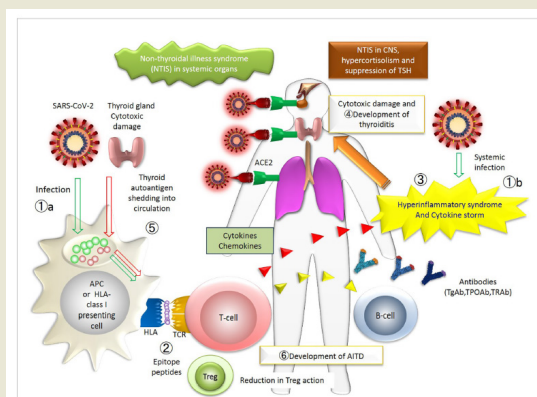
2- SARS-CoV-2 epitope peptide is presented on the surface of HLA, and T-cell recognizes the epitope peptide.

3- Hyperinflammatory syndrome and cytokine storm occur.

4- Thyroid gland is damaged by immune cells.

5- Thyroid autoantigen is shedding into circulation, which is also presented on the surface of HLA.

6- Finally, AITD develops as a consequence of new provocation of the disease or activation of previously existing dormant disease.



Angiotensin-Converting Enzyme 2 (ACE2) on Thyroid and Pituitary Cells

- In many organs including the lung, GI, the liver, the kidney, the skin, the heart, the hematopoietic cells, and the spleen, a direct cellular change by the virus was documented during COVID-19.

- ACE2 expression has been known to impair thyroid function and also the function of the anterior pituitary gland during COVID-19

- So far, the existence of SARS-CoV-2 in the thyroid gland and pituitary gland is not clear by examinations of light microscopy, immunohistochemistry, electron microscopy, and quantitative RT-PCR

- Viral particles of SARS-CoV-2 were found in the frontal lobe of the brain and brain capillary endothelial cells .

- The SARS-CoV-2 infection has been known to impair olfaction and taste sense by affecting CNS.

- Although clear evidence is lacking, infection of the thyrocyte, thyrotroph and corticotroph may result in lowered T3, T4, TSH, ACTH and cortisol.

- The dysregulation of the hypothalamic-pituitary-thyroid axis has been considered at least in part responsible for hypothyroidism in COVID-19.

CONCLUSIONS

- Our understanding of the thyroidal manifestation of COVID-19 is far from complete as is the etiologic view of COVID-19 and thyroid insults.

- Although case reports are definitely important in helping us understand the association, future research, hopefully in a prospective manner with longitudinal analyses, is required.

- This would involve the histologic and cytological examination of the thyroid gland in a large number of patients in order to identify direct evidence regarding the nature and cause of thyroid damage with the COVID-19 virus and the detailed immune response in those patients with thyroid dysfunction.

- We need to clarify if thyroid autoimmunity in COVID-19 is an innocent-by-stander or another culprit in its severity.



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استاد گروه زنان و زایمان- فلوشیپ ناباروری
دانشگاه علوم پزشکی تهران

Introduction

- Covid 19 → transmitted by respiratory
- Droplets → infect pulmonary cell ACE2, TMPRSS2
- December 2019 → Wuhan
- March 12 2020 WHO → Pandemic
- Pregnant woman → greater risk complication & severe disease
↓
- FIGO → recommend suspension routine antenatal care
↓
- Replacement video or telephone consultation

Cause of severe disease in pregnancy

Introduction

- Shift CD4 T → Th2 ↑ → Th1 ↓ altered clearance of infected cell
- Decrease in circulating NK cell
NK → role in the innate immune system → clear viruses
- Decrease in circulating plasmacytoid dendritic cells (PDCS) → production type I interferon ↓
- Increase progesterone → CD4 T cell ↓ → Alteration immun system
- Respiratory system → reduction in total lung capacity → inability clear secretion → severe respiratory infections

Prevention

- PPE & Hand hygiene
- vaccines

سوالاتی که در مورد واکسن مطرح می شود:

- در صورتی که بعد از تزریق واکسن متوجه حاملگی شد چه باید کرد ؟ آیا دوز بعدی تزریق شود ؟ چه زمانی ؟ نوع آن تغییر کند یا خیر ؟
- آیا می بایست بین تزریق واکسن کووید و واکسن آنفولانزا فاصله باشد ؟
- آیا تزریق واکسن در حاملگی همراه با عارضه است ؟
- در صورتی که mRNA واکسن در دسترس نباشد می توان واکسن دیگری تزریق کرد ؟
- چه فاصله ای بین تزریق Anti-D immunoglobulin با واکسن کووید باشد ؟
- آیا لازم است در شرایط کووید حاملگی را به تأخیر انداخت ؟
- دوران کووید چه تأثیری در مادر حامله داشته است ؟
- آیا ابتلا به کووید روی ذخیره تخمدانی اثر می گذارد یا خیر ؟

Clinical findingSign & symptoms

-Fever, cough, headache, muscle aches, sore throat, shortness of breath, loss of taste or smell, nausea & vomiting, fatigue, diarrhea, rhinorrhea

Laboratory

- CBC, CRP
- BUN, Cr
- LFT, BS, LDH
- Di-Dimmer, procalcitonin, troponin

Imaging

- Chest X Ray
- Chest CT

Impact of covid-19 on pregnancy

- 1- Early pregnancy - miscarriage - Teratogen
- 2- Late pregnancy
 - Preterm birth, Preeclampsia
 - Still birth, PROM, IUGR, C/S
- 3- Hospitalization, ICU admission mechanical ventilation
- 4- Intrapartum transmission 2.9-3%

classification

1. Asymptomatic
2. Mild: fever, cough, sore throat, malaise chest normal
3. Moderate: imaging + $\text{Sao}_2 \geq 94\%$
4. Severe: $\text{RR} > 30$, $\text{Sao}_2 < 94\%$
 $\text{Pao}_2/\text{Fio}_2 < 300$ Lung infiltrates $> 50\%$
5. Critical: respiratory failure
shock, multi organ dysfunction mortality rate 0.8%

Complication covid 19 in pregnancy

- Respiratory disorder
- Cardiac disorder (arrhythmias, cardiomyopathy)
- Thromboembolic
- Secondary infection
- Acute kidney failure
- Neurologic
- Cutaneous
- Gastrointestinal and liver
- Psychiatric illness

Prenatal care

- Uninfected pregnant person ACOG, SMFM, RCOG recommend
- Modify prenatal visit (Telemedicine)
- Psychological
- Infected Pregnant
- asymptomatic and mild disease

Close monitoring, self isolation, hydration warning symptom

- Worsening dyspnea
- Fever > 39
- Inability to tolerate oral hydration
- Chest pain
- Confusion
- Obstetric complication
- RR ≥ 20-24/min (Hospitalization), RR > 100/min
- Symptomatic patients (in hospital multidisciplinary team)
- Patient with severe or critical; (ICU admission)
(Level III, IV hospital with obstetric services)

Close monitoring, self isolation, hydration warning symptom

A- Maternal respiratory support

SPO₂ ≥ 95%

If SPO₂ ≥ 95% → measure the partial pressure of oxygen
(Pao₂) > 70% is desirable

B- Prone position

C- VTE prophylaxis

- UFH :

1. First Trimester: 5000U/BID

2. Second Trimester: 7500- 10.000U/BS

3. Third Trimester: 10.000U/BID

- LMWH (40mg/daily)

C- Steroids

1-Dexamethasone (Fetal lung maturity) 26-34 week gestation

6mg/BID for 24 hours

2- Dexamethasone 6mg/daily for 10 days or methylprednisolone, Hydrocortisone

D- Use of Nsaids

1- Nsaids: lowest effective dose for 48 hours

2- Low dose aspirin → safe

E- Antiviral drug therapy

1- Remdesivir → 7-10

2- Tocilizumab → interleukin-6 antagonist other therapy

- Convalescent plasma
- Monoclonal antibody
- Hyper immune globulin

Timing of delivery

1- Non severe or asymptomatic illness 39≥ delivery

39< no medical/ obstetric indication for delivery → intervention is not indication

2- Severe/critical illness

- Severe disease but not intubated delivery > 32 to 34 weeks in setting worsening status <32 delivery not indicated critical

- Severe disease and intubated

32-34 weeks delivery

- Other consider delivery hypoxemic respiratory failure or worsening critical illness

Fetal monitoring

Indication: viable gestational age

- In patients with stable SpO₂: NST: 1-2 daily

- In ICU patients: Continuous monitoring

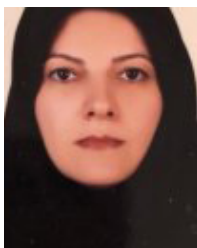
- After recovery:

14 days after symptom resolution

Ultra sound for fetal biometry & fetal growth

- Fetal anomaly scan: 18-23 weeks after then

Fetal surveillance



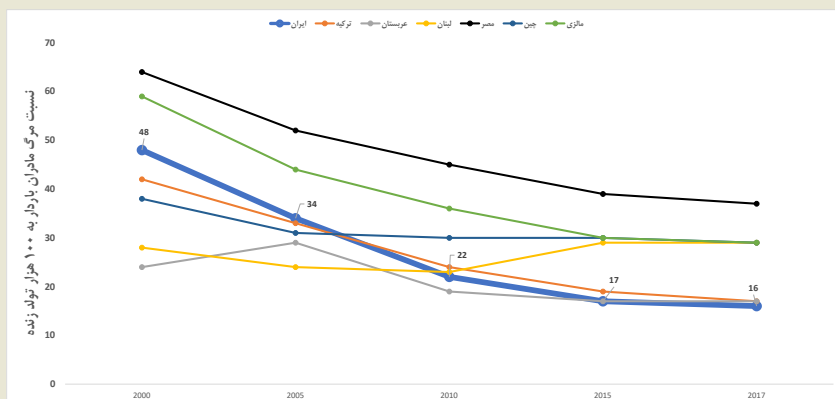
Dr.Nasrin Changizi

Research Associate Professor Perspectives

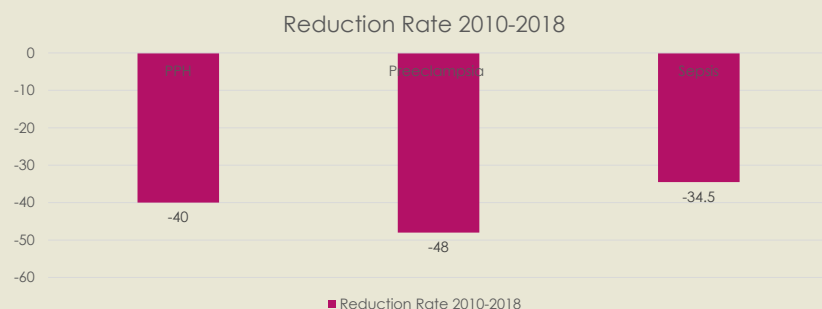
| 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|-------|------|------|------|------|------|------|------|------|
| 22.07 | 21.5 | 19.5 | 19.7 | 18.9 | 20 | 18.1 | 19.9 | 17.7 |

20.99 19.58 18.59

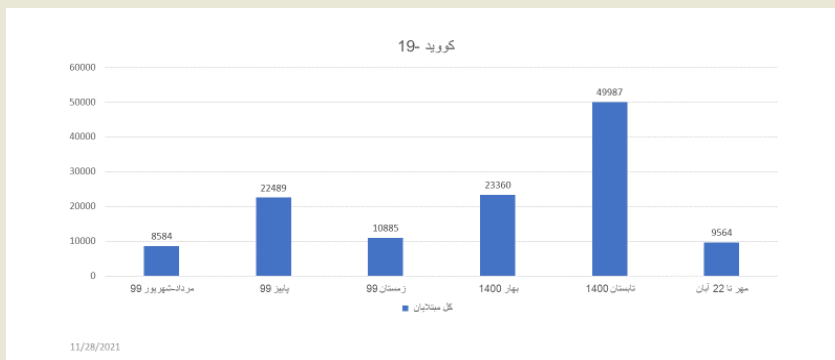
Maternal Mortality Ratio per 100 000 live births 2010-2018



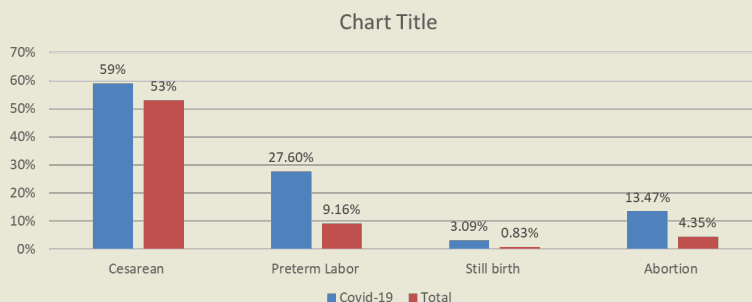
گزارش روند کاهش علل مرگ مادران (خونریزی پس از زایمان، پره اکلامپسی، سپسیس) 2018-2010



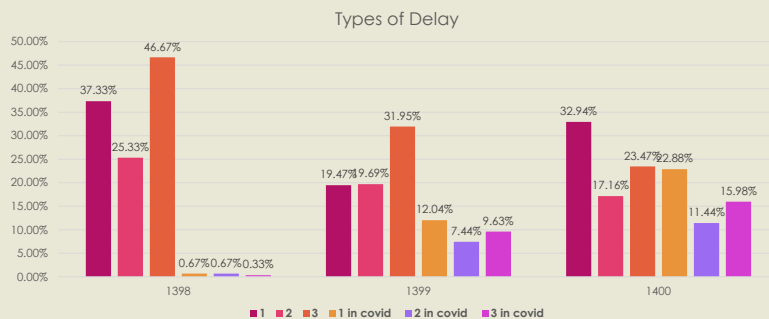
مقایسه روند زمانی بیماری-کووید 19 در مادران 2018-2010



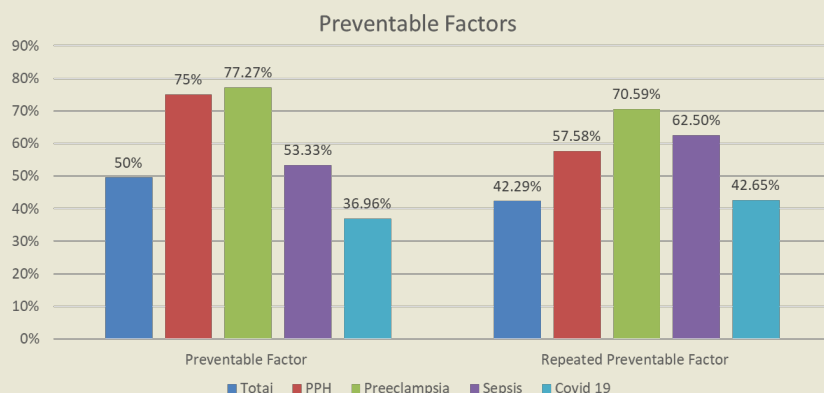
عوارض بارداری و زایمان اول مرداد 1399 - اول مرداد 1400



گزارش نظام مراقبت مرگ مادران 1398-1399-1400



گزارش نظام مراقبت مرگ مادران 1398-1399-1400



- Vaccination
- Covid In Pregnancy Guideline

Women produce more antibodies

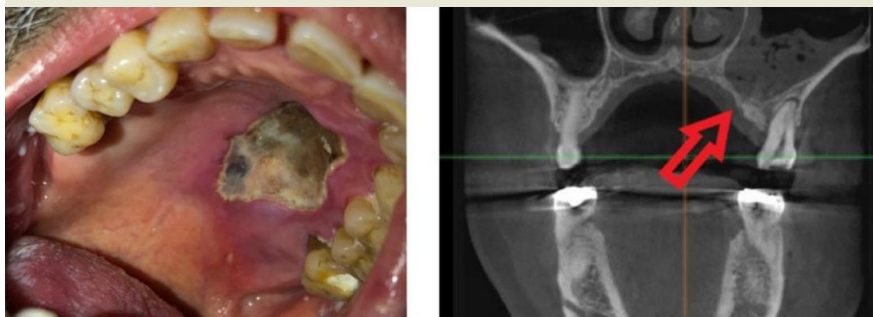
- 1st Type of Delay
- 2nd Type of Delay
- 3rd Type Of Delay
- Preventable Cause Of Maternal Death



Dr Mostafa Esmaeili

Oral & Maxillofacial manifestations of Covid-19

Oral & Maxillofacial manifestations of Covid-19



Introduction

- Since Angiotensin-Converting Enzyme 2 (ACE2) and Transmembrane Serine Protease (TMPRSS2 and TMPRSS4) were described as the host factors associated with SARS-CoV-2 entrance in human cells, the scientific community has been putting effort to identify organs at higher risk of infection or with predictive signs and symptoms for severe coronavirus disease 2019 (COVID-19; Dong et al. 2020; Lippi et al. 2020; Huang et al. 2021).

- Oral cavity is a potentially relevant infection axis with further inflammatory response

- The expression of ACE2 and transmembrane serine protease in salivary glands and oral mucosal epithelia, associated with a confirmed infection by SARS-CoV-2, may also play a role in the virus transmission via saliva, even in asymptomatic individuals

- In some cases, Oral manifestations are the first symptoms and may help early diagnosis and early treatment.

- Role of disease severity in OMF symptoms

Mild to moderate (Before or At the same time)

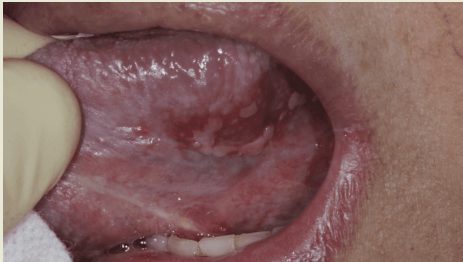
Severe (7 to 24 days after onset symptoms)

Many OMF manifestations may occur

- Taste changes
- Xerostomia
- Irregular ulcers
- White and erythematous plaque
- Blisters
- Petechiae
- Desquamative gingivitis
- Mucormycosis
- Erythema multiform
- Glossitis
- Parotitis
- Halitosis
- Angioedema
- Dental pain (Under expression of ACE2 in dental pulp may worsen pulpitis)
- Jaw pain (Palate, Maxilla, ...)
- Angina bullosa hemorrhagic-like lesion
- Angular cheilitis

...



