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CORONAVIRUS EDITION

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Editorials

Articles

THE CORONAVIRUS EDITION was divided in Issue 1 (March) and 2 (June) of 2020. The aim of these editions is to make a panoramic compilation of the pandemic, presenting all aspects, discoveries, reports about the COVID-19 pandemic and SARS-CoV-2: Epidemiological issues of the COVID-19, the pathophysiology of the disease, immunological responses, gallery photos, treatments, vaccines ongoing, diagnostics of the disease, characteristics genome of the virus and so on. All the data the ISI-SENAI-CMATEC Group used for the issues of JBTH was based on review articles, systematic review, meta-analyses, clinical trials, and guidelines from the best International Centers against COVID-19, index medicus database and reports of World Health Organization (WHO).

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COVER: A lung cell infected by CoV-2. Credit: Public Health Image Library (PHIL) (www.cdc.gov › subtopic › images) and NIAID (https://www.niaid.nih.gov/news-events/novel-coronavirus-sarscov2-images).

The ISI-SENAI-CIMATEC Group writes some articles of this issue in a partnership with the Development and Innovation Laboratory Group of Butantan Institute.

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SENAI CIMATEC in the Scnario of Coronavirus Pandemic

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Historically, every major change is preceded by events that cause large social and economic disruption. The new coronavirus pandemic has posed challenges to the health system, people, and the economy, leading to abrupt social changes. There was a change in the entire world scenario and people's lives were affected in many ways: health care, social behavior and, mainly, in how to establish the parameters of a new economy.

According to a survey by the National Confederation of Industry (CNI), 79% of industries claim to have suffered a reduction in orders. About 53% say the fall was intense. The data showed 86% of the companies are struggling to receive inputs and 83% face problems in transport logistics, both for products and raw materials.

This scenario leads to a great rush to adapting the new social behavior and economic models. New investments in the economic and governmental sector and behavioral and social changes that would happen in years are occurring in a few months, thanks to the tools of industry 4.0.

Industry 4.0 is a concept recently proposed and encompasses the main technological innovations in the fields of automation, control, and information technology applied to manufacture processes. The term appeared in Germany, in the 2011 edition of the Hannover Fair, and proposes to cross the boundaries between the digital, the physical and the biological world.

Thus, although the negative economic impact has been huge since the pandemic was declared by the World Health Organization in March 2020, new achievements are being made by industry 4.0 focused on health, since this impact has caused the world economy to shrink, generating unemployment and social instability.

Developed countries, such as the United States of America, Germany, and Japan, and the main emerging countries, such as China and India, have outlined strategies to strengthen the industrial sector and make industry 4.0 a reality at this time. However, the spread of SARS-COV-2, the virus that caused the COVID-19 pandemic, revealed a bleak reality: most countries were not prepared to face a large-scale health emergency. Also, hospitals are not equipped with a sufficient number of ventilators and respirators, essential equipments to save lives in the most serious cases of COVID-19, and the domestic industrial parks did not have the necessary installed capacity to meet rapidly expanding demand. The wide majority of countries faced their high dependence on the import of these materials or supplies from China, such as personal protective equipment (PPE) for health teams, face shields, gloves, masks surgical, disinfectants, hydroalcoholic gel and masks for the general population. Another bottleneck that has been noted since the beginning of the pandemic was the insufficiency of diagnostic test kits for SARS-COV-2. Thus, given the difficulty in obtaining medical and hospital equipment and materials, which are fundamental for the management of the symptoms of COVID-19, the conversion of industrial production lines has helped many countries to meet the strong increase in demand of many products previously imported, mainly about the manufacture of ventilators, mechanical respirators, and personal protective equipment (PPE).

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Figure 1. Campus of SENAI CIMATEC.

However, despite the negative economic aspect and the need to innovate to reconverting production lines, the industries began to put into practice the knowledge concerning industry 4.0, since Fourth Industrial Revolution gave us the tools we need to battle this global threat (artificial intelligence, Big Data, neural network, IoT). The new technologies have the capability of providing better digital solutions for our daily lives during this crisis. Several benefits help us for mitigating effects of COVID-19 pandemic and searching treatments and vaccines, as follow:

- Providing medical part in time using smart supply chain.
- Using robotic based treatment of the infected patient to reduce medical risks.
- Using virtual reality for training purpose.
- Promoting a flexible working environment of treatment.
- Digital Technologies can help people to perform daily life work during the lockdown.
- Expansion use of the Telemedicine.
- Researchers can employ these technologies for social and media platforms to identify unusual information.
- The creation of resourced databases to track and predict infectious risk.
- Artificial intelligence (AI) could be used to enabling states to manage the caseload.
- AI can be a valuable triage tool through virtual chatbots, a considerably important resource in scenarios of high clinical demand.
- Using of AI to new image methods for COVID-19.
- The power of robots and drones, which have proven instrumental in reducing interpersonal contact by facilitating the delivery of food and medication and the disinfection of public spaces.
- Implementing universal use of masks in conjunction with lockdown efforts, successfully driving a flattening of the curve.
- Implementing curfews to mitigate community transmission and have communicated rapidly, transparently, and thoroughly.

The Fourth Industrial Revolution has equipped society with highly potent tools and we must harness their capabilities, where possible, to win this fight. So, COVID-19 accelerates this process and sentences our definitive entry to the fourth Industrial Revolution.

In this sense, aligned with industry 4.0, SENAI CIMATEC (Figure 1) established a proactive position in the face of the COVID-19 pandemic, promoting research, implementing plans, activities, and actions that contemplate both the redirection of the sector's industries to the health area, as well as the new technologies of industry 4.0. The position of SENAI CIMATEC reaffirms its commitment to society at decisive moments and ensures its efforts in health care against the pandemic.

A Brief Achievements of SENAI CIMATEC Against COVID-19

Leone Peter Andrade[1]*

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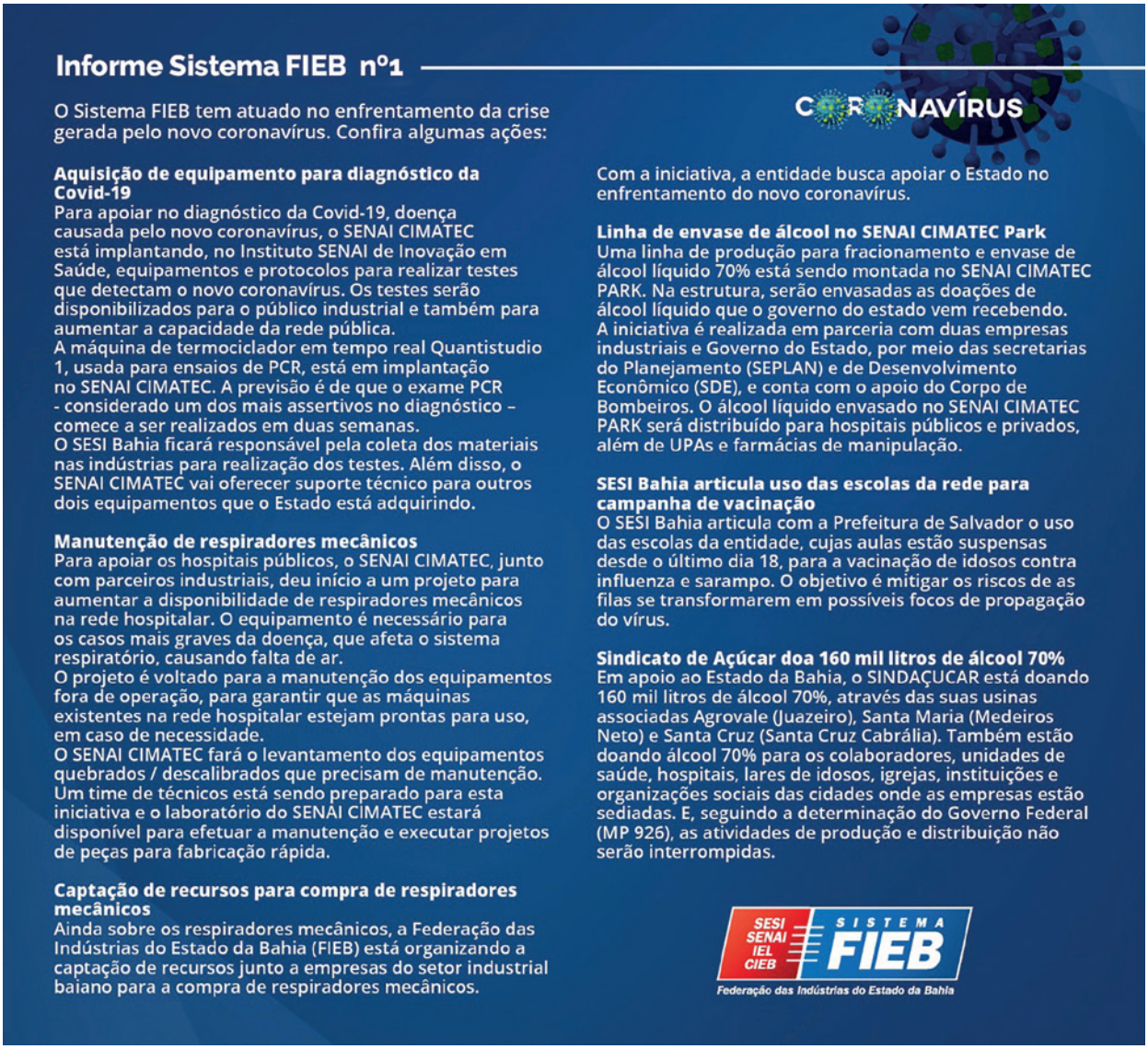
In this brief, we summarized some actions that the SENAI CIMATEC did from March to June 2020, and continues to promoting against the COVID-19 pandemic. We know we have the knowledge to combat and be adapted to this crisis.

March 2020 (Figures 1 and 2)

- Presentations and workshops about the pandemic and a guidance to the SENAI CIMATEC community.

Figure 1. Folder 1 – Actions and activities of SENAI CIMATEC against COVID-19 (March 2020).



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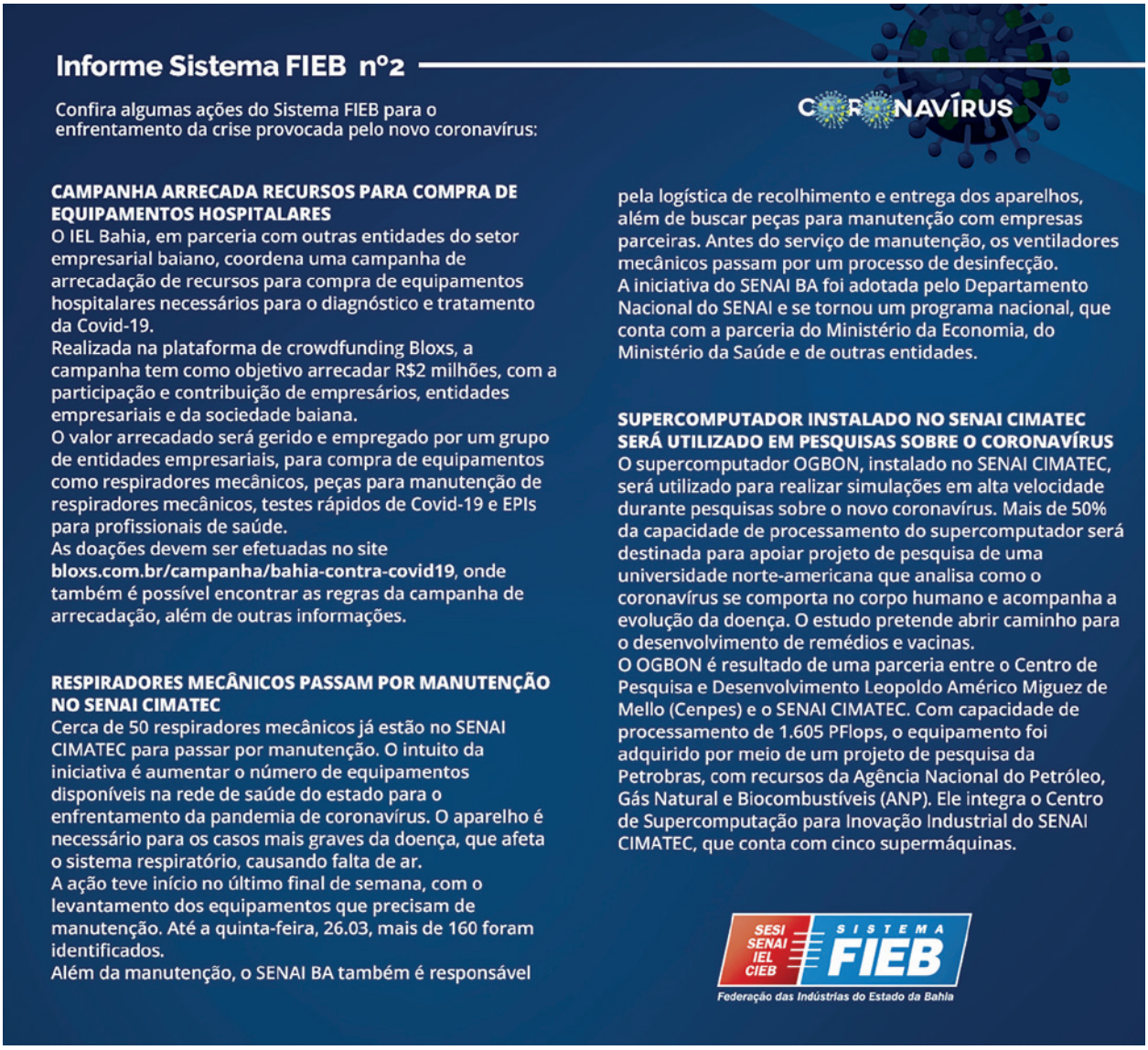
J Bioeng. Tech. Appl. Health 2020;3(1):3-11.

Figure 2. Folder 2 – Actions and activities of SENAI CIMATEC against COVID-19 (March 2020).



- Creation of a COVID-19 contingency plan for the SENAI CIMATEC workers.
- More than 80 projects were contemplated by ISI (SENAI Institute for Innovation in Advanced Health Systems) to help to preventing, diagnosing and treating COVID-19:
  - o Using new technologies of industry 4.0 against COVID-19.
  - o Expansion of the number of ventilators.
  - o In addition to expanding the test network, researchers at SENAI CIMATEC have been implanted a new diagnostic method (approved by World Health Organization) for faster and more effective detection of the new coronavirus (SARS-CoV-2) with the results in 30 minutes.
  - o Creation of new image diagnostic methods through Artificial Intelligence.
  - o Development of rapid tests and personal protective equipment (PPE) that can replace masks, gloves and soaps.
  - o Replacement of pieces and components used in intensive care units (ICUs).
- Opening of distance education courses on industry 4.0 during the pandemic.
- Provision of state-of-the-art laboratories to assist the State of Bahia, Brazil, with carrying out RT-PCR tests for the coronavirus, with fast and accurate results (Figure 3).

- Mitigation of risks related to the coronavirus through the availability of vaccination of the elderly against influenza and measles.
- Fundraising for the purchase of hospital materials.
- Acquisition of diagnostic equipment for COVID-19 (assembly of a molecular biology laboratory for the diagnosis of COVID-19 through the RT-PCR exam within the infrastructure of state-of-the-art laboratories at CIMATEC).

April 2020 (Figures 4 and 5)

- Fundraising for the purchase of mechanical ventilators.

Figure 3. Molecular biology laboratory implemented by CIMATEC to carry out RT-PCR tests on industry professionals from the State of Bahia (Brazil).

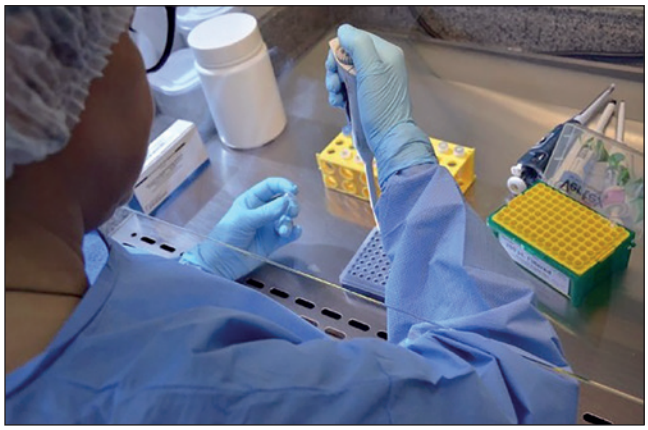


Figure 4. Folder 3 – Actions and activities of SENAI CIMATEC against COVID-19 (April 2020).

Informe Sistema FIEB nº3

Confira algumas ações do Sistema FIEB para o enfrentamento da crise provocada pelo novo coronavírus:

CORONAVÍRUS

CAPTAÇÃO DE RESPIRADORES E LOGÍSTICA DO SENAI BAHIA VIABILIZAM MANUTENÇÃO DE VENTILADORES

Desde o dia 23 de março, profissionais do SENAI Bahia mapeiam as instituições que poderiam necessitar da recuperação de ventiladores pulmonares. Eles entram em contato com Unidades de Pronto Atendimento (UPA), unidades de saúde e hospitais, dando prioridade para as instituições públicas, além de providenciarem a retirada e a entrega dos respiradores.

Outra força tarefa, formada por engenheiros e técnicos do SENAI Cimatec e de outras instituições, corre contra o tempo para disponibilizar os aparelhos que estavam fora de uso. Nem todos estão em condições de conserto, mas, até o dia 02 de abril, 21 equipamentos já tinham sido recuperados. A expectativa é que, com a ação, voltem à utilidade 120 ventiladores.

Como o SENAI Bahia tem unidades na maioria das cidades do interior, essa capilaridade facilita o mapeamento e coleta dos respiradores mecânicos em todo o estado, além da devolução dos aparelhos. Além de Salvador, já foram atendidas unidades de saúde em mais de 30 municípios. Um e-mail foi disponibilizado pelo SENAI BAHIA para que as instituições de saúde possam solicitar o serviço, que está sendo feito de forma gratuita. O contato deve ser feito por meio do faleconoscosenaiba@fieb.org.br.

MINISTÉRIOS PÚBLICOS E FIEB UNIDOS PARA ELEVAR PRODUÇÃO DE ÁLCOOL GEL

O Ministério Público do Trabalho (MPT), o Ministério Público estadual (MP-BA) e a FIEB estão unindo esforços para sensibilizar as empresas industriais baianas a direcionarem suas linhas de produção para a fabricação de álcool em gel ou líquido. Empresas com capacidade para adequar sua linha de produção podem obter de forma rápida e desburocratizada a autorização da Agência Nacional de Vigilância Sanitária (Anvisa).

Um comunicado informando as regras simplificadas para a obtenção da autorização está sendo distribuída às indústrias que poderiam ajustar suas plantas para atender à grande demanda do mercado. A indústria interessada deverá encaminhar e-mail para gimep@anvisa.gov.br, solicitando autorização especial para produção de álcool líquido ou gel, com pedido de excepcionalidade, acompanhado da documentação necessária.

61 MIL PEÇAS DE VESTUÁRIO PARA HOSPITAIS SÃO PRODUZIDAS PELO SETOR DE CONFECÇÃO

Os hospitais da rede pública de saúde do estado começaram a receber, na primeira semana de abril 2,5 mil conjuntos de roupas para médicos e enfermeiros e 3,5 mil camisolas para pacientes. As peças de vestuário estão sendo produzidas por empresários baianos do setor de confecções. A ação é fruto da parceria entre a Secretaria de Desenvolvimento Econômico (SDE), Secretaria do Planejamento do Estado da Bahia (Seplan), o Sindicato da Indústria de Vestuário e Artefatos de Joalheria e Bijuteria do Estado da Bahia (Sindvest), e o Condomínio Bahia Têxtil.

A iniciativa vai ajudar a suprir a demanda por enxovais hospitalares, que aumentou com expansão da rede de atendimento em saúde, em função do enfrentamento ao coronavírus. Por outro lado, a medida contribui para manter 25 empresas participantes em atividade. A parceria prevê a confecção de 61 mil itens de vestuário, sendo 7,2 mil lençóis, 7 mil camisolas, 40 mil roupas privativas, compostas por calça tipo pijama e camisa, e 7,2 mil toalhas de banho, de uso hospitalar. Mas já há um pedido extra de mais 8 mil peças. Com a parceria, é possível adaptar e continuar parte da produção, mantendo a economia baiana ativa.

PESQUISADORES DO SENAI CIMATEC UTILIZAM INTELIGÊNCIA ARTIFICIAL PARA ESTUDOS SOBRE O CORONAVÍRUS

O centro de competência em Inteligência Artificial do CIMATEC, um dos braços do Centro de Supercomputação para Inovação Industrial da instituição (CS2I), está desenvolvendo pesquisas próprias relacionadas ao coronavírus. Uma delas é sobre o suporte ao diagnóstico de Covid-19 em exames de Raio-X e Tomografia Computadorizada.

SESI SENAI IEL CIEB — SISTEMA FIEB

Federação das Indústrias do Estado da Bahia

Figure 5. Folder 4 – Actions and activities of SENAI CIMATEC against COVID-19 (April 2020).

Informe Sistema FIEB nº4

Confira algumas ações do Sistema FIEB para o enfrentamento da crise provocada pelo novo coronavírus:

CORONAVÍRUS

SESI E SINDUSCON INICIAM BLITZ CONTRA A COVID-19

Parceiros históricos nas ações de saúde e segurança no trabalho voltadas para a indústria da construção, o SESI e o Sinduscon Bahia começam, nesta semana, uma ação conjunta para prevenir a incidência de Covid-19 nos canteiros de obra da Bahia. Trata-se da Blitz contra a Covid-19. A medida tem inicialmente como alvo uma população de mais de cinco mil trabalhadores da construção que estão em atividade em 41 canteiros de obras que já aderiram à iniciativa.

A parceria prevê visitas aos canteiros para realizar ações preventivas de saúde e também para orientar sobre o cumprimento do Ofício Circular SEI n. 1088, do Ministério da Economia, que trouxe orientações para as empresas de construção diante da pandemia do coronavírus.

Na área de saúde, o SESI realizará a medição da temperatura corporal bem como orientação e esclarecimento de dúvidas sobre a Covid-19.

O presidente do Sinduscon-BA, Carlos Marden Passos, lembrou da parceria histórica. "O SESI tem uma longa história de parceria com a indústria da construção e vai nos ajudar a orientar as empresas e atuar na prevenção junto aos trabalhadores da construção", acrescentou.

O superintendente do SESI Bahia, Armando Neto, destaca que "neste momento de crise, a entidade não podia deixar as empresas do sindicato sem um apoio". Ele destaca que as ações estão sendo definidas em conjunto com os líderes do sindicato para a visita da blitz aos canteiros indicados pelo Sinduscon.

SENAI CIMATEC E SESI VÃO APLICAR 13.800 TESTES PCR EM TRABALHADORES DA INDÚSTRIA

Numa ação de enfrentamento à pandemia de Covid-19, o SENAI CIMATEC vai realizar testes de PCR em trabalhadores da indústria que apresentem sintomas da doença. Serão feitos 13. 800 exames, a partir do dia 15 de abril.

A iniciativa será realizada em parceria com o SESI, que irá até as empresas interessadas, na capital e no interior do estado, e fará a coleta de material oral e nasal no trabalhador sintomático.

Em seguida, o conteúdo será trazido até o Instituto SENAI de Inovação em Sistemas Avançados de Saúde (ISI SAS), no SENAI CIMATEC, onde foi montado um Laboratório de Diagnóstico Molecular exclusivo para testes da Covid-19. Lá, as amostras serão processadas (etapas de extração, amplificação e diagnóstico). Os resultados são emitidos em cerca de quatro horas após recebimento das amostras.

"Montamos aqui um laboratório nível de segurança NB2, ou seja, com condições adequadas para trabalho com amostras infecciosas, para realizar este teste, que é o que vem sendo feito em todos os laboratórios de referência do país, a exemplo do Lacen", explica a gestora do ISI em Sistemas Avançados em Saúde do CIMATEC, Cleide Guedes.

Testes PCR – Este exame é considerado um diagnóstico molecular padrão ouro, aprovado pela Organização Mundial de Saúde – para o diagnóstico do novo coronavírus. Do material que foi coletado, uma pequena amostra genética é extraída de forma automatizada e amplificada num termociclador. Então, é possível atestar a presença do RNA do vírus.

"De forma resumida, o teste RT-qPCR, conhecido como PCR em tempo real, é um teste de diagnóstico molecular altamente sensível que consegue identificar a presença do novo coronavírus (SARS-CoV2) nas amostras coletadas dos trabalhadores com suspeita da Covid-19", afirma a pesquisadora do ISI SAS do CIMATEC, Bruna Machado.

SENAI CIMATEC PRODUZ "ESCUDOS FACIAIS" PARA DOAR A PROFISSIONAIS DE SAÚDE

Cerca de mil protetores ou escudos faciais (face shields) estão sendo produzidos por dia no SENAI CIMATEC PARK, localizado em Camaçari. A unidade montou uma pequena fábrica para confeccionar o produto, essencial à proteção dos profissionais de saúde que atendem pacientes com a Covid-19. A estimativa é que sejam produzidas 10 mil máscaras faciais.

O equipamento de proteção individual, que funciona como uma barreira entre o profissional e o paciente, está em falta tanto na rede pública como na rede privada de saúde. E a escassez é generalizada: os Estados Unidos e países da Europa, por exemplo, também sofrem com a falta do material de proteção. Como consequência, um número cada vez maior de profissionais de saúde é infectado pelo vírus.

IEL REALIZA LIVES SOBRE CARREIRA E MERCADO DE TRABALHO

O IEL está realizando lives, via Instagram, com profissionais das áreas de Psicologia e Marketing. O objetivo é trabalhar temas sobre desenvolvimento pessoal e mercado de trabalho em meio à crise gerada pela pandemia de Covid-19, a fim de que profissionais de qualquer idade se reinventem antes do retorno das atividades normais. A programação prossegue nos dias 14 e 22 de abril. Dia 14, às 14 horas, o tema é "Um novo mercado de trabalho está surgindo. Como desenvolver e reconhecer as habilidades essenciais para este novo cenário?", com Afonso Monteiro. Já no dia 22.04, também às 14h, a live é sobre "Você é a sua melhor marca. Marketing pessoal: atitudes que fazem diferença na crise", com Ana Carla.

SESI SENAI IEL CIEB SISTEMA FIEB
Federação das Indústrias do Estado da Bahia

- Enabling maintenance of pulmonary ventilators (Figure 6).
- Production of face shield masks for hospitals in Salvador, Bahia, Brazil (industrial conversion).
- Use of the OGBON supercomputer in partnership with a North American universities to analyze the behavior and evolution of the new coronavirus pandemic as well as high-speed simulations for the epidemiology of the disease.
- Use of Artificial Intelligence for new COVID-19 detection methods using x-Rays and Computed Tomography (CT).
- Production and packing of gel alcohol for distribution in industries and hospitals in the

Figure 6. Maintenance of pulmonary ventilators.

State of Bahia, Brazil (industrial conversion) (Figure 7).

- Preparation and distribution of a Guidance to inform companies for preventing COVID-19 in the industrial sector.
- Application of RT-PCR tests to industry workers from all over the State of Bahia, Brazil (more than 13,800 tests).
- The clothing sector produced 61 hospital garments.

May 2020 (Figures 8 and 9)

- Compliance of industries to the new guidelines, mainly for the food sector to

Figure 7. Production and packing of gel alcohol for distribution to industries and hospitals in the State of Bahia, Brazil (industrial conversion).

Figure 8. Folder 5 – Actions and activities of SENAI CIMATEC against COVID-19 (May 2020).

Informe Sistema FIEB nº5

Confira algumas ações do Sistema FIEB para o enfrentamento da crise provocada pelo novo coronavírus:

CORONAVÍRUS

SENAI CIMATEC DESENVOLVE TÚNEL DE DESINFECÇÃO

Um túnel de desinfeção foi desenvolvido pelo SENAI CIMATEC com o objetivo de combater a contaminação e proliferação do novo coronavírus. Baseado em projetos internacionais, o túnel metálico mede 2,5 metros e tem um sistema de distribuição hidráulica que espalha microjatos de uma solução de água e hipoclorito de sódio (água sanitária), durante a passagem de pessoas pelo equipamento.

Em fase experimental, o túnel será testado no Hospital Espanhol, uma das unidades de tratamento para coronavírus em Salvador. A ideia é que os profissionais de saúde passem pelo túnel antes de retirar os equipamentos de proteção individual (EPIs), momento em que estão mais vulneráveis à contaminação.

SESSENTA RESPIRADORES PULMONARES FORAM RECUPERADOS

O trabalho de recuperação de respiradores pulmonares, realizado pelo SENAI Bahia e SENAI CIMATEC, já conseguiu devolver em operação, até o (dia 22.04), 60 aparelhos para cerca de 20 instituições entre hospitais, unidades de Emergência e Pronto Atendimento da capital e do interior. Além da capital, 12 municípios já foram beneficiados com a ação.

O trabalho de recuperação dos aparelhos é feito por uma equipe formada por engenheiros e técnicos do SENAI CIMATEC e das empresas Ford e GPE, que correm contra o tempo para disponibilizar 120 aparelhos que estavam fora de uso.

Como o SENAI-BA tem unidades na maioria das cidades do interior, essa capilaridade facilita o mapeamento e coleta dos respiradores mecânicos em todo o estado, além da devolução dos aparelhos.

Além da Bahia, os pontos de manutenção gratuita existem em 18 estados. Em âmbito nacional, a expectativa é de que sejam consertados entre 3.500 e 4 mil aparelhos por técnicos e voluntários capacitados pelo SENAI CIMATEC para o serviço.

25 CANTEIROS DE OBRAS PASSAM POR BLITZ CONTRA A COVID-19

A Blitz contra a Covid-19, uma iniciativa do SESI-BA e do Sinduscon-BA, já foi realizada em 25 canteiros de obra em Salvador, Candeias e Vitória da Conquista, envolvendo 1.500 trabalhadores do setor da construção civil nestes municípios.

Na iniciativa, as equipes, compostas por engenheiros, técnicos de enfermagem e enfermeiros do trabalho, realizam ações preventivas de saúde e orientam sobre o cumprimento do Ofício Circular SEI número 1247, do Ministério da Economia, direcionado às empresas de construção diante da pandemia do novo coronavírus.

Iniciadas em Salvador, no dia 14.04, as blitze têm atualmente 45 canteiros de obras inscritos em todo o estado. A estimativa é que cerca de cinco mil trabalhadores da indústria sejam envolvidos. A expectativa do SESI e do Sinduscon é que mais empresas da construção façam adesão à iniciativa.

Além do Sinduscon, outros sindicatos da indústria estão procurando o SESI para ampliar a realização das blitze em outros segmentos. Estão previstas visitas a indústrias vinculadas ao Sindvest de Feira de Santana, Sindvest Salvador e Simagran. As blitze também serão realizadas nas 550 empresas participantes do Programa SESI Viva+ em toda Bahia. Além disso, a iniciativa será realizada na região oeste do estado, em parceria com a Associação Baiana dos Produtores de Algodão (Abapa).

SENAI CIMATEC DOA MAIS DE 12 MIL "ESCUDOS FACIAIS"

Mais de 12 mil escudos faciais (face shields) produzidos no SENAI CIMATEC Park, em Camaçari, já foram doados a hospitais, Unidades de Pronto Atendimento (UPA), corporações e secretarias de estado da Bahia e também para o estado do Amapá. As máscaras face shield serão utilizadas por profissionais da área de saúde e de outros serviços essenciais, a exemplo dos bombeiros, durante o combate à pandemia de coronavírus. Com investimento interno de R$ 120 mil, a instituição pretende produzir 20 mil protetores faciais, até que o fornecimento seja regularizado pelas indústrias.

Cerca de mil escudos faciais (face shields) estão sendo produzidos por dia em uma pequena fábrica montada no SENAI CIMATEC Park para confeccionar o produto, que é um equipamento de proteção individual (EPI). Parte do material produzido (cerca de 300 máscaras) foi encaminhada para a capital do Amapá. Os escudos faciais vão ajudar a reforçar a proteção contra o coronavírus.

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Figure 9. Folder 6 – Actions and activities of SENAI CIMATEC against COVID-19 (May 2020).

Informe Sistema FIEB nº6

Confira algumas ações do Sistema FIEB para o enfrentamento da crise provocada pelo novo coronavírus:

CORONAVÍRUS

FIEB PROMOVE LIVES SOBRE TEMAS DE INTERESSE DA INDÚSTRIA
Referências para a indústria na área de relações trabalhistas, o empresário Alexandre Furlan e o consultor Homero Arandas foram os convidados da live promovida pela FIEB, na terça-feira, dia 28.04, no canal da entidade no Instagram, com o tema O que muda nas relações de trabalho?. A iniciativa faz parte da série Diálogos FIEB, que vai discutir temas relevantes para o setor industrial.
Durante a live, eles abordaram as questões judiciais e o papel do governo para reduzir tensões nas relações trabalhistas, além de apresentar o posicionamento do setor produtivo.
Alexandre Furlan é presidente do Conselho de Relações do Trabalho da Confederação Nacional da Indústria (CNI) e vice-presidente da Organização Internacional dos Empregadores (OIE) para a América Latina. Já Homero Arandas, que há mais de 30 anos atua como negociador patronal em acordos coletivos de trabalho, na solução de conflitos trabalhistas e no desenvolvimento de equipes, é presidente do Conselho de Relações Trabalhistas da FIEB e membro do Conselho Temático de Relações do Trabalho e Desenvolvimento Social da CNI.
A próxima live será realizada no dia 5 de maio, às 18h, com o deputado Eduardo Salles, presidente da Frente Parlamentar do Setor Produtivo, e com o superintendente da FIEB, Vladson Menezes. O tema central são os projetos que afetam o setor produtivo baiano e o que se pode esperar da tramitação na Assembleia Legislativa. Acompanhe @sistema_fieb.

DUAS UNIDADES DE SAÚDE GANHAM CÂMARA DE DESINFECÇÃO
Criada pelo SENAI CIMATEC com o objetivo de garantir mais proteção aos profissionais que atuam na linha de frente ao combate da Covid-19, a câmara de desinfecção foi instalada em mais duas unidades de saúde de Salvador. O Instituto Couto Maia e o Hospital Santo Antônio, das Obras Sociais Irmã Dulce (OSID), também passaram a contar com o equipamento, que já estava sendo utilizado no Hospital Espanhol.
Feita de alumínio, a câmara dispõe de uma tubulação de PVC que pulveriza uma solução de hipoclorito de sódio (água sanitária) durante a passagem de pessoas pelo equipamento. O profissional de saúde, ao final do seu turno de trabalho, deve passar pelo túnel, que é um corredor de 2,5 metros, ainda com o Equipamento de Proteção Individual, para que, em seguida, possa retirar o EPI com menor risco de contaminação.
A instituição continua produzindo novas câmaras de desinfecção e estuda a possibilidade de o equipamento ser utilizado em outros ambientes, como shoppings, academias e estações de metrô.

PROGRAMA VAI ORIENTAR 50 MIL TRABALHADORES
Indústrias associadas ao Sindvest Salvador passaram, nesta semana, pela Blitz contra a Covid-19, uma iniciativa do SESI Bahia em parceria com sindicatos da indústria. As blitze fazem parte do Programa Juntos Contra a Covid-19, que tem como meta atingir uma população de 50 mil trabalhadores de mil empresas industriais associadas aos sindicatos da Construção, Vestuário (de Salvador e Feira de Santana) e de Mármores e Granitos, além de 550 empresas clientes do SESI VIVA +. A iniciativa também será realizada na região oeste do estado da Bahia, em parceria com a Associação Baiana dos Produtores de Algodão (Abapa).
O Programa Juntos Contra a Covid-19 tem caráter educativo junto à força de trabalho, mas também esclarece à indústria o passo a passo do protocolo, caso haja algum indício da doença no ambiente laboral. Também é feito um checklist com um plano de ação para que as empresas adotem todos cuidados necessários, desde dimensionamento de EPIs, até sugestão de layouts.
Iniciadas em Salvador, no dia 14 de abril, em parceria com o Sinduscon-BA, as blitze têm atualmente 66 canteiros de obras inscritos em todo o estado. A estimativa é que cerca de seis mil trabalhadores da indústria da construção sejam envolvidos. A expectativa do SESI e do Sinduscon é que mais empresas façam adesão à iniciativa, que deve ser efetuada junto ao sindicato.

SENAI RECUPERA 75 RESPIRADORES PULMONARES
Hospitais, unidades de Emergência e Pronto Atendimento em 40 municípios baianos já foram beneficiados pelo trabalho de recuperação de respiradores pulmonares, realizado pelo SENAI Bahia e SENAI CIMATEC. Até o dia 27.04, 75 aparelhos foram devolvidos em operação. O trabalho é feito por uma equipe formada por engenheiros e técnicos do SENAI e das empresas Ford e GPE, que correm contra o tempo para disponibilizar 120 aparelhos que estavam fora de uso.

PRODUÇÃO DE MÁSCARAS FACE SHIELD SUPERA 20 MIL UNIDADES
Mais de 20 mil escudos faciais (face shield) foram produzidos no SENAI CIMATEC Park, em Camaçari até o dia 24.04. As máscaras face shield foram doadas para hospitais, Unidades de Pronto Atendimento (UPA), corporações e secretarias de estado da Bahia e também para o estado do Amapá.
Equipamento de proteção individual (EPI), a máscara face shield reforça a proteção contra o coronavírus. Os escudos faciais serão utilizados por profissionais da área de saúde e de outros serviços essenciais, a exemplo dos bombeiros, durante o combate à pandemia de coronavírus.