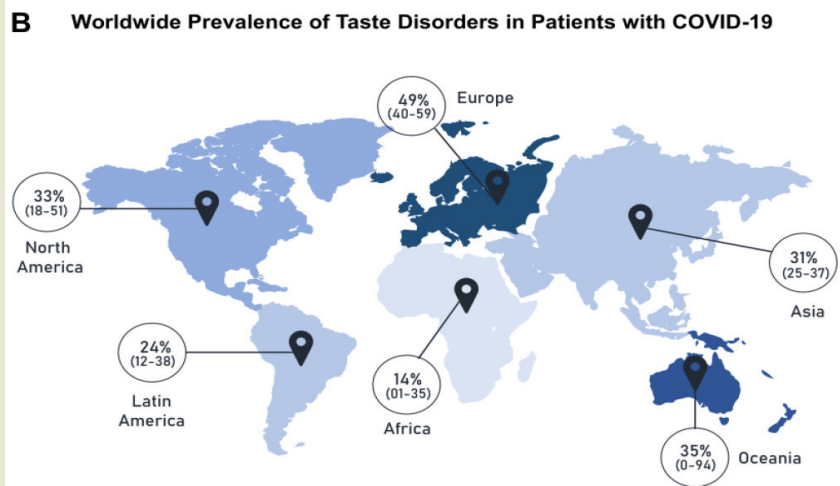
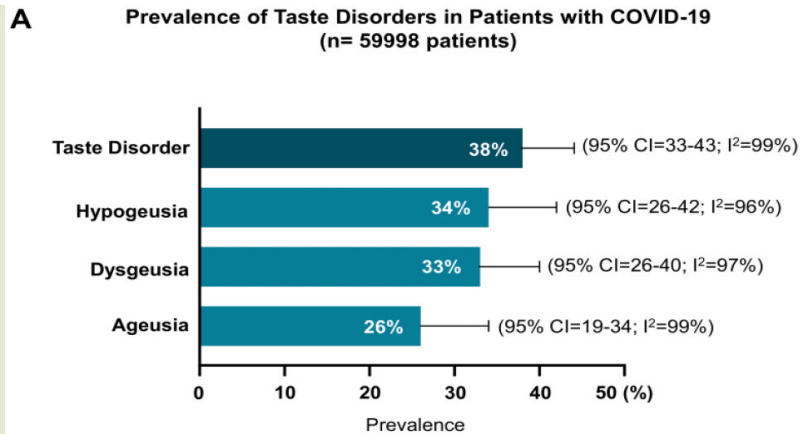


OMF manifestations

- Direct
- Indirect

- Specific
- Non specific

The prevalence of OMF signs and symptoms and whether they result in direct SARS-CoV-2 infection or merely represent secondary manifestations are paramount



Xerostomia

- Data from 1,017 patients with COVID-19 was pooled, and the meta-analysis showed a prevalence of 43%
- Xerostomia seems to appear before the onset of other general COVID-19 symptoms

Xerostomia

- Although xerostomia might be an unspecific symptom with multiple causes, hyposalivation is the main etiologic factor
- Regarding the occurrence of xerostomia in COVID-19, It is also suggested the association with medications, nasal congestion and mouth breathing, nutritional deficiency, diabetes, and the anxiety and distress related to the pandemic or long-term hospitalization
- Whether these signs and symptoms are directly associated with COVID-19 is still a controversial topic.
- The hypothesis suggests that SARS-CoV-2 effects on salivary glands might result in salivary quality and flow impairment, leading to taste disorders, xerostomia, and halitosis
- Xerostomia may also occur as a rare side effect of covid-19 vaccine

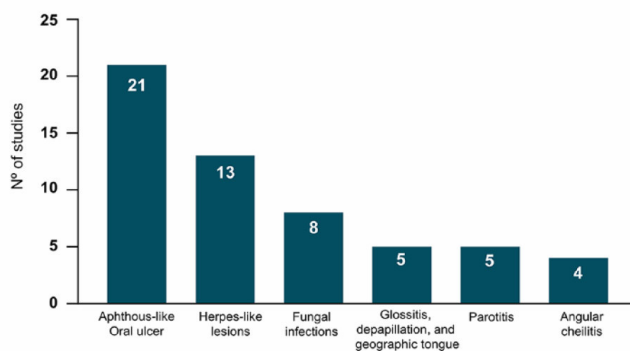
Halitosis

- Halitosis was reported in a case series with 18 patients (Riad et al. 2021) and by 10% of 573 patients with COVID-19 from a cross-sectional study (Abubakr et al. 2021)
- However, a meta-analysis was not feasible, and more studies are necessary to assess this condition.

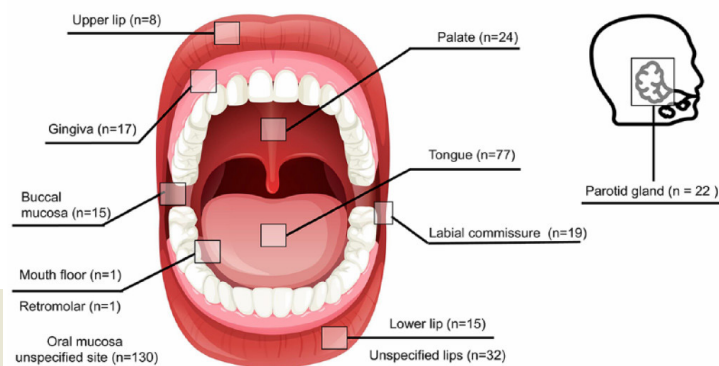
Oral Mucosal Lesions in Patients with COVID-19

- Aphthous-like oral ulcer was the most common oral lesion
- Herpes-like lesions
- Candidiasis
- glossitis/depapillation/geographic tongue
- Mucormycosis
- Parotitis
- Angular cheilitis
- Tongue was the most common specified anatomic location for oral lesions

A The most common oral signs reported in patients with COVID-19



B Occurrence of oral lesions according to anatomical location (n= number of lesions)



Mucormycosis

- Evaluating systemic condition of patient
- Diabetes
- Immunosuppression
- Very high ferritin level
- Importance of early diagnosis by clinical examination, Imaging, Culture and Biopsy
- Clinical manifestaion in oral region:
 - Single necrotic ulcer usually on palate that may expose underlying bone
 - Pain without dental etiology

- Ulcers with black color in covid patient
- Black exudates from mouth or nose
- Nasal congestion
- Eye symptoms
- ...

- Treatment:

- Surgery
- Antifungal therapy
- Follow up



- The triad of xerostomia, taste dysfunction and oral mucosal lesions is common in patients with COVID-19 regardless of their direct or indirect infectious nature.

- Professionals should be aware of persistent symptoms and long-term post-acute complications in patients with COVID-19.



دکتر حسین فودازی
متخصص رادیوتراپی انکولوژی
مدیریت درمان سازمان تامین اجتماعی
بیمارستان شهید دکتر فیاض بخش

Pandemic



Plague Doctor

Wide Hat

In those days, such a hat identified someone as a doctor.

Scalpel

For the opening of buboes.

Leather Gloves

On the neck were a cord for drawing herbs and substances that were supposed to ease off the plague.

The Pomander

On the neck were a cord for drawing herbs and substances that were supposed to ease off the plague.

A Bunch of Garlic

For prevention, the doctor chewed garlic constantly.

Cloak

The doctor's cloak was tucked under the wide-brimmed hat and attached to the floor to hide as much of the body surface as possible. Doctors often spread off clothing with her.

It was believed that this reduces the chance of infection from such victims. It was carried as protection against infection by airborne droplets, as well as from fleas, the main vector of the disease.

Primitive Mask in Form of a Bird's Beak

It was believed that a mask in the form of a bird's beak would repel the plague because the beak was believed to be the source of the disease.

It was believed that the mask made the doctor immune to the disease.

The beak of the mask is thought to have been made of wood or bone and was often decorated with feathers or other materials.

The mask was often made of wood or bone and was often decorated with feathers or other materials.

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What we know about COVID-19?

- According to the WHO, the virus comes from a family of Coronaviridae (CoV). It is officially named as SARS-CoV-2
- Coronaviruses have caused everything from the common cold to the well-known Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV).
- It's a novel strain (nCoV) discovered in 2019, transmitted between both animals and people with incubation period of 2-14 days after exposure.
- Human-human transmission is more common
- No known treatment or immunization

Evidences suggest

- Individuals with cancer are more susceptible to infection than individuals without cancer. Such patients might be at increased risk of COVID-19 and have a poorer prognosis.
- While timely screening is important, the need to prevent the spread of coronavirus and to reduce the strain on the medical system is more important right now.
- Routine visits to health facilities are safe and regular screening tests should be rescheduled after the restrictions to slow the spread of COVID-19 are lifted.

AIM

- Reduce exposure to CoV (high CFR)
- Not to lose control over cancer – intact anti cancer efficacy.
- Reduce work load – manpower and infrastructure become available for COVID treatment.

Cancer-specific case fatality rate

- Most comprehensive data available to date is a Report of the WHO-China Joint Mission on Coronavirus Disease.
- This report indicates that in China, as of the data cut-off (February 20) the case fatality rate for patients with cancer as a comorbid condition and laboratory confirmed infection was 7.6%.
- This is as compared to: overall 3.8%, no comorbid condition 1.4%, cardiovascular disease 13.2%, diabetes 9.2%, hypertension 8.4%, chronic respiratory disease 8.0%.

<https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>

Guidance from ASCO on Cancer patients care during the COVID-19 outbreak

- Elective surgeries at inpatient facilities to be rescheduled if possible.
- Systemic treatments like chemotherapy and immunotherapy, leave cancer patients vulnerable to infection. But stopping anticancer or immunosuppressive therapy is not recommended, as there is no direct evidence to support changes in regimens during the pandemic.
- For patients already in deep remission and receiving maintenance therapy, stopping treatment may be an option.
- Patients advised to switch from IV to oral therapies, which would decrease the frequency of clinic visits.