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continue to provide safe and adequate food to the population.

- Sequence of work focused on research and innovation through the contemplated projects.
- Increase in the number of RT-PCR tests on employees of industries in the State of Bahia, Brazil, quickly and accurately.
- Maintenance of mechanical ventilators, production of gel alcohol and face shield masks.
- Donation of "basic baskets" and face shield masks for adults and children in the community and public hospitals in the State of Bahia, Brazil.
- Immunization of 40,000 industry workers.
- Educational campaigns to combat the coronavirus: "Bahia Contra o COVID-19" and "Amigos da FIEB".
- Fundraising and delivery of 2,400 face shields for health professionals (Around 1,000 face shields are being produced per day - Figure 10) and 630 "basic baskets" for institutions and communities in Salvador (Salvador, Bahia, Brazil).
- Creation of a disinfection tunnel for health professionals by SENAI CIMATEC (in clinical study) (Figure 11).

June 2020 (Figures 12 and 13)

- Recovery of more than 200 mechanical ventilators.

Figure 10. Production of face shield to donnation for hospitals and communities in Bahia state (Brazil) (industrial conversion).

Figure 11. The tunnes of desinfection created by SENAI CIMATEC.

Figure 12. Folder 7 – Actions and activities of SENAI CIMATEC against COVID-19 (May 2020).

Informe Sistema FIEB nº7

Confira algumas ações do Sistema FIEB para o enfrentamento da crise provocada pelo novo coronavírus:

CORONAVÍRUS

REPRESENTANTES DO GOVERNO E PREFEITURA VISITAM SENAI CIMATEC PARK E CONHECEM AÇÕES CONTRA A PANDEMIA

Uma comitiva composta pelo vice-governador do Estado, João Leão, pelo vice-prefeito, Bruno Reis, o senador Roberto Muniz, os deputados Elmar Nascimento e Eduardo Salles, e o presidente da Fecomércio, Carlos Andrade, visitou o SENAI CIMATEC Park, em Camaçari, na segunda-feira, dia 05 de maio. Na oportunidade, foi realizada a entrega à Prefeitura de Salvador de uma doação de 30 mil litros de álcool glicerinado a 80%, para ser usado na desinfecção das unidades do sistema público de saúde da rede municipal. No total, já foram produzidos 70 mil litros de álcool glicerinado, distribuídos também para a rede estadual e entidades da sociedade civil.

O grupo foi recebido pelo presidente FIEB, Ricardo Alban. Eles conheceram de perto o processo de fabricação das máscaras Face Shield (escudos faciais) – mais de 22 mil já foram produzidas – e acompanharam o trabalho dos profissionais no envase de álcool a 70%, que estão sendo realizados no SENAI CIMATEC Park.

Durante a visita, também foram apresentados outros projetos estratégicos desenvolvidos pelo SENAI CIMATEC no combate à COVID-19, como a manutenção de respiradores mecânicos, que até o momento recuperou mais de 85 aparelhos; e o túnel de desinfecção, já instalado nos hospitais Espanhol e Couto Maia, em Salvador.

O presidente da FIEB, Ricardo Alban, destacou que as entidades do Sistema FIEB, convictas dos compromissos que têm com a sociedade e o poder público, foram parceiras de primeira hora no enfrentamento da pandemia. Ele reiterou a importância desta rede de apoio e mobilização social e empresarial.

INDÚSTRIA DE ELETROELETRÔNICOS ADERE À BLITZ CONTRA A COVID-19

O SESI Bahia e o Sindicato das Indústrias de Aparelhos Elétricos, Eletrônicos, Computadores, Informática e Similares de Ilhéus e Itabuna (Sinec), realizaram na terça-feira, 05.05, ação conjunta de prevenção da Covid-19 na unidade da Daten, no município de Ilhéus, envolvendo 153 trabalhadores.

As equipes, compostas por engenheiros, técnicos, enfermeiro do Trabalho e técnica de Enfermagem, realizaram ações preventivas de saúde. Em toda a Bahia, as blitze vão atingir uma população de mais de 50 mil trabalhadores de empresas associadas aos sindicatos da indústria e do SESI Viva+. No segmento de eletroeletrônicos, o Sinec tem 10 empresas associadas, o que corresponde a 860 trabalhadores envolvidos.

IEL PROMOVE ENCONTRO EMPRESARIAL ONLINE

A crise do novo coronavírus impôs desafios para o setor empresarial, que tem buscado se reinventar diante deste novo cenário. Para discutir este tema, o Instituto Euvaldo Lodi (IEL-BA) realiza, no próximo dia 13 de maio, um encontro empresarial online, que vai apresentar cases de empresas que estão inovando para atender as novas demandas do mercado.

Com inscrições gratuitas pela plataforma Sympla, o encontro terá como convidados o diretor regional da empresa Limpidus, Antonio Burity, e o diretor industrial da Aromarketing, Rafael Mamede, com moderação da especialista em Inovação do IEL-BA, Fabiana Carvalho. Mais informações pelo telefone (71) 3343-1530 ou pelo e-mail clubeieldenegocios@fieb.org.br.

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Figure 13. Folder 8 – Actions and activities of SENAI CIMATEC against COVID-19 (May 2020).

Informe Sistema FIEB nº8

Confira algumas ações do Sistema FIEB para o enfrentamento da crise provocada pelo novo coronavírus:

CORONAVÍRUS

SESI REALZA BLITZ COVID-19 EM MAIS DE 100 ESTABELECIMENTOS INDUSTRIAIS

Mais de 100 estabelecimentos industriais, entre fábricas, canteiros de obra e fazendas (agroindústria), totalizando cerca de 10 mil trabalhadores, foram alvo das ações da Blitz contra a Covid-19 que o SESI Bahia está desenvolvendo no estado.
As empresas atendidas são clientes do SESI Viva+, associadas aos sindicatos patronais e à Associação dos Produtores de Algodão (Abapa), do Oeste baiano. Até o momento, nove representações sindicais aderiram à blitz, entre eles o Sinduscon-BA, os Sindvest Salvador e Feira de Santana, o Simagran, Sindiplasba, Sinec, Sindibrita, Sindcosmetic e Sincar.
Com uma equipe multiprofissional, o objetivo do SESI é reforçar recomendações sobre a higienização das mãos, o uso dos equipamentos de proteção individual, os cuidados com objetos de uso pessoal e dos espaços de uso coletivo.
Os técnicos também orientam sobre redução do contingente de pessoal na empresa, estabelecendo horários alternados de trabalho, flexibilização da jornada, home office e liberação de pessoas do grupo de risco, sempre que possível, conforme as orientações do Ministério da Economia.

SESI IMUNIZOU 40 MIL TRABALHADORES CONTRA A GRIPE NA BAHIA

Com foco na promoção da saúde, o SESI-BA realiza anualmente a Campanha de Imunização contra a Gripe. Até o dia 08.05, 40 mil trabalhadores de 260 empresas instaladas no estado da Bahia foram imunizados. A iniciativa cumpre papel importante na prevenção contra infecções pelos vírus Influenza e H1N1 e suas complicações, que afetam a saúde e produtividade dos trabalhadores. Em 2020, a campanha de imunização foi antecipada em razão da pandemia do coronavírus.

SETOR EMPRESARIAL BAIANO DOA CESTAS BÁSICAS E MÁSCARAS

Duas mil e quatrocentas máscaras foram doadas a creches de Salvador e ao Hospital Martagão Gesteira, para proteção de crianças e adultos contra o coronavírus. O material foi adquirido com o recurso arrecadado pela Campanha Bahia Contra a Covid-19, coordenada pelo IEL-BA, em parceria com outras entidades do setor empresarial baiano.

Realizada na plataforma de crowdfunding Bloxs, a campanha teve a participação de empresários, entidades empresariais e da sociedade baiana. Além do Hospital Martagão Gesteira, as máscaras foram doadas para as creches Lar Pérolas de Cristo, Mãe Nildete e Vó Flor, todas localizadas em Salvador.
Já a campanha Amigos da FIEB, liderada pelo CIEB, entregou 630 cestas básicas para instituições e comunidades da capital baiana. Cada cesta básica contou com 14 itens alimentícios, além de materiais de limpeza, como água sanitária e detergente.
A iniciativa foi apoiada pelo IEL-BA, que operacionalizou a arrecadação do recurso, além da aquisição e distribuição dos itens para doação. A campanha beneficiou o Centro Cultural Oficina Reciclável, a Creche Escola Mãe Nildete, a Creche Bezerra de Menezes, o Instituto de Esporte, Cidadania e Inclusão Social, o Movimento Mulheres do Subúrbio Ginga, além de famílias dos bairros de Capelinha de São Caetano e Bom Juá.

HOSPITAIS DA CAPITAL E DO INTERIOR JÁ CONTAM COM TÚNEIS DE DESINFECÇÃO

Três túneis de desinfecção desenvolvidos pelo SENAI CIMATEC foram instalados no dia 12.05, nos hospitais do Subúrbio, Ernesto Simões Filho e Martagão Gesteira, em Salvador. Com os equipamentos, as unidades passam a ofertar mais segurança para os profissionais de saúde que atendem pacientes diagnosticados com Covid-19.
No total, oito hospitais da Bahia já contam com os túneis de desinfecção. No interior, os equipamentos foram instalados nos hospitais Costa do Cacau, em Ilhéus, e Calixto Midlej Filho, em Itabuna. A estimativa é que outras unidades de saúde do estado também recebam o equipamento.
O túnel produzido pelo CIMATEC, sob a supervisão do infectologista Roberto Badaró, pesquisador chefe do Instituto SENAI de Tecnologia da Saúde.

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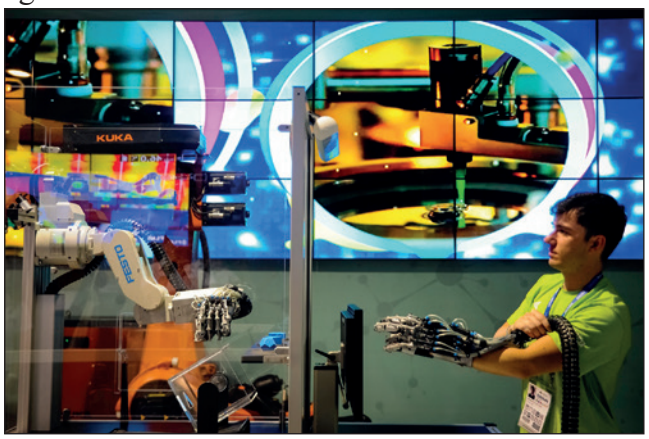
Figure 14. New technologies by SENAI CIMATEC against COVID-19.



- Educational robotics in the fight against COVID-19 (Figure 14).
- Donation of educational licenses to SENAI CIMATEC students by companies.
- Expansion of COVID-19 tests for industries in Bahia (50,000 tests for screening in industries in the State of Bahia, Brazil, providing the rapid IgM / IgG test) (Figure 15).
- Expansion of RT PCR testing in Bahia industries.
- Expansion of the recovery of mechanical ventilators.
- Maintenance of gel alcohol packaging for industries.

Figure 15. Rapid test (IgG/IgM – sorologic test).

- Maintenance of the production of face shield masks for donations in communities and hospitals in the State of Bahia, Brazil.

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History of Pandemics and COVID-19: What We are Learning from this Pandemic to Be Prepared for the Next One

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Since the beginning of human history, the pathogens affect the humankind. The emerge of the new outbreak of coronavirus-19 (COVID-19) is not new in the history of plagues. However, this pandemic has a huge difference from the others due to its ability to affect worldwide at the same time, which brings new perspectives to our future. In this review, we listed some of the worst epidemics and pandemics of human civilization and the new outbreak, presenting the pathogens, the spread, and the consequences for mankind. Our search included articles in the main database (PubMed/Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Exerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), in the high-impact international scientific Journals (Scimago Journal and Country Rank - SJR - and Journal Citation Reports - JCR), such as The Lancet, Science, Nature, The New England Journal of Medicine, Physiological Reviews, Journal of the American Medical Association, Plos One, Journal of Clinical Investigation, and in the data from Center for Disease Control (CDC), National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO). We prior selected meta-analysis, systematic reviews, article reviews, and original articles in this order. We reviewed 192 articles and used 94 from March to June 2020, using the terms coronavirus, SARS-CoV-2, novel coronavirus, Wuhan coronavirus, severe acute respiratory syndrome, 2019-nCoV, 2019 novel coronavirus, n-CoV-2, COVID, n-SARS-2, COVID-19, corona virus, coronaviruses, history of pandemics and epidemics, pathogens, plagues, with the tools MeSH (Medical Subject Headings), AND, OR, and the characters [,“,; /., to ensure the best review topics. We concluded that this pandemic will change the social and economic order, as well as it is the first that affects us at the same time. So, the experience of COVID-19 could teach us how to be prepared for other outbreaks in the future.

Keywords: COVID-19. SARS-CoV-2. Hystory of Pandemics. Humankind. Future.

Introduction

During human history, diseases, and illnesses, especially infectious diseases, have disturbed humanity since the earliest days [1].

The infectious disease outbreaks have been closed the human being. More than 60% of human infectious diseases are caused by pathogens shared with wild or domestic animals [2]. Most emerging viruses come from animals and are zoonotic or vector-borne diseases belonging to the families *Orthomyxoviridae*, *Paramyxoviridae*, *Picornaviridae*, *Coronaviridae*, *Adenoviridae*, and *Herpesviridae*.

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Nevertheless, community-acquired respiratory viruses are critical pathogens such as influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, human coronavirus, human metapneumovirus, rhinovirus, enterovirus, because of the potential to cause millions of deaths and hospitalizations all over the world every year [3, 4].

The zoonoses are responsible for a billion cases of illness in people and millions of deaths every year, and the emerging zoonoses such as COVID-19 pandemic are an actual threat to global health.

In general, the zoones are responsible for human acts, such as changes in land use and extractive industry actions, animal production systems, and widespread antimicrobial applications, which affect the zoonotic disease transmission [2].

The emergence of novel human pathogens and reemergence of several diseases is a particular issue in the current century [5, 6].

Before December 2019, there are 6 strains of coronavirus (CoVs) that can infect humans and cause respiratory diseases: HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1 with mild upper respiratory disease with rare severe infections occurring in infants, young children, and elderly people [7]. The three exception are SARS-CoV-1 and MERS, that was responsible for two outbreaks in 2003 and 2012, respectively. They infect the lower respiratory tract and could lead to a severe respiratory condition in humans. And also the current COVID-19, that since the beginning (December 2019 in Hubei, China) until now (June 3, 2020) spreads for all over the world with a 6,414,473 confirmed cases, and 380,940 deaths [8-10].

The increase of epidemics and pandemics in the last years is a paradox because as more civilized men became, the more likely pandemics would occur (Ebola in 2014-2016, Zika, Dengue, HIV, H1N1, H2N3, and currently COVID-19) [1, 6].

Sometimes the outbreaks change the course of history or ravage millions of lives or signaling to the end of entire civilizations [11]. The social concentration in urban cities, the ease of traveling, the globalization [5], the contact with different populations, and cultural and social behaviors, as well as the destruction of many ecosystems by the human being, the air and water pollution [1, 11], created new opportunities for human and animal interactions, which sped up to such epidemics. And a bad interaction between people, animals, and ecosystems increases the risk of pandemics, such as COVID-19 [10].

However, ecological and evolutionary perspectives can provide valuable insights into pathogen ecology and can inform zoonotic disease-control programs through a multisectoral collaboration, which includes clinicians, public health scientists, epidemiologists, ecologists, and disease ecologists, veterinarians, economists, and others for effective management of the causes and prevention of zoonotic diseases response to zoonotic diseases and elimination or mitigation the transmission routes to prevent future outbreaks [2]. As well as, the healthcare improvements, the new technologies applied to health, the novel discoveries, and the prophylaxis public health, decrease the death rate. Also, the understanding factors that incubate pandemics have been powerful tools in mitigating their impact, despite the critical social and economic repercussions which a pandemic cause in society [1, 11].

In this review, we summarized some of the worst epidemics and pandemics of human civilization until the new outbreak (COVID-19) listing the pathogens, the spread, and the consequences for mankind with the focus in the COVID-19.

A Timeline of the Main Historical Pandemics

We resumed the main epidemic and pandemic of human history over time in Table 1 and Figure 1, and show the respiratory viral outbreaks in Table 2.

The Rage of the Gods

In ancient societies, people believed that gods applied diseases and destruction upon those or communities that deserved their rage [1]. The lack of knowledge about the cause of the epidemic or pandemic leads to millions of deaths. For example, Procopius of Caesarea, a Byzantine historian, determined the origins of the Justinian's plague (*Yersinia pestis*): the disease originated from China and northeast India entered in the Byzantine Empire by Mediterranean ports through land and sea commerce routes to Egypt [1, 11]. Despite Procopius's knowledge about the plague, he accused the Emperor Justinian for the outbreak, invoking God's punishment for his evil actions. Some historians believed that this situation could have destroyed Emperor Justinian's forces to join the Western and Eastern remnants of the Roman Empire, and registered the beginning of the Dark Ages [1, 2, 6, 7, 9, 11].

However, the human knowing of the diseases' causes improved in the course of time, which follows in a radical improvement to recent pandemics [1, 9].

Table 1. The worst epidemic and pandemic worldwide yhrough the years with the number of human deahts.

Name	Time period	Type / Pre-human host	Death toll
Circa	3000 b.C.	No clue	30,000
Plague of Athenas	430 b.C.	Believed to be the smallpox	100,000
Antonine Plague	165-180 A.D.	Believed to be either smallpox or measles	5M
Plague of Cyprian	250-271 A.D.	The scientists have no certain about the cause of the epidemic	5,000 people a day in Rome alone
Japanese smallpox epidemic	735-737 A.D.	Variola major virus	1M
Plague of Justinian	541-542 A.D.	*Yersinia pestis* bacteria / Rats, fleas	30-50M
Black Death (Figures 2, 3)	1347-1351 A.D.	*Yersinia pestis* bacteria / Rats, fleas	200M
New World smallpox outbreak (Figures 4, 5)	1520 – 1971 (erradicated)	Variola major virus	56M
Cocoliztli epidemic	1545-1548 A.D.	*Salmonella paratyphi* C	15M
American Plagues	16th century	Influenza, smallpox (brought to the Americasn by European explorers)	Millions of indigenous people
Great Plague of London	1665 A.D.	*Yersinia pestis* bacteria / Rats, fleas	100,000
Italian Plague	1629-1631 A.D.	*Yersinia pestis* bacteria / Rats, fleas	1M
Great Plague of Marseille	1770-1772 A.D.	*Yersinia pestis* bacteria / Rats, fleas	1M
Philadelphia Yellow Fever	1793 A.D.	Virus / Mosquitoes	>5,000
Cholera pandemics (Figure 6, 7)	1817-1923 A.D.	Believed to be H2N2 (avian origin)	1M+
Third Plague	1885 A.D.	*Yersinia pestis* bacteria / Rats, fleas	12M (China-India)
Yellow Fever (U.S.)	Late 1800s A.D.	Virus / Mosquitoes	100,000-150,000
Russian Flu (spread to all Europe)	1889-1890 A.D.	Believed to be H2N2 (avian origin)	1M
American Polio Epidemic	1916	Poliovirus	Millions of deaths and millions of children defects
Spanish Flu (Figures 8, 9)	1918-1919 A.D.	H1N1 virus / Pigs	40-50M
Asian Flu	1957-1958 A.D.	H2N2 virus	1.1M
Hong Kong Flu	1968-1970 A.D.	H3N2 virus	1M
HIV/AIDS (Figure 10)	1981-present	Virus / Chimpanzees	25-35M
Dengue Fever	1994-present	Mosquitoes *Aedes Aegypti*	Millhions of death
Swine Flu	2009-2010 A.D.	H1N1 virus / Pigs	200,000
SARS (Figure 11)	2002-2003 A.D.	Coronavirus / Bats, Civets	770
Ebola (Figure 12)	2014-2016 A.D.	Ebolavirus / Wild animals	1,000
Zika Virus	2015-present	Mosquitoes of the *Aedes* genus	Millions of birth defects (mycrocephalia)
MERS (Figure 13)	2015-present A.D.	Coronavirus / Bats, camels	850
SARS-COV-2 (COVID-19) (Figures 14, 15)	2019-present A.D.	Coronavirus – Unknown (possibly pangolins)	380,940 [8]

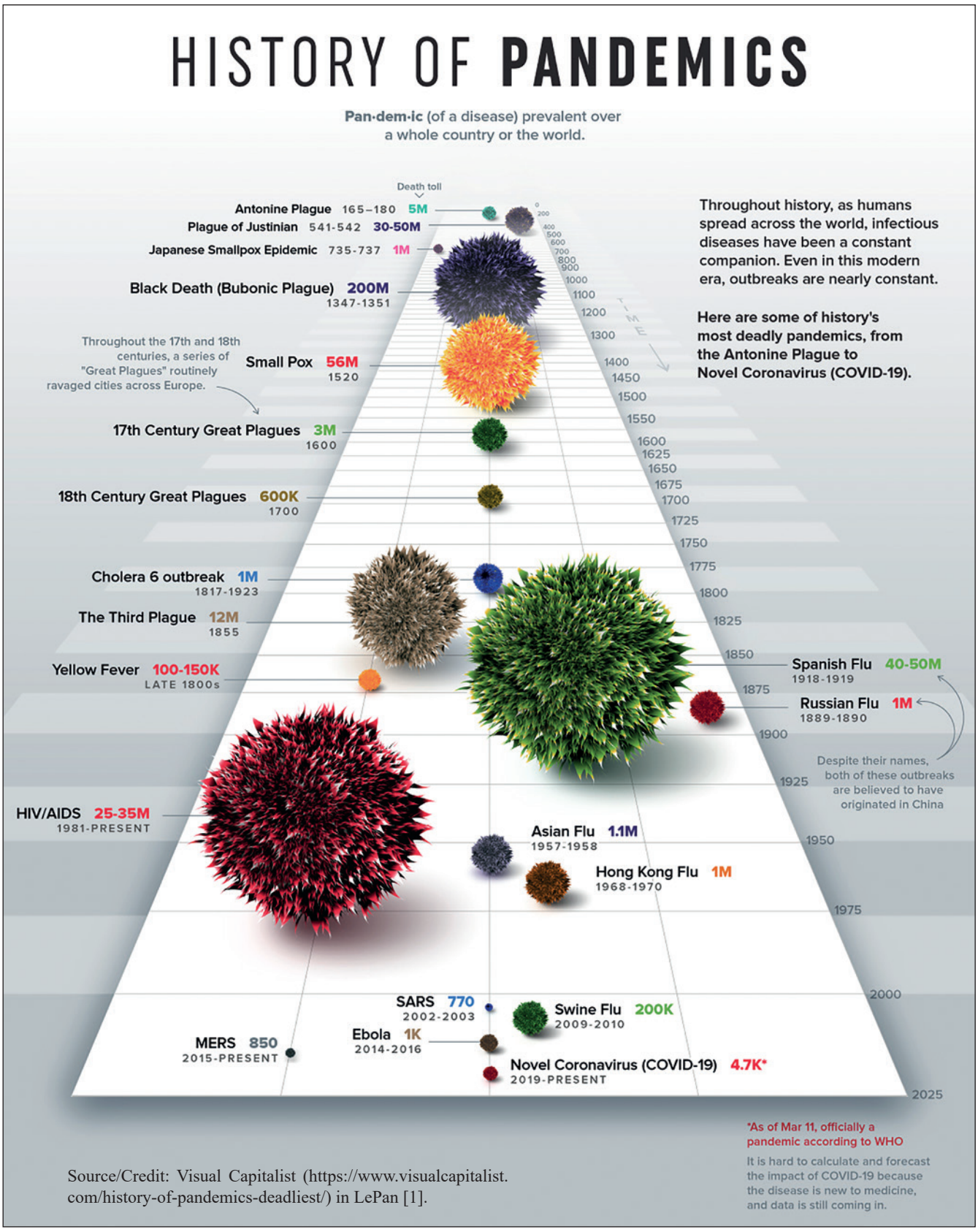
M: million.

Mitigating the Diseases

During the 14th century, port authorities of Venice, Italy, required the ships that arrived from infected ports to stay at anchor for 40 days before landing. The name quarantine came from Italy of the expression, "quarenta giorni", which means 40 days [1, 9].

The health surveillance realized that the 40 days in isolation is sufficient to protect coastal cities from plague epidemics. So, this is one of the

Figure 1. History of pandemics.



Source/Credit: Visual Capitalist (https://www.visualcapitalist.com/history-of-pandemics-deadliest/) in LePan [1].

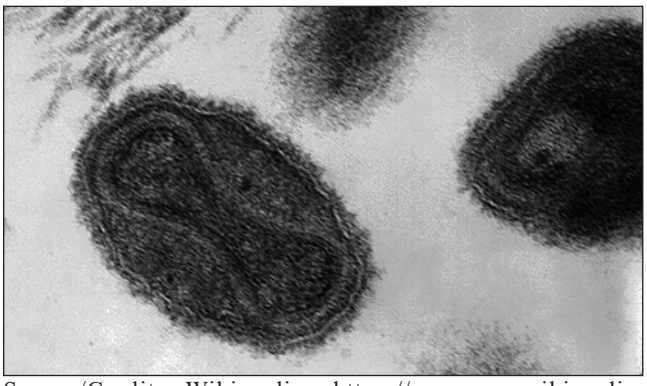
Figure 2. A depiction of "Doctor Schnabel" during the plague in Rome.

Source/Credit: Illustration appeared in a 17th Century. First published by Paul Fürst (1608–1666 CE), from Europas Sprung in die Neuzeit, by Johannes Ebert and colleagues [12].

Figure 3. The spreading of the plague in Medieval period.

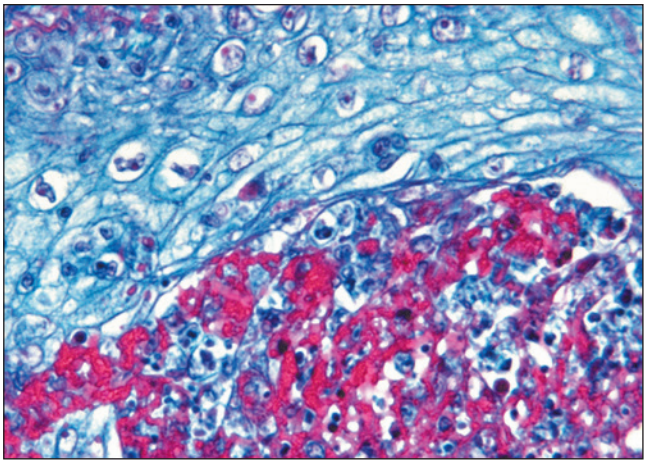
The plague killed a 3/4 from Europe.
Source/Credit: https://nilefm.com/digest/article/5114/7-pandemics-from-human-history-that-make-COVID-19-look-like-a-joke [13].

Figure 4. Micrography of smallpox virus.



Source/Credit: Wikimedia. https://commons.wikimedia.org/wiki/Category:Variola_virus [14].

Figure 5. Smallpox virus attacking a cell.



Source/Credit: Pixnio. https://pixnio.com/?s=smallpox [15].

first sanitary efforts to mitigate diseases spread. Geography and statistical analysis began to be used as a method during the cholera outbreak in London in the 19th century [1, 2].

However, the connections involving urban life play a fundamental role in pandemics [1, 6, 7], notwithstanding the virulent nature of the disease is what will designate the direction of the pandemic [6, 7].

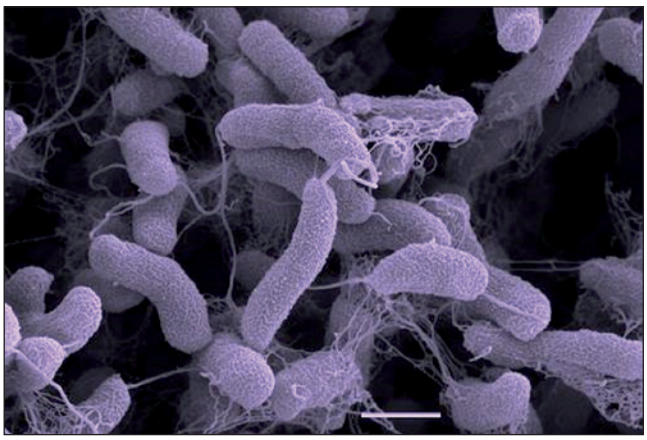
Tracking Infectiousness

Science measures the track of disease infectiousness with a reproduction number (R0), which predicts on average how many susceptible people getting sick could infect

Figure 6. A portrait of transmission of cholera.

"Death's Dispensary": This caricature published during the London cholera epidemic of 1866 was a response to the hypothesis of the English epidemiologist John Snow, who linked the cholera epidemic with sewage seeping into ground water used for drinking (1866)
Source/Credit:http://www.environmentandsociety.org/arcadia/first-cholera-epidemic-st-petersburg [16].

Figure 7. Micrography of *Vibrio cholerae*.

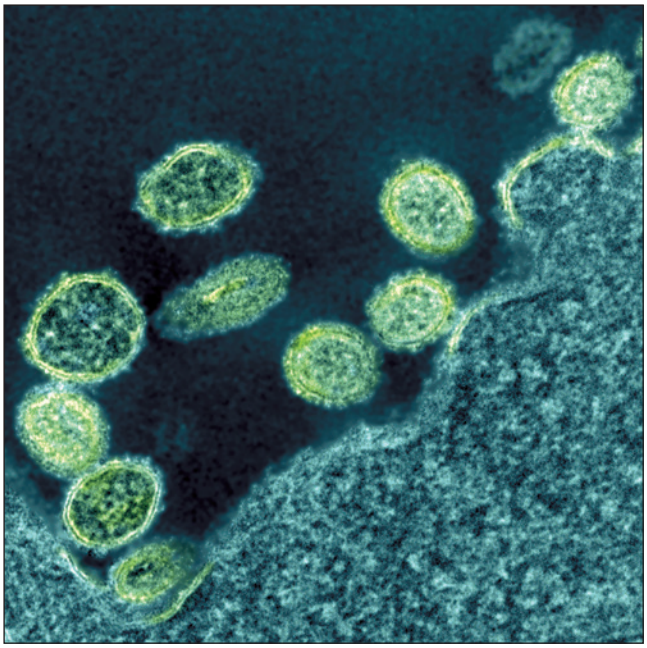


Source/Credit: Luciana Cangussu. https://www.luciacangussu.bio.br/atlas/vibrio-spp/ [17].

Figure 8. Spanish flu (measures of contention).

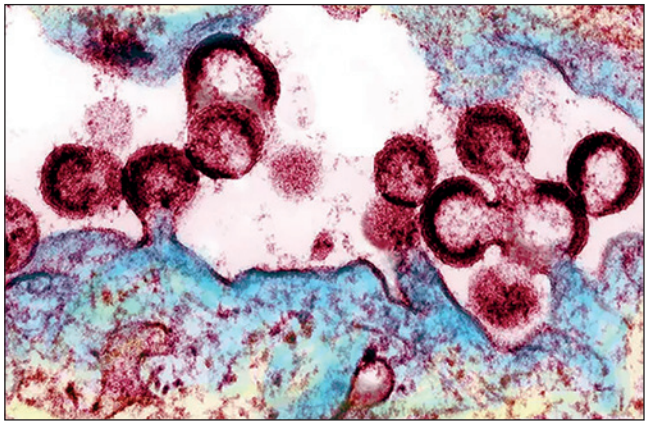
Source/Credit: https://aboutmanchester.co.uk/a-portrait-of-a-pandemic-bbc-marks-the-centenary-of-spanish-flu-revealing-the-untold-stories-of-its-impact-on-people-and-places-across-the-country/. [18, 19].

Figure 9. Influenza virus. Virus particles of 1918 H1N1 (Spanish Flu).



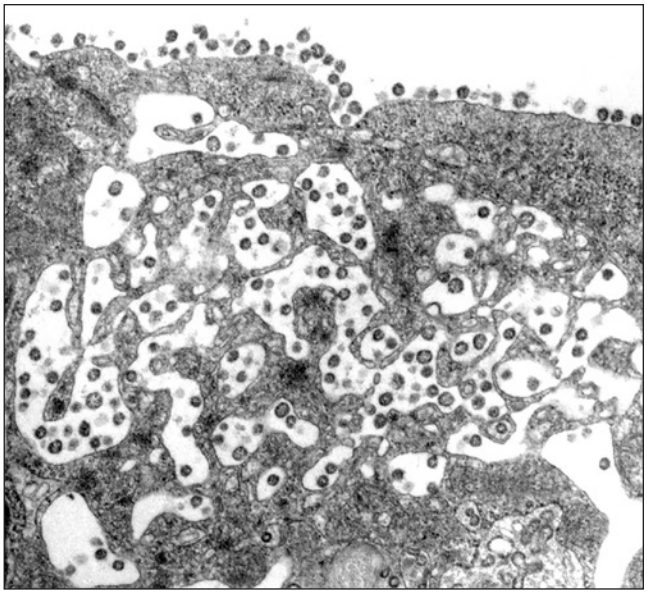
Source/Credit: Electron micrograph of 1918 H1N1 influenza virus particles near a cell. https://www.flickr.com/photos/niaid/30012820867. Credit: NIAID [20].

Figure 10. HIV budding from an infected CD4 cell.



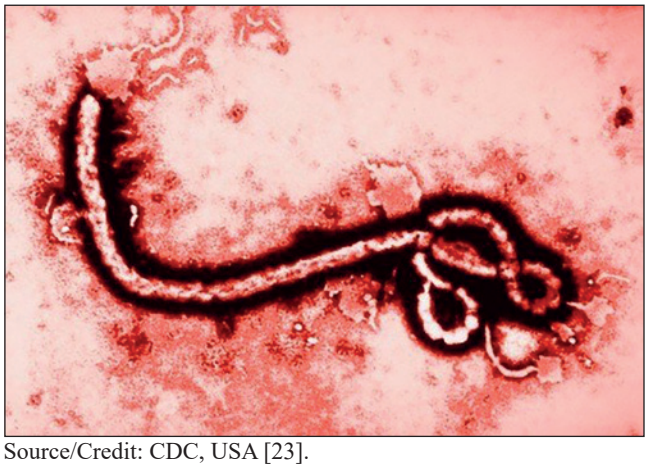
Source/Credit: National Institute of Allergy and Infectious Diseases (NIAID). https://www.niaid.nih.gov/ [21].

Figure 11. SARS-CoV micrography.



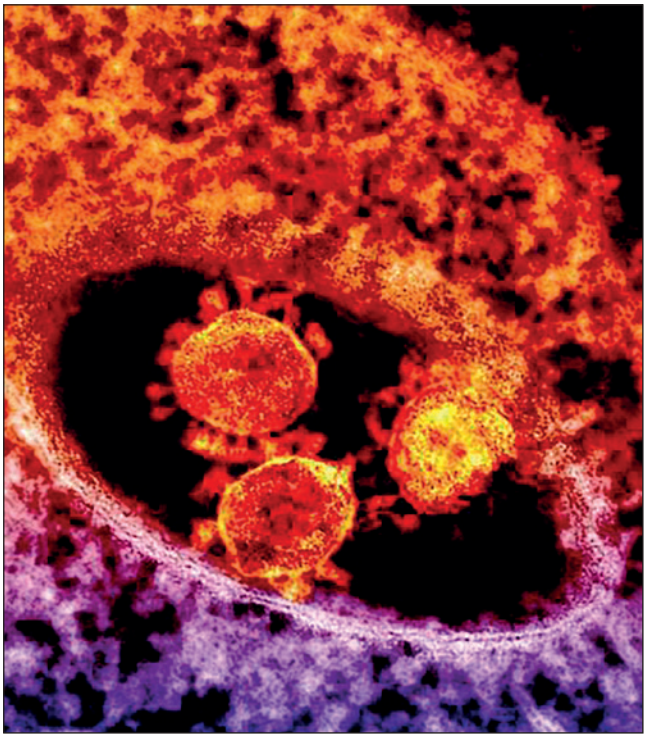
Source/Credit: A SARS-CoV-infected cell with virus particles in vesicles. [22].

Figure 12. Micrography of Ebola virus.



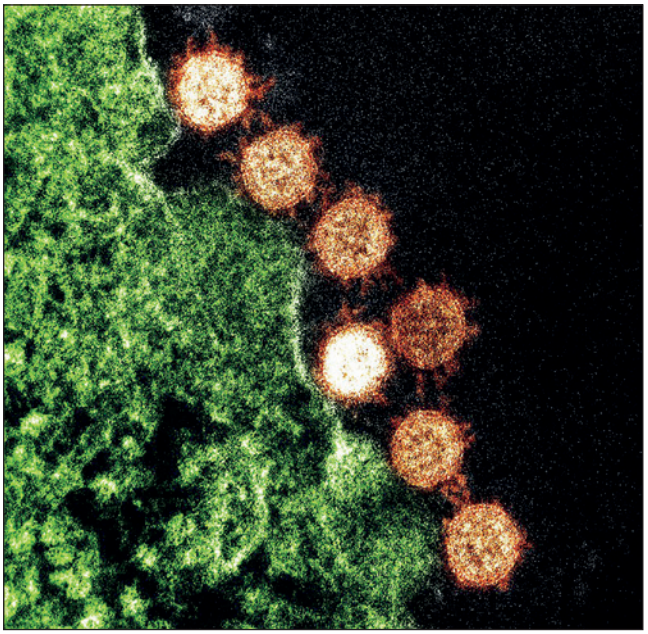
Source/Credit: CDC, USA [23].

Figure 13. Micrography of coronavirus that causes Midle East Respiratory Syndrome (MERS).



Source/Credit: CDC, USA [21, 23].

Figure 14. Electron micrograph of Severe Acute Respiratory Syndrome (SARS-CoV-2) virus particles.