<https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19>

توصیه های کلی برای کاهش میزان عفونت در بخشهای رادیوتراپی

- رعایت دستورات سازمان بهداشت جهانی، وزارت بهداشت درمان و آموزش پزشکی و همچنین مسئولین کنترل عفونت بیمارستان ضروری است.
- بهتر است کادر درمان قبل و بعد از درمان هر بیمار دستان خود را با محلول الکلی ضدعفونی نمایند.
- بهتر است بیماران هنگام ورود به مرکز درمانی همچنین هنگام خروج دستان خود را با آب و صابون بشویند و این امکانات باید برای بیماران فراهم شود.

- در صورت ابتلای تعداد زیادی از بیماران سرطانی به بیماری COVID-19 یک گزینه مناسب این است که یک دستگاه مجزا برای درمان این بیماران اختصاص یابد.
- البته این امر در بسیاری از مراکز رادیوتراپی کشور قابل انجام نیست.
- راه حل دیگر است که بیماران دچار COVID-19 در انتهای روز کاری و با فاصله نسبت به سایر بیماران درمان شوند.

- بیماران جدید لاجرم باید برای جلسه اول ویزیت پذیرفته شوند.
- اکثر بیماران پیگیری نیاز به مراجعه حضوری ندارند.
- در تمام مراکز رادیوتراپی در تمام روزها باید یک نفر مسئول بیماری COVID-19 وجود داشته باشد و نحوه غربالگری و ارجاع موارد مشکوک کاملاً مشخص باشد.

- می توان با اندازه گیری درجه حرارت بدن بیماران و کادر درمان از ورود افراد مشکوک به مرکز درمانی جلوگیری نمود.
- نحوه ورود و خروج بیماران در بخش رادیوتراپی باید به دقت تنظیم شود تا ارتباط بیمار-بیمار و همچنین درمانگران با بیماران به حداقل برسد.
- در صورت امکان بهتر است بیماران از یک درب بخش وارد و از درب دیگر خارج شوند و حتی الامکان وارد بخشهای دیگر مرکز درمانی نشوند.

- زمان بندی درمان نیز باید طوری طراحی شود که بیماران و همراهان حداقل زمان ممکن را در بخش رادیوتراپی سپری کنند.
- باید از تردد غیرضروری کادر درمان رادیوتراپی به بخش های دیگر جلوگیری شود.
- هرگونه وسیله اضافه باید از بخش های درمان جمع آوری شود تا ضدعفونی کردن و آلودگی زدایی بخشهای رادیوتراپی راحت تر و بهتر انجام شود.
- باید تمام بیماران بخصوص بیمارانی که دارای سرفه و ترشحات تنفسی هستند مانند بیماران دچار سرطان ریه و سر و گردن هنگام حضور در بخش رادیوتراپی از ماسک مناسب استفاده کنند.
- شماره تماس بیماران باید در دسترس باشد.
- باید به بیماران اطلاعات کافی در مورد احتمال ابتلا به عفونت COVID-19 داده شده و همچنین ضرورت انجام رادیوتراپی به دقت شرح داده شود.
- تمام پرسنلی که مستقیماً درگیر درمان بیماران هستند باید به تجهیزات حفاظتی شخصی (PPE) مجهز شوند.



- قسمت های مختلف بخش رادیوتراپی باید بر اساس پروتکل های موجود به نواحی مختلف تقسیم بندی شوند و افراد مجاز به ورود به هریک از این قسمت ها و نوع تجهیزات حفاظتی شخصی آنان باید به دقت مشخص گردد.

- تمیز (clean zone)

- نیمه آلوده (semi-contaminated zone)

- آلوده (contaminated zone)

- ماسک های ترموپلاستیک میتوانند سبب سرایت بیماری شوند.

- باید به نحوه نگهداری این ماسک ها در بخش رادیوتراپی دقت شود.

- همچنین میتوان در هنگام درمان، از یک ماسک یکبار مصرف زیر ماسک ترموپلاستیک مخصوص رادیوتراپی استفاده کرد.



اولویت بندی درمان رادیوتراپی

اولویت بندی اول

- درمان تومورهای با پرولیفراسیون سریع که با هدف درمان قطعی تحت (کمو)رادیوتراپی هستند و هرگونه وقفه درمانی باعث کاهش بقا میگردد باید طبق روال عادی ادامه پیدا کند.

- درمان تومورهای با پرولیفراسیون سریع که تحت رادیوتراپی اکسترنال هستند و قرار است پس از آن تحت براکیتراپی قرار بگیرند باید ادامه پیدا کند.

- در مورد تومورهای با پرولیفراسیون سریع که درمان هنوز آغاز نشده است باید بر اساس یافته‌های کلینیکی و پاتولوژیک تصمیمگیری شود.

اولویت دوم

- درمان بیماران دچار تحت فشار قرار گرفتن نخاع که امید به بازیابی عملکرد نورولوژیک وجود دارد باید به سرعت آغاز شود.

اولویت سوم

- رادیوتراپی رادیکال در بیماران با تومورهای کمتر تهاجمی که رادیوتراپی درمان قطعی است.

- رادیوتراپی در بیماران دچار تومورهای تهاجمی که بعد از جراحی باقیمانده تومورال وجود دارد.

اولویت چهارم

- درمان تسکینی در بیمارانی که درمانشان سبب کاهش بار کاری بیمارستانها و کاهش میزان موارد بستری در بیمارستان می شود (به عنوان مثال بیماران دچار هموپتیزی).

اولویت پنجم

- درمان اچوانت در بیمارانی که تحت جراحی کامل قرار گرفته‌اند و احتمال عود آنان در ده سال آینده کمتر از ۲۰ درصد است (به عنوان مثال بسیاری از بیماران دچار سرطان پستان ER مثبت که تحت درمان هورمونی هستند).
- رادیوتراپی پروستات در بیمارانی که تحت درمان ADH نئوآدجوانت هستند.

توصیه های کلی درمانی

- درمان رادیکال و همچنین اچوانت و نئوآدجوانت رادیوتراپی در سرطانهای که ممکن با سپری شدن زمان طلایی از اثربخشی آن کاسته شود بهتر است با رعایت نکاتی که در این دستورالعمل ذکر میشود انجام شود.
- نمونه این سرطانها عبارتند از سرطانهای سر و گردن، سرویکس، لنفوم و رکتوم.

- درمانهای رادیکال و همچنین اچوانت و نئوآدجوانت رادیوتراپی در سرطانهایی که رشد آهسته دارند و بیولوژی تومور اجازه می دهد که درمان به تعویق بیفتد، می توانند به تعویق انداخته شوند.
- سرطان پروستات، سرطان پستان هورمون مثبت (به خصوص در سنین بالاتر)، تومورهای مغزی نخاعی و سرطان پوست از این دسته هستند.

- در مواردی که درمان رادیوتراپی فقط با هدف کنترل لوکال و بدون اثر مشخص روی بقای کلی انجام می شود شاید بهتر باشد درمان انجام نشود و یا به زمان بعد از اتمام پاندمی موکول شود مانند بسیاری از سارکومها

- بهتر است در انجام رادیوتراپی بیمارانی که قسمت زیادی از مغز استخوان

تحت پرتوتابی قرار میگیرد مانند درمان لگن و یا درمان کل مغز و نخاع (CSI) با دقت تصمیمگیری شود و در صورت امکان این درمانها به تعویق بیفتند.

- درمان رادیوتراپی تسکینی برای کنترل درد بهتر است به تعویق انداخته شود و بیمار با دارو کنترل شود.
- درمان رادیوتراپی تسکینی برای مواردی مثل خونریزی غیرقابل کنترل و دیسفاژی باید با در نظر گرفتن تمام جوانب انجام شود.

ادامه درمان رادیوتراپی

- تکلیف مشخص نیست!
- ولی با توجه به اینکه بسیاری از بیماران تحت رادیوتراپی دچار ضعف ایمنی هستند ابتلا به COVID-19 ممکن است در این بیماران کشنده باشد.
- در این مورد بیماران مبتلا به بدخیمیهای توراسیک در معرض خطر بیشتری هستند.

ابتلای بیمار حین درمان

- تصمیم به ادامه درمان علاوه بر ضرورت انجام رادیوتراپی بر اساس اندیکاسیون- های خاص هر سرطان، به شدت بیماری COVID-19 نیز بستگی دارد.
- در بیماران مشکوک به COVID-19 بهتر است درمان بلافاصله قطع شود تا خطر سرایت بیماری به دیگران به حداقل برسد و سپس درمورد نحوه ادامه درمان تصمیمگیری شود.

کاهش قابل ملاحظه تعداد پرسنل

- از قبل پیشبینی شود.
- تعداد حداقلی از پرسنل که قادر به انجام درمان هستند در بخش حضور

داشته باشند.

شاید بهتر باشد درمانهای پیچیده کمتر انجام شود و بیشتر درمانها به صورت تکنیکهای مرسوم استاندارد و یا هیپوفراکشن انجام شود. اگرچه بهتر است پرسنل درمانی برای کاهش میزان سرایت در مراکز مختلف حضور نداشته باشند، ممکن است این امر ناگزیر باشد.

شیمی درمانی همزمان با رادیوتراپی

- سود اضافه کردن شیمی درمانی تعیین شود.
- داروهای استفاده شود که با میزان کمتری از نوتروپنی و ترومبوسیتوپنی همراه هستند.

دستورالعمل پیشنهادی در درمان سرطانهای مختلف.