Colorized transmission electron micrograph of Severe Acute Respiratory Syndrome (SARS-Cov-2) virus particles (orange) found near the periphery of an infected cell (green). Image captured and color-enhanced at the NIAID Integrated Research Facility in Fort Detrick, Maryland.
Source/Credit: NIAID, USA [21].

Figure 15. Collecting a sample of SARS-CoV-2 from bat.

Source/Credit: https://edition.cnn.com/2020/03/19/health/coronavirus-human-actions-intl/index.html [24].

others. For example, measles in on the top of the list with R0 range 12-18, which means that one person can infect 12-18 people (Figure 16) [1, 11].

Urbanization and Disease's Spread

From small hunting and gathering tribes to the metropolis, the development connections, the increasing the populations in urban cities, passenger air traffic doubled in the past decade, and the rise of the contact of people with a globalization world created a good environment for the diseases to spreading and provoking a pandemic [1, 7, 11].

The COVID-19 Pandemic

Animals and Coronaviruses

The coronaviruses caused a wide range of animal diseases [10]. In the second half of the 20t^{h} century, many research proceeded with these viruses due to their capability to cause severe disease in cattle and pets such as pigs, cows, chickens, dogs, and cats (Figure 17) [10, 37, 38].

The History of Coronaviruses

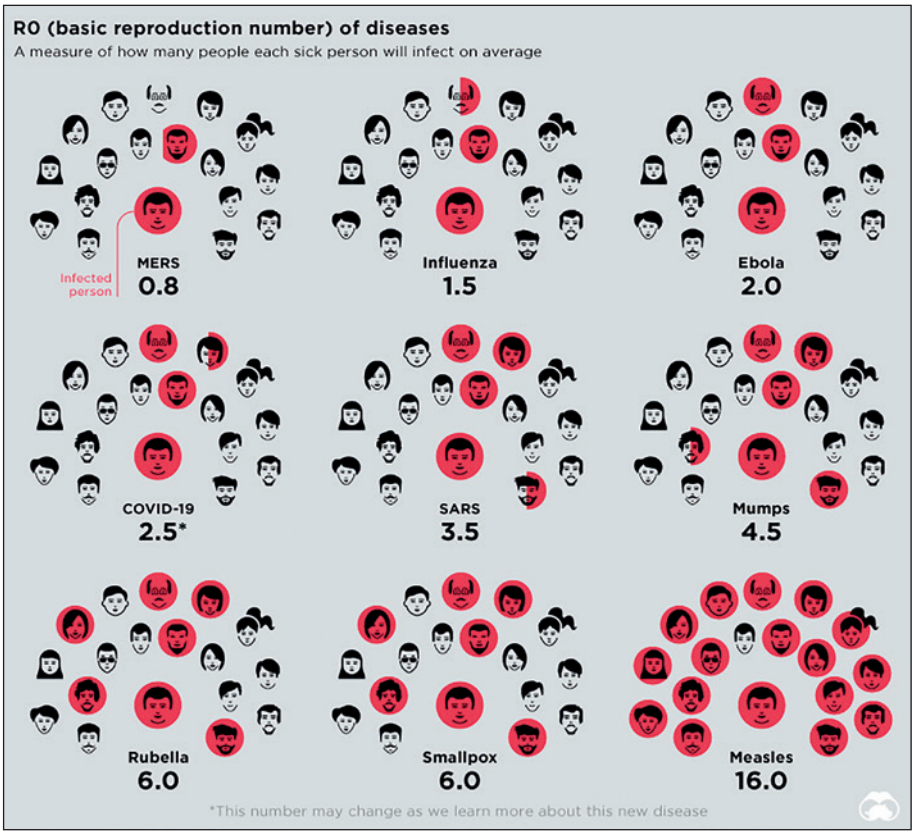
We sumarized in Table 3 a brief history of coronavirus, except to COVID-19.

Table 2. Outbreaks of emerging and reemerging respiratory viral infections.

Virus	Year	Region
Spanish Flu H1N1	1918	Spain [25]
Asian flu H2N2	1956	East Asia [26]
HCoV-229E HCoV-OC43	1960	The different part of the World [27]
Hong Kong Flu H3N2	1968	Hong Kong [26]
Hantavirus pulmonary syndrome	1993	USA [28]
Influenza A H5N1	1997	Hong Kong [26]
Influenza A H9N2	1999	Hong Kong [26]
Human metapneumovirus	2001	Netherlands [29]
SARS CoV	2002–2003	Guangdong, China [30]
Human CoV NL63	2004	Netherlands [31]
Influenza A H7N7	2004	Netherlands [26]
Human CoV HKU1	2005	China [31]
Triple reassortant H3N2 Influenza A	2005	Canada [26]
Bocavirus	2005	Sweden [32]
Influenza A H1N1 pmd09	2009	Mexico [26]
Adenovirus 14	2010	USA [33]
Influenza (H3N2)	2011	USA [34]
MERS-CoV	2012	Saudi Arabia [35]
Influenza A H7N9	2013	China [26]
Influenza A H10N7	2014	China [26]
SARS-CoV-2	2019	China [36]

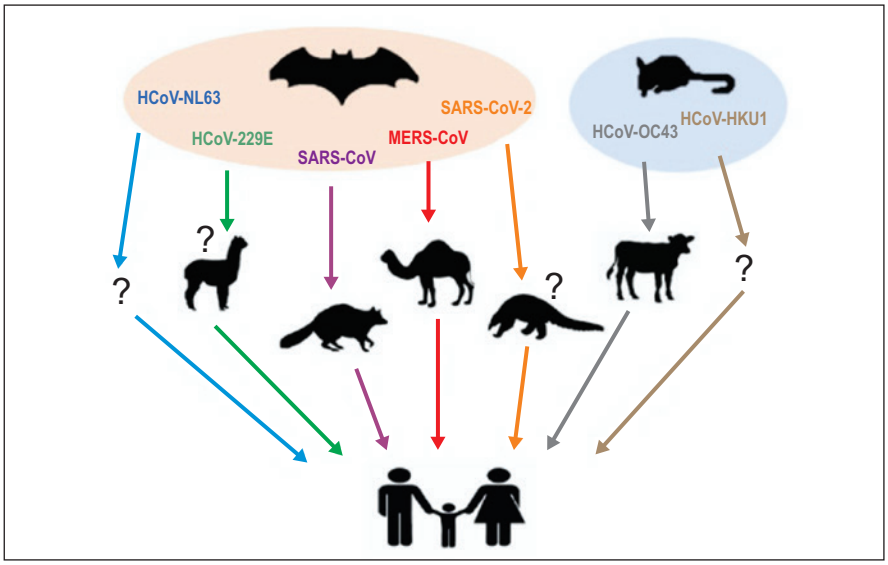
Source/Credit: Çelik and colleagues [6].

Figure 16. R0 (basic reproduction number) of diseases.



Source/Credit: Visual Capitalist in https://www.weforum.org/agenda/2020/03/a-visual-history-of-pandemics [1].

Figure 17. Animal hosts of HCoVs.



Blue, green, purple, red, orange, grey, brown arrows represent the transmission of HCoV-NL63, HCoV-229E, SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-OC43 and HCoV-HKU1 from their natural hosts (bats or rodents) to the intermediate hosts (camelids, civets, dromedary camels, pangolins or bovines), and eventually to the human population. No concrete evidence exists on the intermediated host(s) of HCoV-NL63 and HCoV-HKU1, which was shown as a question mark (?). Source/Credit: Ye and colleagues [39].

Table 3. Summary of animal coronavirus origins.

Discovery	Year/Description	Virus Name	Animal hosts	Intermediate hosts	References
Beaudette & Hudson	1937	IBV	Bats	Chickens with respiratory disease	40
Cheever and colleagues	1949	MHV	Rats	Murine and hepatitis viruses	7
Discovery that the three coronavirus genus described were related	1946 / 1960	HCoVs	Bats Rodents	Transmissible gastroenteritis in swine	7
Tyrrell & Bynoe / Hamre & Procknow	1965 (The first human coronavirus, and resemble avian IBV)	B814	Bats Rodents	Chickens	41, 42
Almeida & Tyrrell	1967 The morphology of the virus is identical to B814 and IBV	HCoV 229E	Bats	Camelids (?)	43-46
[1] HCoV OC43 / OC43 or 229E	1967	HCoV OC43	Rodents	Bovines	7, 47
[2] SARS Pandemic	2002/2003	SARS-CoV	Bats	Palm civets	47-59
HCoV-NL63	2004	HCoV-NL63	Bats	Unidentified	60, 61
HCoV-HKU1	2005	HCoV-HKU1	Rodents	Unidentified	47
MERS-CoV (Camels serve as the bona fide reservoir host of the virus)	2012	MERS-CoV	Bats	Dromedary camels	48, 62-72
SARS-Cov-2	2019	SARS-Cov-2	Bats	Pangolins (?)	73

[1] Six further strains were recovered using the organ culture technique, including the prototype strains HCoV OC43 as well as three strains considered antigenically unrelated to either OC43 or 229E. [2] The appearence of SARS-Cov was in the Guangdong province, China. In 2002 to 2003, an unusual and often deadly form of pneumonia that lead to a severe acute respiratory syndrome (SARS). It spreads to moere than 29 countries. The SARS-CoV began in Guangdong exotic markets where live animal are held, traded and sold to restaurants in response to the demand for exotic food. Small mammals, such as civet cats, sold in these markets were found to harbour viruses closely related to SARS-CoV, and the initial interspecies transmission to humans probably came from these markets.

The History of COVID-19

The first reported patient with COVID-19 was admitted to the Central Hospital of Wuhan on 26 December 2019, 6 days after the start of the disease, with fever, chest tightness, dry cough, dyspnea, body-pain, and weakness for one week of the symptom's presentation. The radiological findings revealed bilateral lung glassy opacities. Hasöksuz and colleagues [37] reported that the Wuhan Centre for Disease Control and Prevention led an epidemiological investigation and found that the patient worked at a seafood market where a variety of live wild animals (including hedgehogs, badgers, snakes, and birds) were available for sale. However, no bats were available for sale, and the patient reported no exposure to live poultry but possible contact with wild animals [37, 74]. In a sequence of quick events, what the first patient brought with him spread worldwide.

We summarized the dates and events below:

- 31 December 2019 – WHO China Country Office informed that cases of pneumonia with an unknown etiology had been identified in Wuhan City, in the Hubei province of China [37, 75].
- The authorities of China communicated to WHO a total of 44 patients with pneumonia of unknown etiology from 31 December 2019

through 3 January 2020. No causal agent had been identified during this period.

- 7 January 2020 – The Chinese researchers isolated and identified a new type of coronavirus 2019 (2019-nCoV), which received the name "Wuhan Coronavirus". WHO renamed it to SARS-CoV-2 [76.]
- 11 and 12 January 2020 – WHO received more details from the National Health Commission in China, indicating that the outbreak was directly associated with the seafood markets in Wuhan City [37].
- 12 January 2020 – China globally shared the genetic sequence of the novel coronavirus [77].
- 13 January 2020 – The Ministry of Public Health of Thailand reported the first imported case of lab-confirmed novel coronavirus (2019-nCoV) from Wuhan, Hubei Province, China [77].
- 15 January 2020 – The Ministry of Health, Labour, and Welfare of Japan (MHLW) also recorded an imported case of the novel coronavirus (2019-nCoV) from Hubei Province, China [78].
- 20 January 2020 – The National IHR Focal Point (NFP) for the Republic of Korea communicated the first case of a novel coronavirus, also from Wuhan, China [79].
- 30 January 2020 – WHO declared a global public health emergency.
- By the end of March 2020, the virus spread all over the world, which leads to a large global outbreak [80].
- 3 June 2020 – 6,414,473 confirmed cases, 380,940 deaths and 2,753,935 recovered [8].

Origin and Evolution of SARS-CoV-2

The association of SARS-CoV-2's first cases with the Hubei (China) seafood market implied that the place represented a role in the early spreading [81, 82]. However, whether the outbreak began and what is the original host(s) of SARS-CoV-2 remain unclear [82]. The first genome sequence analysis of SARS-CoV-2 was performed from six patients [83]. First of all, SARS-CoV-1 and MERS-CoV were compared with SARS-CoV-2, and this analysis presented a high homology of nucleotides with SARS-CoV-1, and poor association with MERS-CoV [83], which suggests that SARS-CoV-1 and SARS-CoV-2 might relate to the same species. Nevertheless, profound research showed that coronaviruses with high similarity to the human SARS-CoV-1 or civet/pangolin (?) SARS-CoV-like virus were isolated from horseshoe bats, which leads to the conclusion that the bats were the potential natural reservoir of SARS-CoV whereas masked palm civets/pangolin (?) are the intermediate hosts [57, 59, 84-87]. The phylogenetic analysis of SARS-CoV-2 showed that the virus is a Betacoronavirus genus, subgenus Sarbecovirus and is related to two bat-derived SARS-like coronaviruses [74, 77, 83, 84, 88-90].

Xu and colleagues determined that the genome sequence of SARS-CoV-2 had a 96.2% identity throughout the genome of BatCoV RaTG13, a bat coronavirus detected n Yunnan province [83]. Moreover, the phylogenetic analysis of the full-length genome of RaTG13 demonstrated that the receptor-binding protein spike (S) gene and RNA-dependent RNA polymerase (RdRp) gene were the closest relatives with the SARS-CoV-2 [83]. But, despite the similarities from the viruses, the SARS-CoV-2 changed topological position in the phylogenetic analysis: SARS-CoV-2 was closer to bat-SL-CoVZC45 in the S gene phylogeny but felled in a basal position within the subgenus Sarbecovirus in the ORF1b tree [74]. This discovery suggests a probable recombination results in this group of viruses. Despite current evidence pointed the origin of SARS-CoV-2 from bats virus [74, 77], an intermediate host between humans and bats might exist. Lu and colleagues [77] suggested four reasons for such consideration:

1. Most bat species hibernates in the period that the outbreak began (December) in the Wuhan city (China);
2. No bats in the Huanan seafood market were sold or found;
3. The sequence identity between SARS-CoV-2 and bat-SL-CoVZC45 or bat-SL-

CoVZXC21 - the closest relatives - is lower than 90%, suggesting an intermediate host;

4. There is an intermediate host between bats and humans. For example, masked palm civet and dromedary camels are the intermediate hosts for SARS-CoV-1 [54] and MERS-CoV, respectively (Figure 18) [91].

Ji and colleagues [92] found that SARS-CoV-2, bat-SL-CoVZC45, and snakes had similar synonymous codon usage bias, and speculated that snake might be the intermediate host [92]. Nevertheless, no SARS-CoV-2 has been isolated from the snake yet.

Hence, another suspicious about the host of SARS-CoV-2 fell on the pangolins as a natural reservoir, since an analysis of the genome from Malytan pangolins showed two sub-lineages related to SARS-CoV-2 [93]. This Pangolin-CoV's whole genome had 91.02% similarity with SARS-CoV-2 and 90.55% similarity with Bat-CoV RaTG13 [94]. Proteomic analysis exhibited that the S1 subunit of Spike glycoprotein (S) was more nearly related to that of SARS-CoV-2 compared to BaT-CoV RaTG13. Moreover, five amino acid residues of the S protein of SARS-CoV-2 combining with the ACE2 receptor are equal in Pangolin-CoV [94]. Interestingly, the furin identification motif, necessary to the S1/S2 cleavage, is absent in both Pangolin-CoV and BaT-CoV RaTG13 [94]. This furin identification sequence is intact within the SARS-CoV-2. The discovery of coronavirus close to SARS-CoV-2 from pangolin insinuates that pangolin is the possible intermediate host [76] (Figure 19). However, the roles of bat and pangolin as the natural reservoir and intermediate host still need further researches.

The timeline of the origin of SARS-CoV-2 is represented in Figure 20.

Conclusion

The COVID-19 pandemic continues. Huge efforts and progress have been done since the beginning of the outbreak in pathogen monitoring, mitigating process, identifying sources, basic etiology, clinical treatment, drug testing, and vaccine development. Future research on viral replication, pathogenesis, antiviral drugs, and other aspects of SARS-CoV-2 will contribute to the treatment and prevention of the virus.

However, given the emergence of COVID-19 pneumonia as a new infectious disease with interspecies transmission from animals, we should reflect on the origin of the human pathogen and learn from our experience because the globalization put worldwide together, and a pandemic could devastate the human civilization. The high lethality viruses such as SARS-CoV-1, MERS-CoV, H5N1, H7N9, Ebola, and emerging 2019-nCoV is as an alarm to the world.

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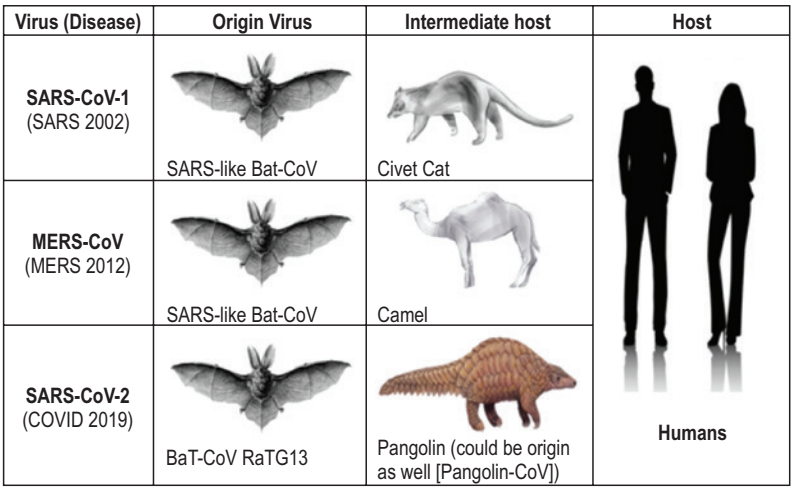
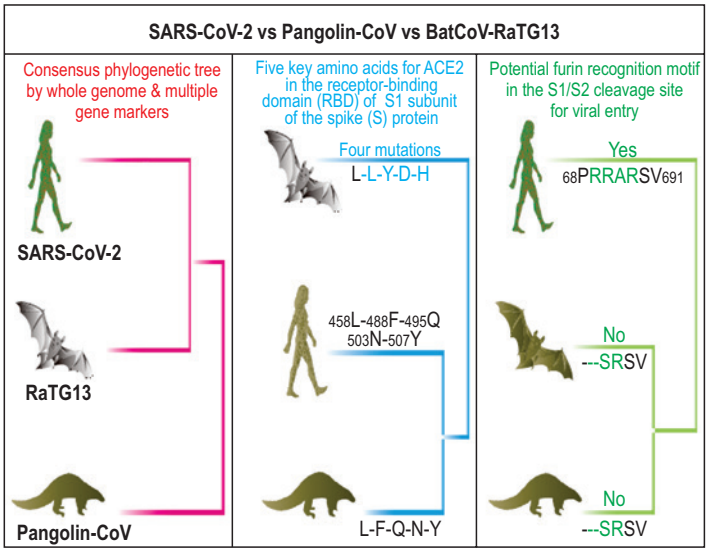
Figure 18. Summary of the natural reservoir, intermediate host and target in major coronaviruses.



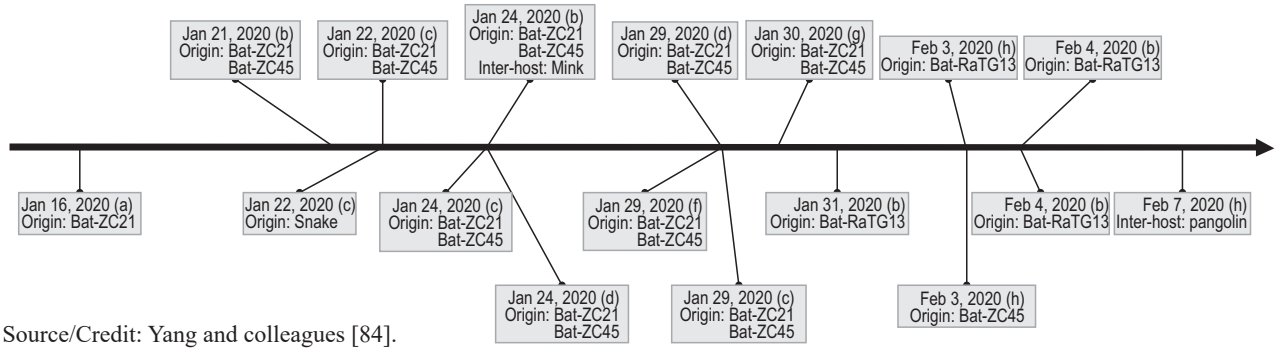
Source/Credit: Kakodkar and colleagues [76].

Figure 19. SARS-CoV-2 *vs* Pangolin-CoV *vs* BatCoV-RaTG13.



Source/Credit: Zhang and colleagues [94].

Figure 20. The origin and inter-host timeline of SARS-CoV-2.



Source/Credit: Yang and colleagues [84].

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The Epidemiology, Transmissions and Risk Factors of SARS-CoV-2

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The outbreak of a novel coronavirus (SARS-CoV-2) and associated COVID-19 disease in late December 2019 has led to a global pandemic, spreading very quickly and causing a more than 500,000 deaths in less than six monhs of the ourbreak. The incidence differs by country and depends on many agents, such as population density, demography, the amount of testing people and reporting, and actions of mitigation strategies, provisions of sanitary and education of the society. In this article, we presented the current studies about the epidemiology of COVID-19, including the transmission routes of the SARS-CoV-2, the incubation period, the reproduction number (R0), the case fatality risks (CFR), comorbidities and measures prevention against COVID-19. We searched the articles in the main database (PubMed/ Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Exerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), in the high-impact international scientific Journals (Scimago Journal and Country Rank - SJR - and Journal Citation Reports - JCR), such as The Lancet, Science, Nature, The New England Journal of Medicine, Physiological Reviews, Journal of the American Medical Association, Plos One, Journal of Clinical Investigation, and in the data from Center for Disease Control (CDC), National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO). We prior selected meta-analysis, systematic reviews, article reviews and original articles in this order. We reviewed 235 articles and used 131 from March to June 2020, using the terms coronavirus, SARS-CoV-2, novel coronavirus, Wuhan coronavirus, severe acute respiratory syndrome, 2019-nCoV, 2019 novel coronavirus, n-CoV-2, covid, n-Sars-2, COVID-19, corona virus, coronaviruses, epidemiology of COVID-19, risk factors, viral spreading, transmissions, routes, animals incubation, period, R0, CFR, comorbidities, prevention, with the tools MeSH (Medical Subject Headings), AND, OR, and characters [,“,; /., to ensure the best review topics. We concluded that the epidemiological data is very important to predict the transmission risks rate, purpose public political policies of mitigating the disease, and protect the vulnerable population. Also, it is important reconsider the legislation about wild animals, the potential intermediate host(s) of various viruses, as well as the conditions of live for animals for human comsuption to prevent future outbreaks.
Keywords: COVID-19. SARS-CoV-2. Epidemiology. Transmission. Risk Factors.

Introduction

Epidemiological and a Brief Overview of COVID-19 Outbreak

An outbreak of pneumonia of unknown origin was reported in Wuhan, Hubei (China) in December 2019 [1-3]. When the virus started to spread, the patients were being diagnosed with severe acute respiratory infection symptoms, or acute respiratory distress syndrome, acute respiratory failure, and some with serious complications leading to death [1, 4]. On January 7, 2020, the Chinese Center for Disease Control and Prevention (CCDC) identified the novel coronavirus, and on February 11, 2020, World Health Organization (WHO) named the epidemic disease as a 2019-new coronavirus disease (2019-nCoV, now called COVID-19) [5]. The name coronaviruses are attributed to their appearance - they look like a corona, or crown, because of the presence of spike glycoproteins on their envelope (Figure 1).

Coronaviruses belong to the family *Coronaviridae* (order Nidovirales). It is an RNA-virus and its genome has approximately 26–32 kilobases [8]. The family of coronaviruses is divided into four genera: *Alpha*, *Beta*, *Gamma*, and

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Delta-coronavirus. Seven human coronaviruses (HCoVs) have been recognized until now. These viruses typically affect the respiratory tracts of birds and mammals. In humans, CoVs generally cause a common cold; notwithstanding, some recent CoVs can cause more critical diseases, including severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV) [9, 10]. The *Alphacoronavirus* genus includes HCoVNL63 and HCoV-229E, while the *Betacoronavirus* genus, HCoV-OC43, HCoV-HKU1, SARS-CoV-1, MERS-CoV, and the novel SARS-CoV-2 [11-16].

In general, bats and rodents are the reservoirs for *alphaCoV* and *betaCoV*, and the reservoir for *deltaCoV* and *gammaCoV* is not certain. So, the reservoir of these viruses is in wild animals that infrequent spillover into humans, so an intermediate host species has to exist to infect humans. On March 19, 2020, Pradhan and colleagues revealed that the Pangolin-CoV genome showed 91.02% and 90.55% nucleotide correspondence with SARS-CoV-2 and BatCoV RaTG13, respectively. This study gives the first report of a potential nearly related the SARS-CoV-2 to Pangolin-CoV, recognizing the pangolin the most likely intermediate host for the new coronavirus [17] (Figure 2).

So, after infection with SARS-CoV-2, the virus binds to the human angiotensin-converting enzyme 2 receptors (ACE2) abundantly located on respiratory tract and also intestinal, uroepithelial cells, salivary gland duct epithelium in the human mouth, and other epithelial organs [19, 20]. Figure 3 presents the life cycle and mechanism of pathogenicity of SARS-CoV-2.

This article aimed to present the current studies about the epidemiology of COVID-19, including the transmission routes of the SARS-CoV-2, the incubation period, the reproduction number (R0), the case fatality risks (CFR), comorbidities and measures prevention against COVID-19.

Epidemiology of COVID-19

Geographical Distribution

Since the beginning of the epidemic in late December 2019, SARS-CoV-2 has spread quickly to countries and territories all over the world [22]. The incidence of the disease differs by country and states and depends on many circumstances, including population density and demographics, the amount of testing and reporting, and the mitigation strategies [23-25]. Globally, more than seven million confirmed cases of COVID-19 have been reported. As of June 11, 2020, COVID-19 has affected 7,403,713 people in 188 countries and territories worldwide and left 417.174 deaths [26]. The source for the epidemiology of this emerging pandemic can be found in many websites such as John Hopkins Coronavirus Research Center [26], World Health Organization (WHO) Coronavirus Disease Dashboard [27], Worldmeters [28], Healthmap Coronavirus [29], Uptodate Worldwide Coronavirus [30], COVID-19 Health Data [31], Centers for Disease Control and Prevention (CDC) [32], Our World in Data-COVID-19 [33] (Figures 4-7), which present dashboards, metrics, infographics about the virus spreading, as well as all news about the novel SARS-CoV-2.

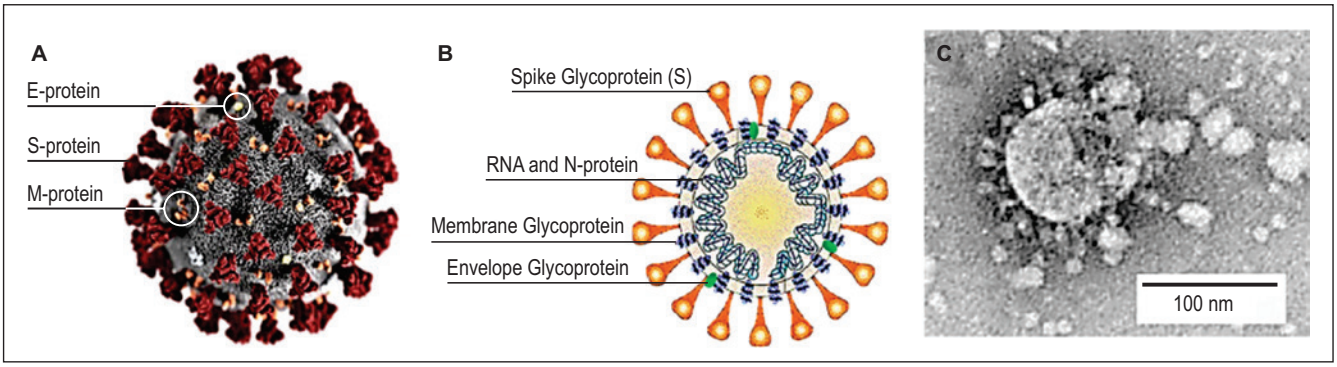
Epidemic Curve of Infection

The epidemic curve of COVID-19 is a statistical chart used in epidemiology to visualize the onset of the outbreak. The epidemic curve is currently being divided into three zones (Table 1) [34].

Transmission of COVID-19

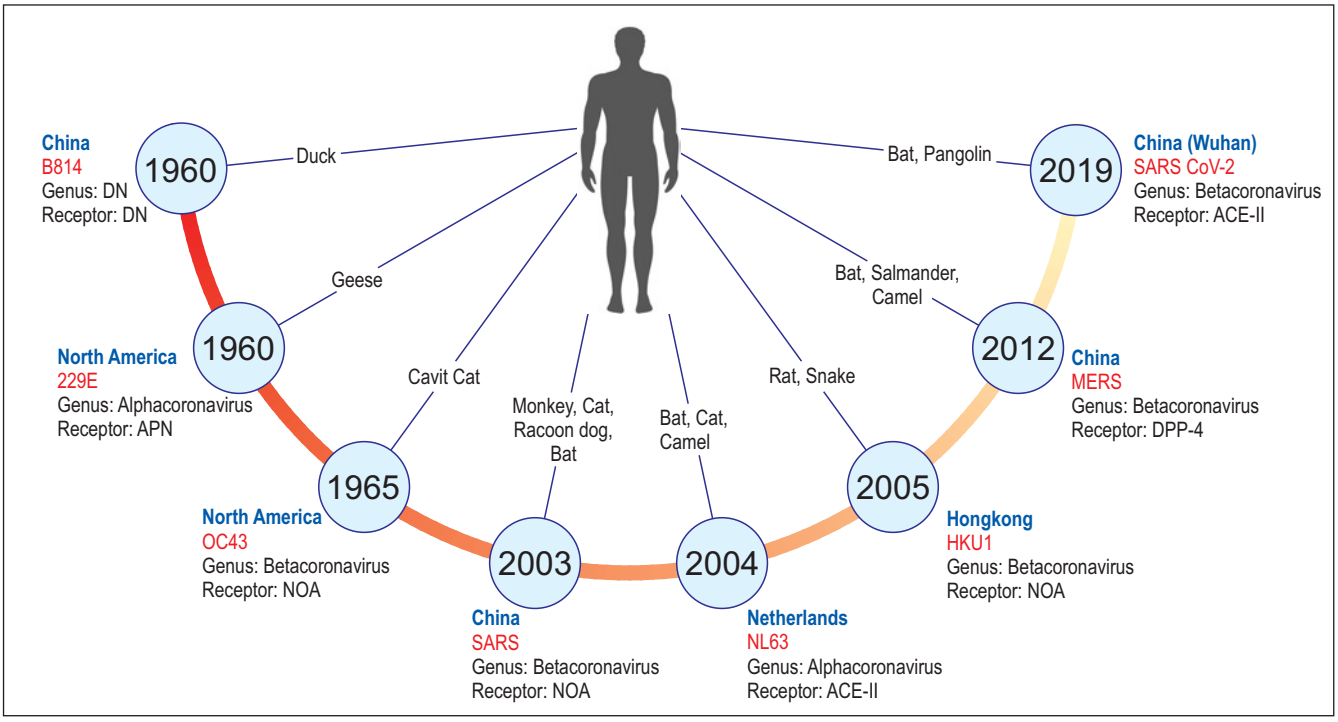
In contrast to SARS-CoV-1 and MERS, the worldwide spread of SARS-CoV-2 demonstrates the differences in how the virus may be transmitted [35], and also its association with high viral loads in the upper respiratory tract [36] and significant asymptomatic carriage [37-40].

Figure 1. Structure of SARS-CoV-2.



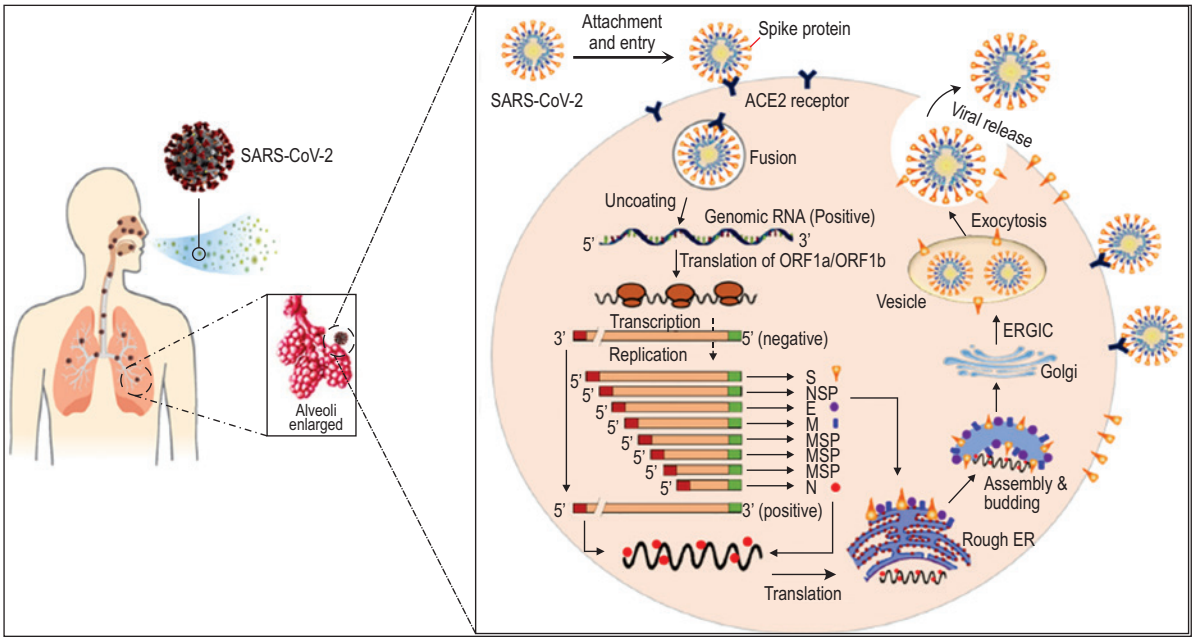
(A) Illustration of the SARS-CoV-2 virion created at the Centers for Disease Control and Prevention (CDC). The spikes on the outer edge of the virus particles look like a crown, giving the disease its characteristic name. (B) Schematic representation of the structure of SARS-CoV-2. It has four structural proteins, S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope. (C) An electron microscopic image of a thin section of SARS-CoV-2 within the cytoplasm of an infected cell, showing the spherical particles and cross-sections through the viral nucleocapsid [6].
Source/Credit: Tarek and colleagues [7].

Figure 2. Timeline of coronavirus.



CS, Coronavirus strain; APN, amino-peptidase-N receptor; ACE-II, Angiotensin-converting enzyme II; NOA, N-acetyl-9-O-acetylneuraminic acid; DPP-4, Dipeptidyl peptidase 4; SARS, Severe acute respiratory syndrome; SARS CoV-2, Severe acute respiratory syndrome-2 also known as COVID-19/2019-nCoV; MERS, Middle East Respiratory Syndrome.
The hypothesis emerged through the ingesting of an infected animal (probably a Pangolin) by a human cause the animal-man transmission of the virus and due to close contact with an infected person, the virus is further transmitted to healthy persons. However, there are no documented cases of direct bat-human transmission [7].
Source/Credit: Adapted from Pradhan and colleagues [18].

Figure 3. SARS-CoV-2 life-cycle in human lung cells.