- درمان بصورت استاندارد 5 روز در هفته آورده شده مگر اینکه متفاوت ذکر شده باشد.
- شواهد این دستورالعمل در بسیاری از موارد به قدرت شواهد درمانهای استاندارد نیستند.
- این پیشنهادات طبق نظرات متخصصین این حوزه در شرایط بحرانی مطرح شده اند.
- انجام این نوع درمانها در شرایط غیربحرانی نیاز به شواهد علمی بیشتری دارد.
- با توجه به اینکه اکثر درمانهای پیشنهادی بصورت هیپوفراکشن هستند، توجه ویژه به بیحرکت سازی بیمار و حفاظت ارگانهای در خطر (OAR) ضروری است.

سرطان پستان

- درمان هیپوفراکشن: تصمیمگیری در مورد نحوه انجام هیپوفراکشن باید به صورت فردی و جداگانه برای هر بیمار صورت گیرد.
- رادیوتراپی حین جراحی:
- اطلاعات در مورد نتایج طولانی مدت کامل نیست.
- در شرایط بحران بیماری COVID-19 میتوان این درمان را به عنوان جایگزین رادیوتراپی اکسترنال در نظر گرفت تا رفت و آمد بیماران و همراهان به مراکز درمانی به حداقل برسد.

بیمارانی که جراحی حفظ پستان شده اند

- در بیماران هورمون مثبت HER2 منفی بدون مشخصات پاتولوژیک پرخطر پس از شرح دقیق شرایط به بیمار میتوان از درمان بوسست صرف نظر نمود.
- در بیماران مسن و early stage که فایده رادیوتراپی در بقای کلی چندان مشخص نیست خطر ابتلا و احتمالاً مرگ ناشی از COVID-19 قابل توجه است شاید بهتر باشد از انجام رادیوتراپی صرفنظر شود.

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- در بیماران هورمون مثبت که شیمی درمانی هم دریافت کرده اند و هم اکنون تحت درمان هورمونی هستند با در نظر گرفتن جمیع شرایط و مرحله بیماری میتوان انجام رادیوتراپی ادجوانت را تا 5 ماه به تاخیر انداخت.

- DCIS: از آنجایی که رادیوتراپی در بسیاری از موارد DCIS اثر مشخصی بر بقای بیمار ندارد و تاثیر آن بر کنترل موضعی میتواند قابل چشم پوشی باشد، پس از صحبت با بیمار بهتر است از رادیوتراپی این بیماران صرف نظر شود.

- رادیوتراپی اکسترنال APBI:

- بیماران early stage بر اساس کرایتریای ASTRO PBI:
- 28.5 الی 30 گری در 5 فراکشن روزانه
- 38.5 گری در 10 فراکشن 2 بار در روز.

رادیوتراپی اکسترنال کل پستان:

- بیماران early stage لنف نود منفی که نیاز به بوست ندارند:
- 28-30 گری در 5 فراکشن هفتگی (یک بار در هفته) بر اساس تریال FAST
- 26 گری در 5 فراکشن روزانه بر اساس تریال FAST forward (این تریال همچنان در حال انجام است و نتایج بقای طولانی مدت مشخص نیست).
- در موارد DCIS بهتر است از درمان صرفنظر شود ولی در صورت ضرورت بهتر است از روش تریالهای FAST و یا FAST forward ذکر شده در بالا استفاده شود.

رادیوتراپی اکسترنال کل پستان به همراه لنف نود:

- درمان بصورت 40 گری در 15 فراکشن روزانه توصیه میشود.
- بوست:

دوز بوست بهتر است در اکثر بیماران حذف شود مگر بیماران زیر ۴۰ سال و یا بیماران بالای ۴۰ سال که دارای فاکتورهای خطر مولکولار و یا پاتولوژیک هستند. در صورت ضرورت دادن دوز بوست همزمان (integrated) ارجح است.

بیمارانی که ماستکتومی شده اند

- در بیماران T1-2 N1 که فاقد فاکتورهای خطر مولکولار و پاتولوژیک هستند میتوان از درمان رادیوتراپی ادجوانت صرف نظر کرد.
- در بیمارانی که نیازمند درمان chest wall هستند درمان بصورت 40-43.5 گری در 15 فراکشن روزانه توصیه میشود.

سرطان پروستات

- در شرایط بحرانی میتوان درمان سرطان پروستات را به تعویق انداخت و یا در صورت نیاز از روشهای هیپوفراکشن استفاده نمود.
- بیماران با ریسک پایین: پیگیری بصورت active surveillance و اندازهگیری PSA بعد از 6 ماه توصیه میشود.
- بیماران با ریسک متوسط و مطلوب: پیگیری با اندازهگیری PSA بعد از 3 الی 6 ماه توصیه میشود.
- در این دسته از بیماران شواهد علمی امکان تعویق رادیوتراپی به مدت سه تا شش ماه در مقالات وجود دارد.

بیماران با ریسک متوسط و نامطلوب: در این بیماران نیازمند رادیوتراپی می-توان درمان ADT را به مدت 4 الی 5 ماه ادامه داد و سپس اقدام به انجام رادیوتراپی نمود.
حتی شواهدی وجود دارد که نشان می دهد شروع رادیوتراپی بعد از 8 ماه نیز احتمالاً safe خواهد بود.

بیماران با ریسک بالا: در بیماران با ریسک بالا درمان ADT به مدت ۲ الی ۴ ماه مناسب است و باید انجام شود.
شواهدی نیز وجود دارد که در بیماران پس از انجام رادیکال پروستاتکتومی که نیازمند رادیوتراپی هستند نیز میتوان با انجام ADT درمان رادیوتراپی را به تعویق انداخت.

درمان رادیکال

- 60 گری در 20 فراکشن 5 روز در هفته برای تمام گروههای خطر. در این درمان نیازی به تعبیه fiducials نیست.
- در بیماران با ریسک پایین و متوسط میتوان از درمان 36.25-40 گری در 5 فراکشن استفاده کرد. در این روش نیاز است که fiducials برای بیمار تعبیه گردد.

- در بیماران با ریسک متوسط نامطلوب و ریسک بالا میتوان از درمان 42.7 گری در 7 فراکشن (3 روز در هفته) استفاده نمود. این درمان ارجح است که با تعبیه fiducials انجام شود.

- در بیماران با ریسک بالا و یا متاستاتیک بالای ۷۵ سال و یا زیر ۷۵ سال با کوموربیدیتی متوسط میتوان از درمان ۳۶ گری در 6 فراکشن (1 فراکشن در هفته) استفاده نمود. در این درمان نیازی به تعبیه fiducials نیست.

- رادیوتراپی سرطانهای سر و گردن بخصوص مواردی که به قصد درمان قطعی انجام میشود جزو اولویتهای اول درمان رادیوتراپی هنگام بحران است.
- در این بیماران ارجح است با رعایت نکات حفاظتی درمان انجام شود.

درمان قطعی

- در این بیماران میتوان از هیپوفراکشن به صورت modest استفاده کرد.
- فواید افزودن شیمیدرمانی به رادیوتراپی در سرطانهای سر و گردن ثابت شده است ولی این فایده با افزایش سن کمتر میشود.
- بنابراین پیشنهاد میشود تجویز شیمیدرمانی همزمان با رادیوتراپی محدود به بیماران زیر ۶۰ سال با PS مناسب باشد.
- 65 گری در 30 فراکشن.
- 66 گری در 33 فراکشن (6 روز در هفته)
- 55 گری در 20 فراکشن (شواهد علمی کمتری دارد و با احتیاط استفاده شود).

متاستاز مغزی

- درمان رادیوتراپی بیماران با متاستاز مغزی بدون علامت با در نظر گرفتن جمیع شرایط بهتر است به تعویق انداخته شود.
- در موارد ضروری روشهای زیر پیشنهاد می شوند:
- در بیماران با 1-3 متاستاز و PS خوب و بیماری خارج مغزی کنترل شده درمان پیشنهادی SRS بصورت 15-20 گری در 1 فراکشن است.

- در سایر موارد درمان تسکینی به صورت ۲۰ گری در 5 فراکشن توصیه میشود.
- در بیماران با پروگنوز بد و PS نامناسب درمان 6 گری در 2 فراکشن توصیه میشود.

متاستاز استخوانی

- بهتر است حتی‌الامکان به تعویق انداخته شود.
- در صورت ضرورت روشهای زیر پیشنهاد می‌شوند:
- در بیماران بدون شکستگی 6-10 گری در یک جلسه
- در بیماران دچار شکستگی و یا پس از جراحی درمان 20 گری در ۵ جلسه

سرطان رکتوم

- در بیماران دچار کانسر رکتوم در شرایط بحرانی بهتر است عمل جراحی که عوارض کمتری دارد (از نظر نیاز به بستری شدن در بیمارستان) انجام شود به عنوان مثال به جای عمل جراحی LAR، عمل هارتمن انجام شود.
- در بیماران دچار کانسر رکتوم در شرایط بحرانی، انجام رادیوتراپی short-course و سپس جراحی تأخیری به انجام رادیوتراپی long-course ارجح است مگر اینکه درگیری قابل ملاحظه دیواره‌ی لگن وجود داشته باشد.



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MSK Manifestations of COVID-19

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Disclosure

- Director of the “Ortho Response to COVID-19 pandemic”
- Delegate for the MSIS guideline for “Resuming Elective Surgeries in the US”
- Editorial Board at JROS, RAA
- Reviewer for JBJS, JOA, The Knee ...
- Consultant at Ortho Medical Companies

COVID MSK manifestations

- Direct effects of the virus
- Effects of hyper-coagulation/ inflammation
- Side effects of prevention/ treatment

Direct virus effects

ACE2 or TMPRSS2 receptors are the main sites for virus entry to the cell

Either ACE2 or TMPRSS2 is expressed in

- | | |
|-----------|-------------|
| - muscle | - cartilage |
| - Menisci | - synovium |
| - bone | |

Direct virus effects

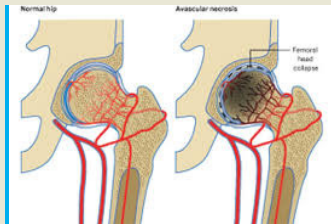
- Myalgia
- Fatigue
- Arthralgia/ Arthritis
- Osteonecrosis
- SK infections (Consumption Immuno-compromisation)

Effects of hyper-coagulation/ inflammation

- VTE
- Stroke
- osteonecrosis
- limb gangrene (COVID-19 toes)
- pressure sores
- COVID toes

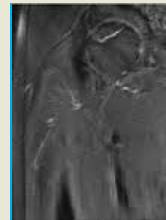
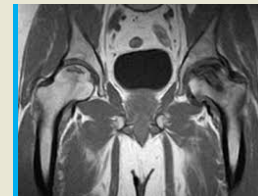


VTE



Osteonecrosis

- Prevention



COVID

- toes



Side effects of prevention/ treatment

- Sedentary life style leading to decompensation, MSK pain
- Pressure sores
- MSK infections
- Osteonecrosis
- Osteoporosis

Treatment

- Prevention of osteoporosis and osteonecrosis
- Specific treatment for distinct pathologies
- Acetaminophen/NSAIDs for nonspecific pain
- Exercise-based regimes
- Multi-disciplinary support
- Orthopaedic rehabilitation



B. SOBOUTI M.D

PROFESSOR OF PEDIATRIC infectious diseases

Iums

2021

Introduction

- Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization (WHO) designated the disease COVID-19, which stands for coronavirus disease 2019. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV. The WHO declared COVID-19 a pandemic on March 11, 2020.

Assessment of severity

- We use the definitions of severity provided in the multicenter interim guidance on the use of antivirals for children with COVID-19:

- Mild or moderate disease – No new or increased supplemental oxygen requirement
- Severe disease – New requirement for supplemental oxygen or increased requirement from baseline without new or increased need for ventilatory support (noninvasive or invasive)
- Critical disease – New or increased need for noninvasive or invasive mechanical ventilation, sepsis, multiorgan failure, or rapidly worsening clinical trajectory

Management of hospitalized children

- Provision of respiratory support, including supplemental oxygen and ventilatory support (noninvasive or invasive); respiratory status may change suddenly after approximately one week of symptoms.
- Provision of fluid and electrolyte support.
- Provision of empiric antibiotics as indicated for community-acquired or health care-associated pneumonia; continuation of empiric antibiotics should be determined by cultures and other microbial tests and clinical condition. Bacterial coinfections appear to be infrequent.
- Monitoring for cytokine release syndrome by monitoring blood pressure for hypotension, oxygen saturation for worsening hypoxemia, and biomarkers.
- Provision of thromboprophylaxis – Interventions to reduce the risk of venous thromboembolism (VTE) may be warranted for children hospitalized with COVID-19

SARS-COV-2 Antiviral therapy for select patients

- Potential indications – Decisions to use antiviral therapy should be individualized according to disease severity, clinical trajectory, existing evidence of effectiveness, and underlying conditions that may increase the risk for progression.

Remdesivir is dosed according to weight as follows: ≥ 3.5 to < 40 kg: 200 mg IV loading dose on day 1, followed by 10 mg/kg IV every 24 hours ≥ 40 kg: 200 mg IV loading dose on day 1, followed by 10 mg/kg IV every 24 hours The usual duration of therapy is up to 5 days for children with severe disease; for children with critical disease who are not improving after 5 days, the duration may be extended to up to 10 days. Remdesivir should not be administered with hydroxychloroquine or chloroquine, because coadministration may decrease remdesivir's antiviral activity. Remdesivir is a prodrug of a nucleotide analog that inhibits RNA-dependent RNA polymerase and has activity against coronaviruses.

- Reported adverse effects of remdesivir include nausea, vomiting, and transaminase elevations. In a review of compassionate use of remdesivir in 77 children hospitalized with severe SARS-CoV-2 infection, 33 percent had adverse events and 16 percent had serious adverse events, most of which were related to COVID-19 or underlying conditions (hypoxia, acute respiratory failure, recurrence of acute lymphocytic leukemia). The only adverse events to occur in more than one patient were elevation of serum aminotransferases (in nine) and anemia (in two). Cases of bradycardia attributable to remdesivir have also been reported, Baricitinib is a Janus kinase inhibitor used for the treatment of rheumatoid arthritis. In addition to its immunomodulatory effects, it is thought to have antiviral effects through interference with viral entry. Baricitinib may provide a mortality benefit for select patients

- Hydroxychloroquine and chloroquine

- Lopinavir-ritonavir

- Glucocorticoids

- Dexamethasone

- Prednisolone

- Methylprednisolone

- Hydrocortisone

- Glucocorticoids plus tocilizumab

- Tocilizumab is dosed according to patient weight

- Tocilizumab should be used with caution in immunocompromised individuals as very few were included in randomized trials. Administration of live vaccines, measles, mumps, rubella, varicella) should be deferred for at least two weeks after the final infusion of tocilizumab ; some experts would wait at least four weeks before administration of live vaccines.

- Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects.

Both beneficial and deleterious clinical outcomes have been reported with use of corticosteroids (mostly prednisone or methyl prednisolone) in patients with pulmonary infections. In patients with *Pneumocystis jirovecii* pneumonia and hypoxemia, prednisone therapy reduced the risk of death. However, in outbreaks of previous novel corona virus infections (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance. In severe pneumonia caused by influenza viruses, corticosteroid therapy appears to result in worse clinical outcomes, including secondary bacterial infection and death.

- Corticosteroids have also been studied in critically ill patients with acute respiratory distress syndrome (ARDS) with conflicting results. Use of corticosteroids in patients with ARDS was evaluated in seven randomized controlled trials that included a total of 851 patients. A meta-analysis of these trial results demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI, 0.59–0.95) and duration of mechanical ventilation (mean difference -4.93 days; 95% CI, -7.81 to -2.06 days)

- Systemic corticosteroids used in combination with other agents including antivirals and immunomodulators such as tocilizumab (see Interleukin-6 Inhibitors) or baricitinib (see Kinase Inhibitors) have demonstrated clinical benefit in subsets of hospitalized patients with COVID-19.

- If dexamethasone is not available, alternative glucocorticoids (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.

- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (oral or intravenous)²⁴ are:

- Prednisone 40 mg
- Methylprednisolone 32 mg
- Hydrocortisone 160 mg

- Half-life, duration of action, and frequency of administration vary among corticosteroids.

- Long-acting corticosteroid: Dexamethasone; half-life 36 to 72 hours, administer once daily.

- Intermediate-acting corticosteroids: Prednisone and methylprednisolone; half-life 12 to 36 hours, administer once daily or in two divided doses daily.

- Short-acting corticosteroid: Hydrocortisone; half-life 8 to 12 hours, administer in two to four divided doses daily.

- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see Hemodynamics for more information. Unlike other corticosteroids previously studied in patients with ARDS, dexamethasone lacks mineralocorticoid

activity and thus has minimal effect on sodium balance and fluid volume.

- Budesonide is a synthetic, inhaled corticosteroid with potent glucocorticoid activity and weak mineralocorticoid activity. It has broad anti-inflammatory properties and has Food and Drug Administration-labeled indications in the management of chronic respiratory diseases including asthma and chronic obstructive pulmonary disease. Certain inhaled corticosteroids have been shown to impair viral replication of SARS-CoV-2²⁵ and downregulate expression of the receptors used for cell entry.^{26,27} These mechanisms support the potential of inhaled corticosteroids as therapeutic agents for COVID-19. However, observational studies of individuals who were chronic inhaled corticosteroid users have found that its use either had no effect on COVID-19 outcomes or increased risk of hospitalization.

- The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients and caution is warranted when extrapolating recommendations for adults to patients aged <18 years. The Panel recommends using dexamethasone for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Corticosteroids are not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., administered via a nasal cannula only).

- Use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated and may be harmful; therefore, such use should be considered only on a case-by-case basis. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days. Corticosteroid use has been described in the treatment of multisystem inflammatory syndrome in children (MIS-C) in multiple case series. It is the second most used therapy after intravenous immunoglobulin for MIS-C.^{42,43} Please refer to Special Considerations in Children for more information on the management of MIS-C.

- All children in the study developed a serious disorder following COVID-19 infection. This condition, called multi-system inflammatory syndrome in children (MIS-C), is thought to affect 1 in 50,000 children with SARS-CoV-2 infection.

- the new disorder, which is also called paediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS), affects children of all ages but is more common in older children and teenagers. The disorder generally occurs 2-6 weeks after infection with the SARS-CoV-2 virus.

- The illness is characterised by persistent high fever, often accompanied by abdominal pain, vomiting, red eyes and red rash. Severely affected children have developed heart inflammation, with shock and failure of multiple organs.

- Fortunately, with optimal treatment the majority of affected children have recovered well. However, worldwide most reports suggest a fatality rate of 2-4%.