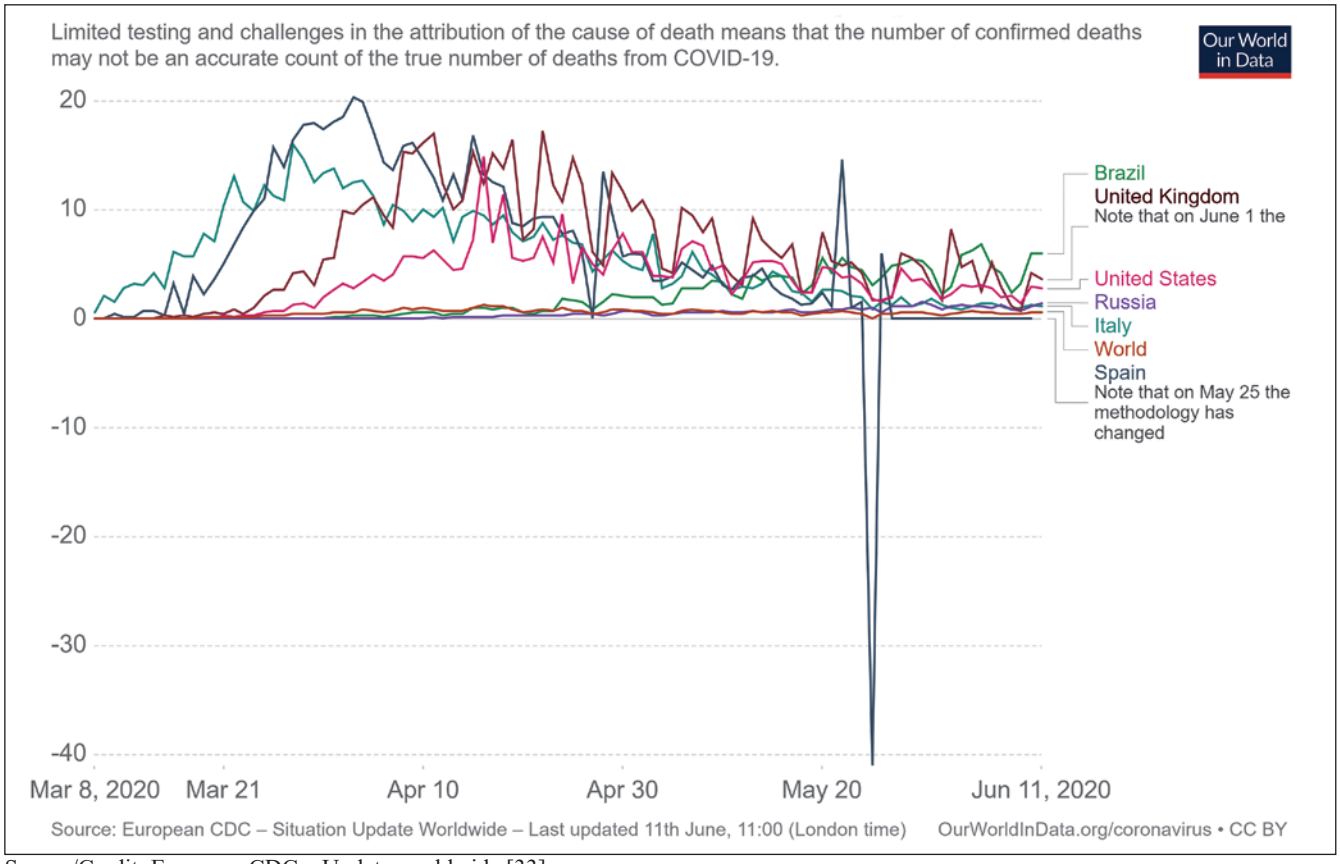


Coronavirus is most often transmitted by droplets while sneezing and coughing and its journey begins in the first days after infiltration from the upper respiratory tract. The spike proteins of SARS-CoV-2 binds to ACE2 receptors. The virion then releases the RNA genome into the cell and translation of structural and non-structural proteins follows. ORF1a and ORF1ab are translated to produce pp1a and pp1ab polyproteins, which are cleaved by the proteases that are encoded by ORF1a to yield non-structural proteins. This is followed by assembly and budding into the lumen of the ERGIC. Virions are then released from the infected cell through exocytosis [21].
Source/Credit: Tarek and colleagues [7].

Figure 4. The dashboard of the John Hopkins Coronavirus Research Center (June 11, 2020).

Source/Credit: The John Hopkins Coronavirus Research Center [26].

Figure 5. Daily confirmed COVID-19 deaths per million people.

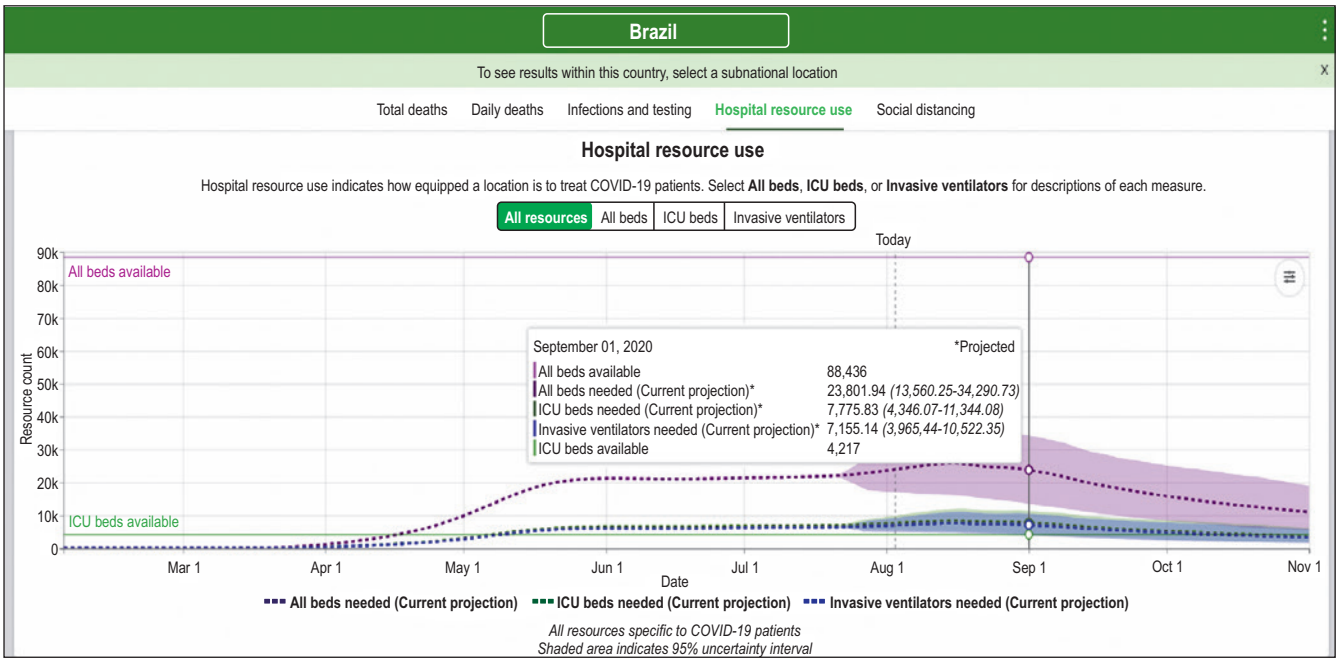


Source/Credit: European CDC – Update worldwide [33].

Figure 6. Projection of deaths to Brazil until September 1st, 2020.

Source/Credit: COVID-19 Health Data [31].

Figure 7. Projection of hospital resource of Brazil until September 1st, 2020.



Source/Credit: COVID-19 Health Data [31].

Table 1. The three zones of an epidemic curve infection.

Zones	Descripton
Increasing	Country demographics, age distribution, the preparedness of health system to an outbreak, implementation of some preventive measures, country reaction time to a pandemic, the reaction of society to new implementing rules. This period takes generally 3 or 4 weeks for COVID-19.
Plateau	The disease incidence is stable. It takes 2 or 3 weeks for COVID-19 concerning daily country reports.
Declining	In this phase, it is possible to see the decline of the infection data. 2 or 3 weeks later disease activity could be detected very low levels for COVID-19.

Transmission Route

As the outbreak advanced, person-to-person spread became the principal mode of transmission [41]. Thus the usual transmission routes of COVID-19 are through direct transmission person-to-person (cough, sneeze, droplet inhalation transmission, and airborne) and contact transmission if a person touches an infected surface and then touches his or her eyes, nose, or mouth, according to multiple studies [20, 40-48]. The surface route depends on the quantity of the RNA virus in the fomite, and because on some surfaces the virus can live for long periods, the contamination can occur this way [45, 49, 50]. The exact routes of person-to-person's COVID-19 transmission are still unclear. However, it is well known that it happens via respiratory droplets, and droplets typically do not go more than two meters [41]. Also, the amount of viral load in the droplets is high and it could explain the number of spreading the disease so easily. Although studies have shown that respiratory infection by COVID-19 is spread mainly by droplet inhalation or contaminated surfaces, SARS-CoV-2 was also detected in non-respiratory specimens (stool, blood, saliva, ocular secretions), but the role of these specimens in the transmission is uncertain [40-48]. Huang and colleagues [51], and Belser and colleagues [52] have been suggested that the transmission could be done through saliva, feces and conjunctival samples from confirmed cases of COVID-19, indicating that the transmission of COVID-19 is not limited to the respiratory tract.

In a systematic review, Zhang and colleagues [54] presented that viruses could be identified in oral swabs, anal swabs, and blood samples of the patients, and highlights that the anal swabs and blood could test positive when oral swab tested negative in some cases. Cheng and colleagues [55] detected the possible transmission through the ocular surface due to a contaminated health professional that was using the mask N95 but with no protection for the eye. Furthermore, Wax and colleagues [56] and Peng and colleagues [57] have detailed specific recommendations for the prevention of COVID-19 spread in Odontology. They suggested a scale of preventive strategies to mitigate the virus spread in the dental clinic setting, such as checking the patient's body temperature, the use of rubber dam isolation to block aerosol, and the usage of personal protective equipment (PPE) (masks, goggles, gloves, caps, face shields) for all healthcare providers, and reported airborne through aerosols formed during medical procedures (odontology and surgery) that could transmit the COVID-19. A Germany study also reported one case of COVID-19 infection in which the transmission of the virus may have occurred through contact with asymptomatic patients [58]. This research suggests that infected patients possibly start to drop viruses before the beginning of any symptoms [59], and those asymptomatic carriers could spread the virus without knowing [60-62]. Another study observed that an asymptomatic patient had similar viral loads to symptomatic patients in the samples of nasal and throat swabs [36].

Airborne Transmission

New studies propose that SARS-CoV-2 can be spread through particles smaller than droplets, which could persist in the air over time and distance [34, 35]. However, the significance of this finding to the epidemiology of COVID-19 and its clinical implications is not clear. Other studies have found viral RNA in ventilation systems and air samples of hospital rooms of patients with COVID-19, but the cultures for the feasibility of the virus were not made in these studies [63-65]. Nevertheless, studies using high-speed imaging to visualize respiratory exhalings have proposed that respiratory droplets may be carried in the air and have horizontal directions beyond two meters when speaking, coughing, or sneezing [34, 41, 66]. Gou and colleagues found that air samples were positive in many different sites of wards [67]. We do not know yet whether detected SARS CoV-2 in air samples are viable or not, or whether detected viral loads are high enough to cause COVID-19 [34, 64]. However, airborne precautions are recommended when aerosol-generating procedures are executed [41].

Fecal Transmission

Fecal transmission is an unanswered question. However, recent evidence supports the possibility of a fecally mediated route of COVID-19 transmission [34, 46, 67-76]. Wu and colleagues [77] detected positive fecal samples in patients with gastrointestinal (GI) symptoms but negative respiratory tract samples for 11 days.

Amirian [67] highlights the implications for public health of preventing potential fecal transmission if oral-fecal transmission of SARS-CoV-2 will be confirmed [73]:

a. Areas with inadequate sanitation could be a location for the virus spreading [72, 78, 79].
b. Strict preventive measures should be taken by healthcare workers and laboratory staff since they constitute possible targets when handling stool or fecal samples from SARS-CoV-2 infected patients [72]. Currently, the CDC recommends that virus isolation and cultures be handled in biosafety level 3 (BSL-3) settings, whereas routine diagnostic testing is performed in a BSL-2 laboratory [80].
c. Hygienic food preparation will be another key consideration due to the contact of the hand with the food [81]. Thus, public health agencies should engage in educational tactics for staff who handle food [67].

It is not clear yet if the virus detected in stool samples is sufficient to transmit the virus.

Nevertheless, these findings highlight the urgent need for further research on potential fecal-oral transmission and the possible significance and/or sequelae of viral presence in the GI tract [67]. Preventive strategies should be a high public health priority due to a large number of people that this route could reach [82].

Maternal-Fetal Transmission

Schwartz [83] did not find any intrauterine or transplacental transmission from 38 infected pregnant women to their fetuses. Dashraath and colleagues [84] and Chen and colleagues [85] in other studies also reported that there is no definitive evidence of vertical transmission, followed by other studies [34, 86]. The virus did not appear in samples of amniotic fluid, as well as seems to be not transmitted through the placenta [34, 83].

Transmission Period

People infected with SARS-CoV-2 can be contagious before onset of symptoms and sometimes there some cases that no symptoms at all are evident but the person is spreading the virus [6, 87]. That is why asymptomatic and presymptomatic transmission is a challenge to contact tracing, and this is an important target group to be controlled. Thus, testing becomes even more crucial to stopping the virus spreading [88]. Aditionally, viral shedding might be longer than previously thought [34].

Reproduction Number (R0) and Incubation Period

The basic reproduction number (R0) is an epidemiologic metric that describes the transmissibility cases that could be caused by 1 infected patient in a susceptible population. So, for R0>1, the number of infected is likely to increase; for R0<1, the transmission is likely to decline and die out. The reproductive number updated along with the development of the outbreak and interventions [89, 90].

This number is largely used in infectious diseases. For COVID-19, it was estimated based on the study of Li and colleagues [22] to be 2.2 (meaning that one patient has been spreading the infection to 2.2 other people). As there were many studies with different R0 and incubation periods, we described all the numbers that the main authors have reported (Table 2).

However, in some important studies, another metric was used, such as the incubation period, which is the interval from initial exposure to an infectious agent to the onset of any symptoms or signs it causes. For COVID-19, Li and colleagues [22] predicted 5.2 days (mean), and Sanche and colleagues [93, 94] found that a serial interval was different when public health measures are implemented or not.

Several research groups reported an estimated R0 of the outbreak depending on distinct estimation methods and the validity of underlying assumptions. Also, the discrepancy may be due to the sample number and different stages of the pandemic. Thus, based on the authors of Table 1, we can conclude that even in the same geographic region, different R0 values can be calculated by using different methods, and the R0 is much larger before the control measures than after, implying that SARS-CoV-2 is highly contagious and more infectious than initially estimated. This conclusion is consistent with the widespread of SARS-CoV-2 within a short period time and was also echoed by the finding that SARS-CoV-2 spike (S) protein had 10- to 20-fold higher affinity to human angiotensin-converting enzyme 2 (ACE2) receptor than that of SARS-CoV-1 based on the Cryo-EM structure analysis of S proteins [103].

Yuan and colleagues [104] prefer to use other metrics, the real-time reproduction number (Rt) instead of basic reproduction number (R0), to show the Rt values for Italy, Germany, France, and Spain as 3.1, 4.43, 6.56, and 3.95, respectively.

All of this literature lays the foundation to set 14 days as the medical observation period if any exposure occurred. This number was based on of the presented studies and the definition of the

Table 2. The R0 of COVID-19 and the incubation period.

Author	R0	Incubation Period (days)	Other observations
Wu and colleagues [91]	2.68	Not defined	January 2020
Li and colleagues [22]	2.2	5.2 95%CI, 4.1–7.0 days), with the 95th percentile of the distribution at 12.5 days	January 2020 97.5% of the infected subjects will develop symptoms within 12.5 days
Zhao and colleagues [92]	2.24 [95% confidence interval (CI) 1.96-2.55] to 3.58 (95% CI 2.89-4.39)	Not defined	January 2020
Sanche and colleagues [93]	1.4-3.0	5.7 (95% CI, 3.8–8.9 days)	After public health measures
Sanche and colleagues [94]	4.7-6.6		Before public health measures
Liu and colleagues [95]	3.8 (1.4-6.49)	Not defined	January 2020 – a review of 14 studies
Bauch and colleagues [96]	3.0	Not defined	January 2020 (Before public health measures were implemented)
Yang and colleagues [97]	3.77	4.75 days (interquartile range: 3.0–7.2 days)	January 2020 (4,021-case study)
Backer and colleagues [98]	Not defined	6.46 (95% CI, 5.6– 7.7 days)	Travels histories to and from Wuhan and symptom onset dates
Lesser and colleagues [99]	Not defined	4.0 (95% CI 3.6–4.4 days)	Systematic review
Park and colleagues [100]	Not defined	Range 4.5–5.2	-
Lipsitch and colleagues [101]	Not defined	7.5 (95% CI, 5.3–19 days)	-
Guan and colleagues [75]	Not defined	Up to 24	-
Lauer and colleagues [102]	Not defined	1-9	-

incubation period (IP), which means the interval between the potential earliest date of contact of the transmission source (wildlife or person with suspected or confirmed case) and the potential earliest date of symptom onset (i.e. cough, fever, fatigue or myalgia) [105]. So, accorging to current studies, the incubation period for COVID-19 is 14 days following exposure, and 5.1 days is the median incubation period [75, 102, 104, 105].

Viral Shedding

The interval during which an individual with COVID-19 is infectious is not precisely determined [41]. The detection of viral RNA does not necessarily indicate the presence of the infectious virus. For example, it seems that viral RNA levels of COVID-19 from upper respiratory samples appear to be higher soon after symptom onset compared with later in the illness [36, 76, 106, 107]. Also, Wölfel and colleagues [76] presented nine patients with mild COVID-19 in which infectious virus was isolated from naso/oropharyngeal and sputum specimens during the first eight days of illness, but not after this interval, despite continued high viral RNA levels at these sites.

A chinese study presented a model based on the timing of infection among 77 transmission pairs in which the authors suggested that the infectiousness started 2.3 days before symptom onset, peaked 0.7 days before the symptom onset, and declined within seven days [73]. These findings raise the possibility that patients might be more infectious in the earlier stage of infection [41]. Nevertheless, the transmission of SARS-CoV-2 from asymptomatic individuals (or individuals within the incubation period) has been documented [60, 87, 108-110]. Arons and colleagues [111] used reverse transcription-polymerase chain reaction (RT-PCR)-positive for samples from the

respiratory tract in presymptomatic and asymptomatic patients as early as six days before the development of typical symptoms. However, the extent to which asymptomatic or presymptomatic transmission occurs and how much it contributes to the pandemic remains unknown.

It is not clear how long a person remains infectious due to the duration of viral RNA shedding is variable. Some studies suggest the presence of the virus depends on the severity of illness [40, 76, 112, 113]. More studies are still necessary to support this theory. Liu and colleagues [112] reported repeated negative PCR tests on nasopharyngeal swabs by 10 days after the onset of symptoms, and tests were positive for longer in patients with more severe illness. In contrast, Xiao and colleagues [114] reported 56 patients with mild to moderate illness that the median duration of viral RNA shedding from naso- or oropharyngeal specimens were 24 days, and the longest was 42 days. Yet, according to the Centers for Disease Control and Prevention (CDC), three days after recovery, if patients present detectable viral RNA in upper respiratory samples, the RNA concentrations are generally low and difficult to transmit [115]. Nevertheless, Zhou and colleagues [113], in a retrospective multicenter cohort study presented 20 days for the median duration of viral shedding (IQR 17.0–24.0) and 37 days for the longest duration of viral shedding in survivors.

Concerning how long the virus stays in surfaces, it depends on the nature of the surface, pH, temperature, and relative humidity. The virus persistence time varies from 1 to 9 days, but it could be higher. [116] (Figure 8). However, if the surface is adequately clean, the virus is inactivated. The United States Environmental Protection Agency (USEPA) recommended some disinfectants against COVID-19 (Table 3).

Case Fatality Risk (CFR), Comorbidities and Risks for Disease and Death

The case fatality risk (CFR) for COVID-19 is estimated to be 0.25% to 4.7% [117, 118]. It is dependent on the presence of comorbidities, age, gender, and geographic location [51]. The CFR depends on prognosis factors such as male, elderly patients aged >60 years, comorbidities (cardiovascular diseases, hypertension, diabetes, pulmonary disease), severe pneumonia at baseline and a delay from onset to diagnosis (>5 days substantially elevated the CFRs) [75, 101, 119-121]. So, CFRs in patients with cardiovascular disease, diabetes, hypertension and respiratory disorders were as high as 10.5%, 7.3%, 6.0% and 6.3%, respectively [122].