- Heart complications

- Interferon-beta 1b
- convalescent plasma from recovered COVID-19 patients
- Outpatient monoclonal antibody therapy
- Adequate vitamin D intake
- Zinc
- Vitamin C
- Selenium

Multi systemic inflammatory syndrome in children (MISC)

- IVIG
- Dexamethasone
- Enoxaparin
- Methylprednisolone
- Tocilizumab(ACTEMRA)
- Infliximab



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Coronavirus disease 2019 (COVID-19)

- Is an illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- In throughout the world, fewer cases of COVID-19 have been reported in children than in adults.
- Most cases in children are mild, and treatment consists of supportive care.



Cough & Fever Cough & Fever

It is important to note that these symptoms may not always be present; thus, a high index of suspicion for SARS-CoV-2 infection is required in children.

Other symptoms include the following:

Shortness of breath
Pharyngeal erythema/sore throat
Diarrhea
Myalgia
Fatigue
Rhinorrhea
Vomiting
Nasal congestion
Abdominal pain
Conjunctivitis
Rash
Loss of sense of taste (ageusia) and/or smell (anosmia)

- COVID-19 have varying degrees of signs and symptoms, ranging from no symptoms (asymptomatic) to severe symptoms and can be fatal.
- Because some of the symptoms of flu, COVID-19, and other respiratory illnesses are similar, the difference between them cannot be made based on symptoms alone.

The characteristic signs and symptoms of COVID-19.

- COVID-19 can sometimes cause a person to suddenly lose their sense of smell (anosmia) or taste (ageusia).
- Red, swollen eyes: Some COVID-19 patients have experienced red, itchy, and swollen eyes that resemble conjunctivitis (or pink eye).
- Skin rashes: Mostly seen in younger patients, COVID-related skin rashes range from hives and little red bumps to sores on the toes, what some experts refer to as 'COVID toes.'

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Children and pregnant women

- are more vulnerable to influenza virus and COVID-19 symptoms on the other hand are milder in pregnant women and children.

“Very young children seem to be somewhat less likely to become ill with COVID.”
Flu, on the other hand, **“actually tends to make very young children very sick.”**

Both COVID-19 and Flu

- can spread from person-to-person between people who are in close contact with one another (within about 6 feet).
- Both are spread mainly by large and small particles containing virus that are expelled when people with the illness (COVID-19 or flu) cough, sneeze, or talk.
- These particles can land in the mouths or noses of people who are nearby and possibly be inhaled into the lungs. In some circumstances, such as indoor settings with poor ventilation, small particles might be spread further than 6 feet and cause infections.

CHILDREN TRANSMISSION

They noted that children are more likely than adults to have upper respiratory tract involvement, including nasopharyngeal carriage.

They may also have prolonged respiratory and fecal shedding.

Family clustering appears to play a major role in disease transmission.

Most of the children had exposure to a patient with COVID-19 in the household or community.

Mother-to-fetal transmission

- Based on limited data, no confirmed cases of vertical mother-to-fetus intrauterine transmission of the virus have been reported.
- Newborns whose mothers had been admitted owing to their COVID-19 infection had a higher risk of premature delivery.
- To date, SARS CoV-2 has not been detected in breast milk.

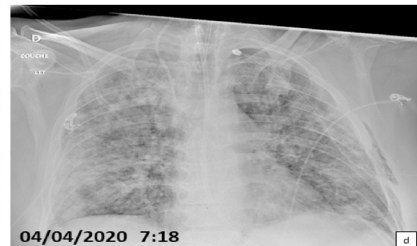
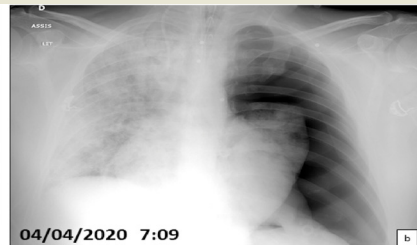
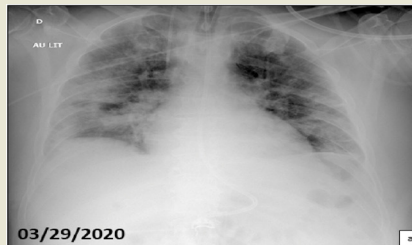
Diagnosis

Primary Lab tests:

- Lymphopenia (< 3000 in < 1 year, < 2000 in $1 < \text{year} < 5$, < 1000 in > 5 year)
- Increased levels of liver and muscle enzymes and lactate dehydrogenase
- Increased myoglobin and creatine kinase isoenzyme levels
- Elevated C-reactive protein (CRP) level
- Elevated erythrocyte sedimentation rate
- Increased procalcitonin level
- Elevated D-dimer

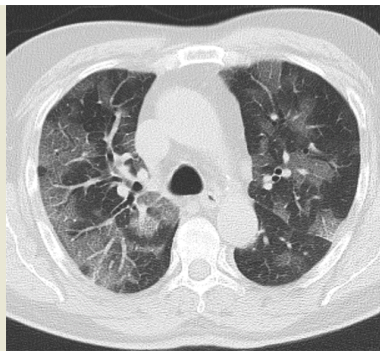
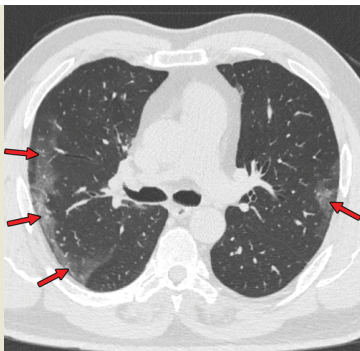
Common chest radiograph findings in children with COVID-19 pneumonia include:

- **Bilateral distributed peripheral and subpleural ground-glass opacities and consolidation.**



Mother-to-fetal transmission

- Ground-glass opacities/nodules
- Consolidation with a surrounding halo sign
- Bilateral or local patchy shadowing
- Interstitial abnormalities



- Chest imaging is not generally recommended for initial screening of mildly symptomatic or asymptomatic children with suspected COVID-19 unless they are at risk for disease progression or have worsening symptoms.
- An initial chest radiograph may be appropriate for children with moderate to severe symptoms, and a chest CT scan may be warranted if the results could affect clinical management.
- A series of chest radiographs may be useful to assess therapeutic response, evaluate clinical worsening, or determine positioning of life support devices.

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❑ Clinical criteria

Any person with at least one of the following symptoms :

Cough

Fever

Shortness of breath

Sudden onset of anosmia, ageusia or disguise

❑ Diagnostic imaging criteria

Radiological evidence showing lesions compatible with COVID-19

❑ Laboratory criteria

Detection of SARS-CoV-2 nucleic acid in a clinical specimen

❑ Epidemiological criteria

At least one of the following two epidemiological links:

- a) Close contact with a confirmed COVID-19 case in the 14 days prior to onset of symptoms
- b) having been a resident or a staff member, in the 14 days prior to onset of symptoms, in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed

Close contact (within 6 feet of someone for a total of ≥ 15 min)

❑ Covid-19 stages:

- **Zero:** Asymptomatic 4%
- **One:** Early infection 51%
- **Two:** Respiratory phase 39%
- **Three:** Hyper inflammation 5%

The WHO case definition for MIS-C

- An individual aged < 18 years presenting with fever(>3 days), laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND

- No alternative plausible diagnoses; AND

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

- Also unlike KD, affected children have been predominantly in the 5-9 and 9-14 age groups.

The pathophysiology of MIS-C in children has been described in its initial stages, with COVID-19 infection triggering macrophage activation followed by helper T-cell activation.(2-6 weeks later)

This in turn leads to massive cytokine release with B-cell and plasma cell activation and the production of antibodies, which leads to immune dysregulation and a hyperimmune response.

- World Health Organization criteria for MIS-C. Among 614 children with suspected MIS-C, 246 received primary treatment with IVIG alone, 208 with IVIG plus glucocorticoids, and 99 with glucocorticoids alone.

Twenty-two children received other treatment combinations, including biologic agents, while 39 received no immunomodulatory therapy.

MIS VS Kawazaki Disease

- The data suggest that the SARS-CoV-2-associated cases occurred in children who were older than the children with Kawasaki-like illness diagnosed prior to the COVID-19 epidemic.

- In addition, the rates of cardiac involvement, associated shock, macrophage activation syndrome, and need for adjunctive steroid treatment were higher for the SARS-CoV-2-associated cases.

- Many patients with MIS-C have abnormal markers of cardiac injury or dysfunction, including Troponin and Brain Natriuretic Protein(BNP).

Consists mainly of supportive care, including oxygen therapy in children with hypoxia.

Remdesivir (5-10 days)

- The only antiviral drug that has received full approval from the FDA for treatment of COVID-19.

It is indicated for treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg.

An emergency use authorization remains in place to treat children younger than 12 years who weigh at least 3.5 kg.

The FDA expanded to use in all hospitalized patients with confirmed or suspected COVID-19 disease, regardless of oxygen status.

Corticosteroids (Dexamethasone):

- National Institutes of Health (NIH) suggests that dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who are on moderate to severe respiratory symptoms or mechanical ventilation.
- MIS-C patients

Convalescent plasma

- The decision to treat patients < 18 years of age with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

Monoclonal Antibodies

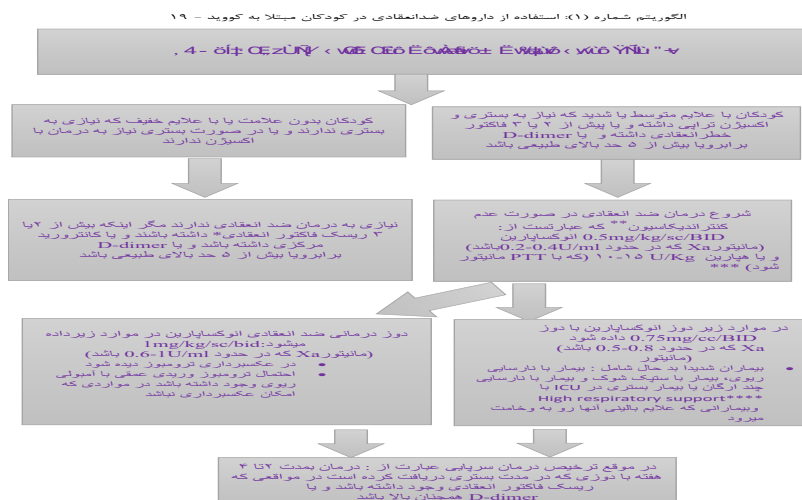
- EUAs have also been granted for outpatient monoclonal directed therapies (ie, casirivimab plus imdevimab, bamlanivimab plus etesevimab) for individuals aged 12 years and older who test positive and are at high risk of severe COVID-19 or hospitalization

Tocilizumab (Actemra)

- As a single dose; may repeat dose in 12 hours if signs/symptoms worsen or do not improve.(up to 3 dose)
- maximum dose: 800 mg/dose
- A baseline absolute neutrophil count (ANC) of $\leq 2000/\text{mm}^3$ or greater and $\geq 100.000/\text{mm}^3$ or greater are required before initiating Tocilizumab (in special condition platelet count of $\geq 50.000/\text{mm}^3$ is acceptable)
- Do not initiate Tocilizumab in patients with baseline increased ALT or AST levels

Thrombotic complications

- Further injury to the endothelial tissues results in microthrombi formation and can lead to thrombotic complications such as pulmonary embolism, venous thrombosis, and thrombotic arterial complications as seen in severely ill patients.



Vaccine types:

- Inactivated whole virus vaccines
- Protein-based vaccines (Recombinated)
- Viral vector vaccines
- RNA and DNA vaccines
- Weakened live virus vaccines

- The FDA has granted emergency use approvals for 3 SARS-CoV-2 vaccines since December 2020.

Two are mRNA vaccines – (Pfizer) and (Moderna), whereas the third is a viral vector vaccine – (Johnson & Johnson).

On May 10, 2021, the FDA extended the EUA for the Pfizer vaccine to include younger adolescents aged 12-15 years. On October 29, 2021, the FDA further expanded the EUA for the Pfizer vaccine to include children aged 5-11 years.

تازه های کووید

Covid 19

The Comprehensive National Congress On Covid 19

- The American Academy of Pediatrics strongly recommends that children and adolescents aged 5 years and older receive the COVID-19 vaccine.

COVID Death

- The CDC reports that 121 deaths related to SARS-CoV-2 infection occurred among persons younger than 21 years of age in the United States from February to July 2020.
- Of the persons who died, 63% were male, 10% were aged < 1 year, 20% were aged 1-9 years, and 70% were aged 10-20 years.
- Ninety-one (75%) had an underlying medical condition.

Risk for severe disease

- Those with underlying conditions (eg, congenital heart disease, bronchial pulmonary hypoplasia, respiratory tract anomaly, abnormal hemoglobin level, or severe malnutrition)

Those with immune deficiency or immunocompromised status (eg, as a result of long-term immunosuppressant use).

The following conditions indicate a greater likelihood of severe disease:

- Tachypnea
- Persistent high fever for 3-5 days.
- Poor mental response, lethargy, disturbance of consciousness, and other changes of consciousness.
- Abnormally increased levels of enzymes, such as myocardial and liver enzymes and lactate dehydrogenase.
- Unexplained metabolic acidosis.
- Chest imaging findings indicating bilateral or multi-lobe infiltration, pleural effusion, or rapid progression of conditions during a very brief period.
- Age younger than 3 months.
- Extrapulmonary complications.
- Coinfection with other viruses or bacteria.

Co-Infection

- Slightly more than half of the children who underwent nucleic acid testing for common respiratory pathogens showed co-infection with pathogens other than SARS-CoV-2.
- This finding illustrates the need to test for COVID-19 even in the setting of other confirmed viral infections.

The residual symptoms that can occur after a SARS-CoV-2 infection in children :

- Respiratory symptoms, such as cough, chest pain, and exercise-induced dyspnea
- Cardiac involvement, including myocarditis
- Anosmia and/or ageusia, which typically resolve in several weeks in children
- Neurodevelopmental impairment, such as delays or changes in cognitive, language, academic, motor, or mood/behavior domains
- Cognitive “fogginess” or fatigue, which may manifest as inattentiveness or slower reading or processing
- Physical fatigue and/or poor endurance
- Headache, which is common both during and after SARS-CoV-2 infection
- Mental and behavioral health problems



Mohammad Taher ,MD

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- At the end of presentation, participants should be familiar with:
- 1- Direct and indirect effects of COVID-19 on liver
- 2- Evaluation of LFT abnl in COVID-19 infected pts
- 3- Impact of COVID-19 on patients with chronic liver disease
- 4- Management of cirrhosis and chronic liver diseases during COVID-19 infection

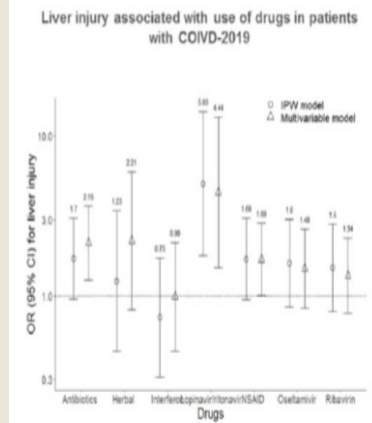
- **SARS-Cov-2 binds to cells through ACE2 receptors**
- As ACE2 occurs on liver & biliary epithelial cells, the liver is a target for infection
- **Summary of 12 reports describe abnl LFTs in 10-58% with mixed impact on outcomes**
- **Rare cases of severe acute hepatitis**

- Cholestatic enzyme elevation were rare
- AST predominance was common
- * Not correlated with CK level/muscle injury
- * Appears to reflect true hepatic injury
- * No clear demographic or comorbidities associated with injury

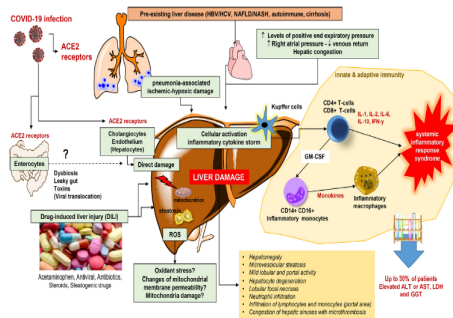


Liver Injury During COVID-19 Infection Indirect effects

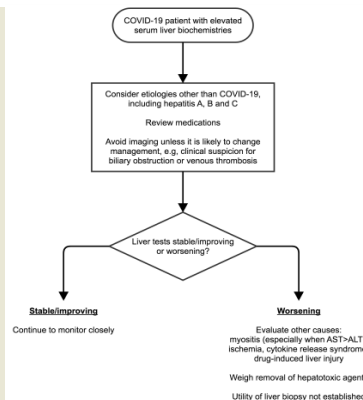
- Many critically ill
- Prevalent chronic liver disease??
- Drug induced liver injury



Pathogenesis of liver damage during COVID-19 infection



Evaluation of pts with COVID-19 & Elevated LFT



Impact of COVID-19 on CLD

NAFLD/NASH

- Preventing liver disease progression through intensive lifestyle intervention, including nutritional guidance, weight loss advice, and diabetes management
- Treatment of arterial hypertension
- ACE inhibitors or ARB do not increase the risk of COVID-19 infection or severe complications or death
- Early admission should be considered for all pts with NAFLD who become infected with SARS-CoV-2

Impact of COVID-19 on CLD

Autoimmune Liver Diseases

- Advise against reducing immunosuppressive Tx to prevent COVID-19
- Reductions should only be considered under special circumstances (e.g. medication-induced lymphopenia, or bacterial/fungal superinfection in severe COVID-19)
- To minimize systemic glucocorticoid exposure consider budesonide to induce remission
- Paucity of data to make recommendations for pts with PBC, PSC or IgG4-related dis
- All pts should receive vaccination for Streptococcus pneumoniae and influenza

Impact of COVID-19 on CLD

HCC

- The specific risk of COVID-19 in pts with HCC remains undefined
- Care should be according to guidelines including continuing systemic treatments and evaluation for LT
- Multidisciplinary HCC boards
- Full HCC surveillance should resume

Impact of COVID-19 on CLDCirrhosis

- Vulnerable to both the consequences of COVID-19 and to the adverse effects of delayed or altered standard of care during the COVID-19
- Infected with SARS-CoV-2 are at high risk of new or worsening hepatic decompensation
- All pts with new or worsening hepatic decompensation or ACLF should be tested for COVID-19 even in the absence of respiratory symptoms
- Do not need to update labs only for LT listing
- Prophylaxis against SBP, GIB and HE to avoid hospitalization

- Abnormal liver enzymes need evaluation
- HBV or AIH flare? Alcohol? COVID-19?
- No need to reduce immunosuppression for asymptomatic/COVID-19 neg. pts
- Social distancing, Hand washing ...
- Telephone/video visit
- Do not need to update labs only for LT listing
- COVID-19 cause LFT abnormality, ALI or ACLF
- All pts with ACLF should be tested for COVID-19 even without respiratory symptoms
- High Mortality of COVID-19 in cirrhotic pts
- HBV & HCV Tx continue in pts w/o COVID-19
- HCC surveillance should be resumed
- Maintain HCC multidisciplinary Boards