In a meta-analysis, Yang and colleagues [123] evaluated 46,248 patients from eight studies, and described the most prevalent comorbidities in COVID-19 as hypertension, diabetes mellitus, cardiovascular diseases, and respiratory diseases, and also reported that these comorbidities were more likely present in severe patients. In another meta-analysis, Emani and colleagues [124] listed that hypertension, cardiovascular diseases, diabetes, smoking, chronic obstructive pulmonary disease, malignancy, and chronic kidney disease were most often detected comorbidities among hospitalized patients. Also, an Italian report showed that the most frequent comorbidities related to COVID-19 cases were hypertension, diabetes, ischemic heart disease, and chronic renal failure (72%, 31.5%, 27.4%, and 23.5%, respectively), and the patients with no comorbidities the CFR rate was of 2.8% [125]. In a pooled analysis, the risk of severe disease and mortality was higher in hypertensive patients nearly 2.5 fold, and it increases especially among advanced aged individuals [126].

Regarding gender, males are often more affected than females. However, men have more comorbidities and bad habits than women, like smoking and drinking [127].

Uncertain Risk of Animal Contact

Despite there not being certainty about the transmission of SARS-CoV-2 by animals, including pets, to people, some studies have already found the virus in dogs and cats. There

Table 3. Different surfaces and how long the virus survives.

Surface	Lifespan of COVID-19 virus
Food#	It does not seem to spread through food
Paper and tissue paper**	3 hours
Cooper*	4 hours
Aluminum#	2-8 hours
Cardboard*	24 hours
Wood**	2 days
Cloth**	2 days
Stainles steel*	2-3 days
Prolypoylene plastic*	3 days
Glass*	4-5 days
Metal#	5 days
Ceramics#	5 days
Paper money**	4 days
Outside of surgical mask**	7 days

* At 69.8 to 73.4 °F (21 to 23°C) and 40% relative humidity. ** At 71°F and 65% relative humidy.
Source/Credit: New England Journal of Medicine*; The Lance Microbe**; CDC#, FDA#.

Table 4. List of disinfectants for use against SARS-CoV-2/COVID-19 and how long the virus is inactivated.

Desinfectant agent	Composition/%	Time of desinfection (min)
Quaternary ammonium salt	Alkyl (C14 60%, C16 30%, C12 5%, C18 5%) dimethyl derivatives benzyl ammonium chloride 25% Alkyl (C-12 68%, C-14 32%) dimethyl ethylbenzyl ammonium chloride 25.0%	10
Hydrogen peroxide and Peroxyacetic acid	1. Hydrogen peroxide:0.5% 2. Peracetic acid: >14- 17, Hydrogen peroxide: >20-<30 and Acetic acid: >15-<20 Peracetic acid: 15%; Hydrogen peroxide: 22%	5 1 1
Hydrogen peroxide;	3.30%	5
Ammonium carbonate and Ammonium bicarbonate	1.38%	5
Octanoic acid	5-10%	2
Phenolic	Ortho-benzyl-parachlorophenol: 3.03%; Orthophenyl phenol: 3.40%	10
Quaternary ammonium ethanol	Didecyldimethyl ammonium chloride:0.33% Ethanol:72.5%	1
Sodium chlorite	30.5%	10
Sodium hypochlorite	6.0%	10
Ethanol	Ethanol: 15-30% Butane: 15-32% Propane:5-10% 2,2'-(ethylene dioxy)diethanol: 5-10%	0.5
Hypochlorous acid	0.017%	10
Quaternary ammonium; Isopropanol	Propan-2-ol:50-100% V/V Quaternary ammonium compounds: #2% Benzyl-C7-17-alkyldimethyl chloride: #5%	0.5
Silver ion; Citric acid	Silver: 0.003% Citric acid:4.846%	1
Sodium hypochlorite; Sodium carbonate	4.0% 1.0%	0.5

was no evidence that the viral load is sufficient to cause infection in humans. When it comes to SARS-CoV-2 infection in animals, there have been few reports and it seems that it could vary in the specimens. Shi and colleagues [128] infected ferrets, cats, and dogs with SARS-CoV- 2 through intranasal viral inoculation. The virus replicated effectively, especially in cats and ferrets. They also replicated the virus in dogs, but they appeared to be less responsive overall to the infection, and pigs and poultry were not susceptible to the infection. However, since there are doubts if the pets could transmit the virus to people and the apparent susceptivity of some animals to SARS-CoV-2 infection, the CDC recommends that pets should be kept away from other animals, people outside of the home, and people with confirmed or suspected COVID-19 should avoid contacting with their pets, for the duration of their self-isolation period [129].

Prevention*

Preventing the spread of COVID-19 includes considering horizontal isolation or vertical isolation. The vertical isolation could be done when the rate of infection is controlled and the health public system can support the amount of patients. Horizontal isolation is necessary when the rate of infection is in ascension, in order to flatten the curve. For preventing viral circulation as well as to protect ourselves, it is necessary to adopt social conducts such as those discriminated by WHO and CDC:

a. Isolation of the affected person (self-quarantine);
b. Self-quarantine if you come from an affected place (hospitals) or country;
c. Washing your hands frequently and carefully;
d. Avoid touching your face including mouth, nose, and eyes;
e. Cover your mouth and nose when coughing and sneezing;
f. Travel restrictions from and to the affected countries;
g. Maintaining high-level hygienic condition in-home and surroundings;
h. Use self-protection (adequate mask, protection glasses, alcohol 70%);
i. If you need to go outside, use the self-protection item (“h”);
j. Avoid social gathering;
k. Avoid closed places;
l. Maintaining good nutrition;
m. Take social distancing seriously by keeping a distance of 1.5 meters from another person (using self-protection – item “h”).

Vaccine development and medicines take time. Henceforth, it is extremely important to follow guidance on social separation, frequent hand washing, and disinfecting home and workplaces [18, 130, 131].

Conclusion

SARS-CoV-2 is a global threat without effective drugs or vaccines available, and it is spreading fast, affecting worldwide populations, and especially poor people. We described the epidemiology of the disease, the issue of the transmission, and the risk to get ill - especially for old people and those with comorbidities -, the R0 number and CFR, and the prevention policies. Despite the current mortality rate being low, there is evidence that it could be high if the infected person does not have access to medical care. If a large number of people get sick, and we do not manage to flatten the curve with social isolation politics, it will result in the collapse of the health care system, and then the mortality rate will increase fastly. While there is no drug to block the virus and a vaccine does not exist, following social distance is crucial. Meanwhile, the intermediate host and the mechanism of the cross-species spread of the virus should be further investigated, and legislation should be employed to restrict the sale of wild animals, the potential intermediate host(s) of many viruses, to prevent future outbreaks.

*Please check our article “Clinical Trials for COVID-19 – An Urgent Response” in this issue (pages 98-105).

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Pathogenesis, Clinical Manifestations and Laboratory Findings of the COVID-19

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Since the beginning of the pandemic of new coronavirus, scientists are trying to elucidate the mechanisms of SARS-CoV-2 replication in the human body, its genome, and the behavior of the virus into cells. Also, at the beginning of the outbreak, they found that the unique problem of the virus is the severe acute respiratory syndrome pneumonia, however, new discoveries revealed that the virus affects major organ systems in the human body, causing injuries and letal damages. In addtion, the tests for diagnosing the virus has became a priority. So, based on the literature review, we showed in this article the mechanisms of the virus into cells, the symptoms, the clinical course of the disease, and the main injuries caused in the human body's systems by the SARS-CoV-2, and the laboratory findings. We based our research in the articles of the main database (PubMed/Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Exerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), in the high-impact international scientific Journals (Scimago Journal and Country Rank - SJR - and Journal Citation Reports - JCR), such as The Lancet, Science, Nature, The New England Journal of Medicine, Physiological Reviews, Journal of the American Medical Association, Plos One, Journal of Clinical Investigation, and in the data from Center for Disease Control (CDC), National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO). We prior selected meta-analysis, systematic reviews, article reviews and original articles in this order. We reviewed more than 317 articles and used 235 from March to June 2020, using the terms coronavirus, SARS-CoV-2, novel coronavirus, Wuhan coronavirus, severe acute respiratory syndrome, 2019-nCoV, 2019 novel coronavirus, n-CoV-2, covid, n-Sars-2, COVID-19, corona virus, coronaviruses, pathogenesis, clinical manifestations, symptoms, body systems, damage, injuries, laboratory, diagnosis, with the tools MeSH (Medical Subject Headings), AND, OR, and characters [,",;; /., to ensure the best review topics. We concluded that the virus could affect and damage the respiratory system, cardiovascular system, digestive system, urogenital system, and central nervous system. It makes the treatment harder than the physicians found at the beginning of the pandemic. We are initiating our understanding of this new virus and the effect in patients during the symptoms and after them. A deeper understanding of this virus from biomedical research and epidemiological observation will provide important clues to etiologic research, diagnosis, differential diagnosis, treatment, and prognostic assessment against COVID-19.
Keywords: COVID-19. SARS-CoV-2. Pathogenesis. Organ Systems. Injuries. Laboratory Findings.

Introduction

In March 2020, the World Health Organization (WHO) declares a new pandemic that began in Wuhan, Hubei Province, China, and spreads worldwide. The disease, called COVID-19, causes severe acute respiratory syndrome by an RNA-virus of the Family Coronaviridae, named SARS-CoV-2 [1-4]. However, in addition to affecting the pulmonary system, there are many other clinical features of the disease and other affected organs that were not knows at the beginning of the pandemic. Now, studies reveal that this new virus compromises lungs, kidneys, liver, and central nervous system. In this article, we present the pathogenesis of the COVID-19 infection, clinical features, and laboratory findings about COVID-19 trough reviewed studies, systematic review, and meta-analysis.

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Pathophysiology of COVID-19

ACE2 (angiotensin-converting enzyme 2) is the receptor that allows SARS-CoV-2 to enter into the cells to trigger infection [5, 6]. ACE2

is a multifunctional protein whose primary physiological role is the enzymatic conversion of angiotensin (Ang) II to Ang-(1-7), and Ang I to Ang-(1-9) [7]. The involvement of ACE2 in severe acute respiratory syndrome (SARS) infection occurs due to the binding in the coronavirus receptor [8]. This bond between SARS-CoV-2 spike protein and ACE2 promotes the virus to infiltrate the lung's alveolar epithelial cells, where it is overexpressed, by processes involving cell surface-associated transmembrane protein serine 2 (TMPRSS2) [9] (Figure 1). Inside the host cell, the RNA virus begins its replication conducting to newly formed genomic RNA, which is processed into virion-containing vesicles that join with the cell membrane to release the virus [9].

According to Wu and colleagues [11], SARS-CoV 2 is sprayed principally through the respiratory tract by droplets and respiratory secretions. The RAS/ACE2 appears to be interrupted by SARS-CoV-2 infection, which likely has a pathogenic role in critical lung injury and respiratory failure in COVID-19.Nevertheless, ACE2 is not only expressed in the lungs' cells, it also highly expressed in the human heart, vessels, gastrointestinal tract, and other human tissues, which can cause severe damage to the body system (Figure 2) [12-14].

Cytokine Storm and Inflammation

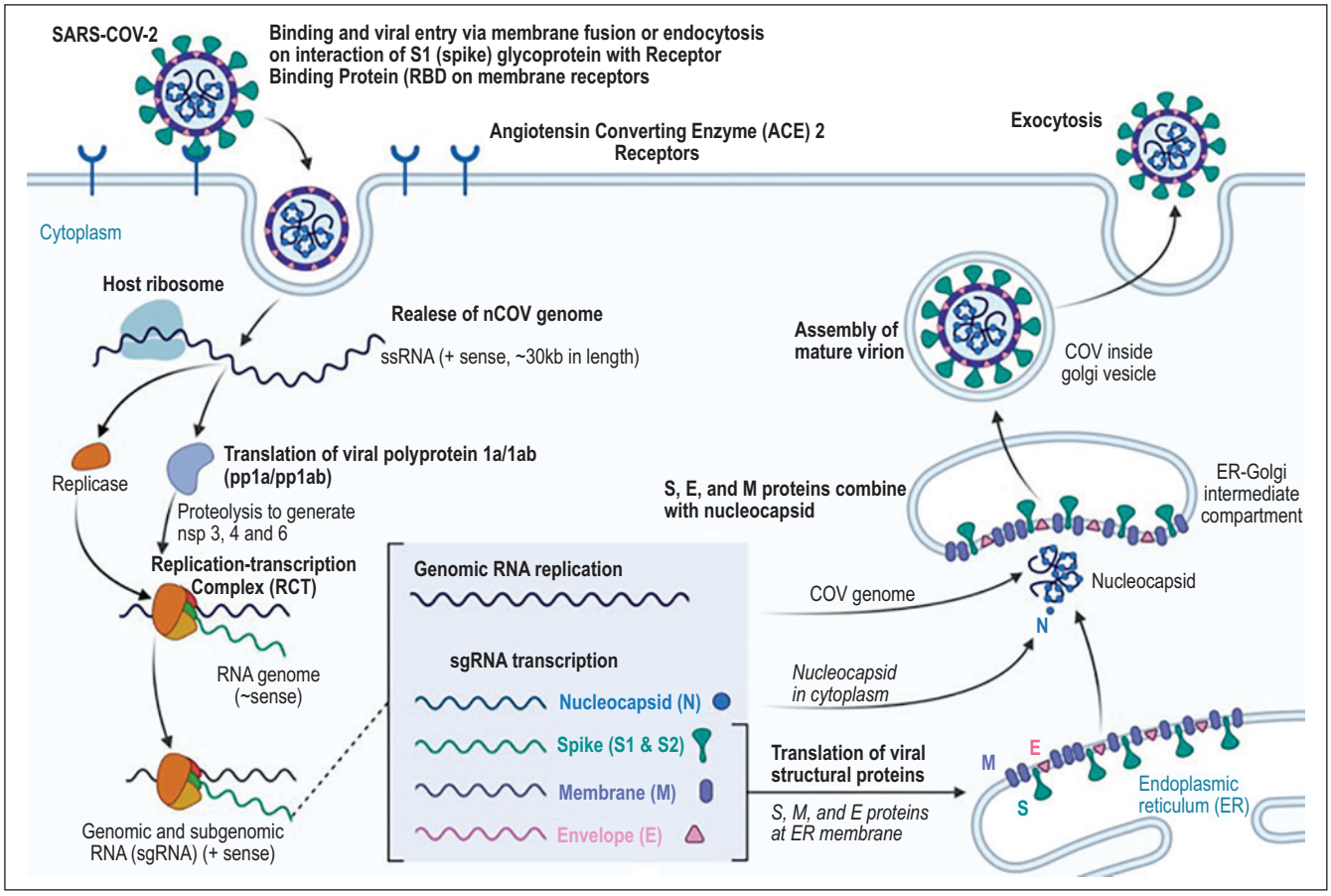
Previous studies have confirmed that the immune abnormality is related to the pathogenesis of SARS-CoV infection [15]. Several studies suggested that an overexpression of the immunological system, called cytokine storm, is the main contributor to the severity of the disease. Cytokine storm syndrome (CSS) is a systemic inflammatory response usually caused by viral infections. It is also called cytokine release syndrome (CRS) and characterized by an overexpression of the immunologic system with excessive numbers of pro-inflammatory cytokines (e.g., interleukin-1β (IL-1β), IL-6, interferon-γ (IFN-γ), IFNγ inducible protein-10 (IP-10), monocyte chemoattractant protein-1(MCP-1), granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein-1α (MIP-1α), tumor necrosis factor-α (TNF-α). CSS is significantly raised in COVID-19 patients [16, 17].

The protagonist in the CSS is the interleukin 6 (IL-6), which is produced and delivered by activated leukocytes and acts on plenty of cells and tissues. Cytokine IL-6 seems to be the core of cytokine storm due to its ability not only to amplify cytokine storm by stimulating the production of other pro-inflammatory cytokines but also results in vascular leakage, interstitial edema [18]. Moreover, IL-6 has also been shown to weaken papillary muscle contraction, which causes myocardial dysfunction, as well as promoting the differentiation and activation of B lymphocytes, and stimulating production of acute-phase proteins. [19]. IFNγ is also another cytokine regarded as a marker of cytokine storm, causing cell apoptosis through regulating the JAK/STAT1 axis and p38-MAPK1 [20]. Nevertheless, anti-inflammatory cytokines such as IL-4 and IL-10 are also increased in COVID-19 patients, and their levels are also related to disease severity [16, 17], demonstrating the close relation between pro- and anti-inflammation. Uncontrolled inflammatory process caused by the cytokine storm has the potential to lead to injury multi-organs, septic shock, and organ failure [21].

In COVID-19 disease, SARS-CoV-2 invades host cells, replicates, and releases viruses via a process in which programmed cell death is triggered off by inflammation (pyroptosis). This process activates the innate and adaptive immune systems.

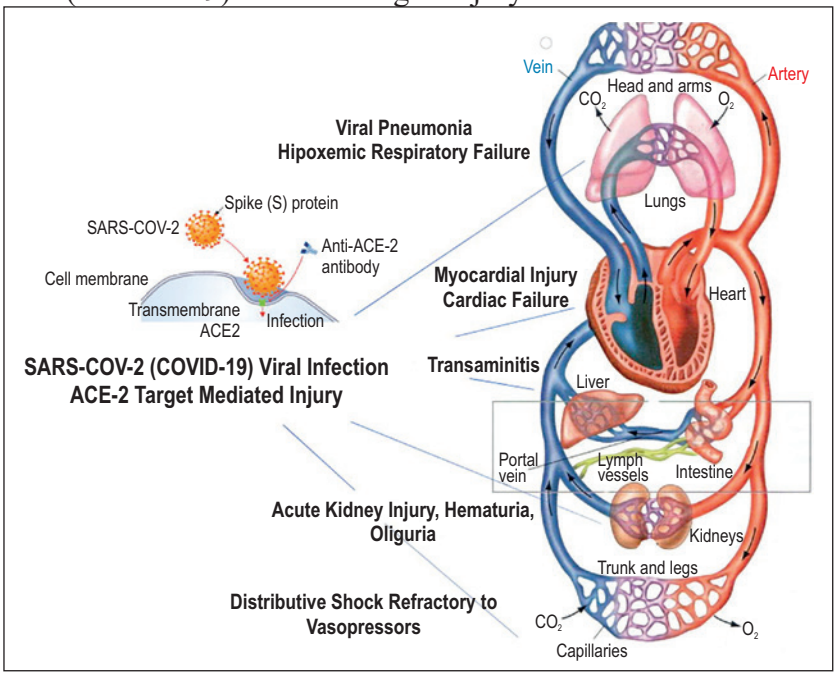
The viral infection leads epithelial cells and alveolar macrophages into the lungs to generate a large number of inflammatory cytokines and chemokines (Figures 3 and 4), which attract monocytes, macrophages, and T cells to the infection site, producing more inflammatory cytokines, which creates a feedback loop. The accumulation of T-cells in the lungs also provokes a reduction in the blood levels of lymphocytes (i.e.,

Figure 1. The machinery of SARS-CoV-2 getting into the human cell.



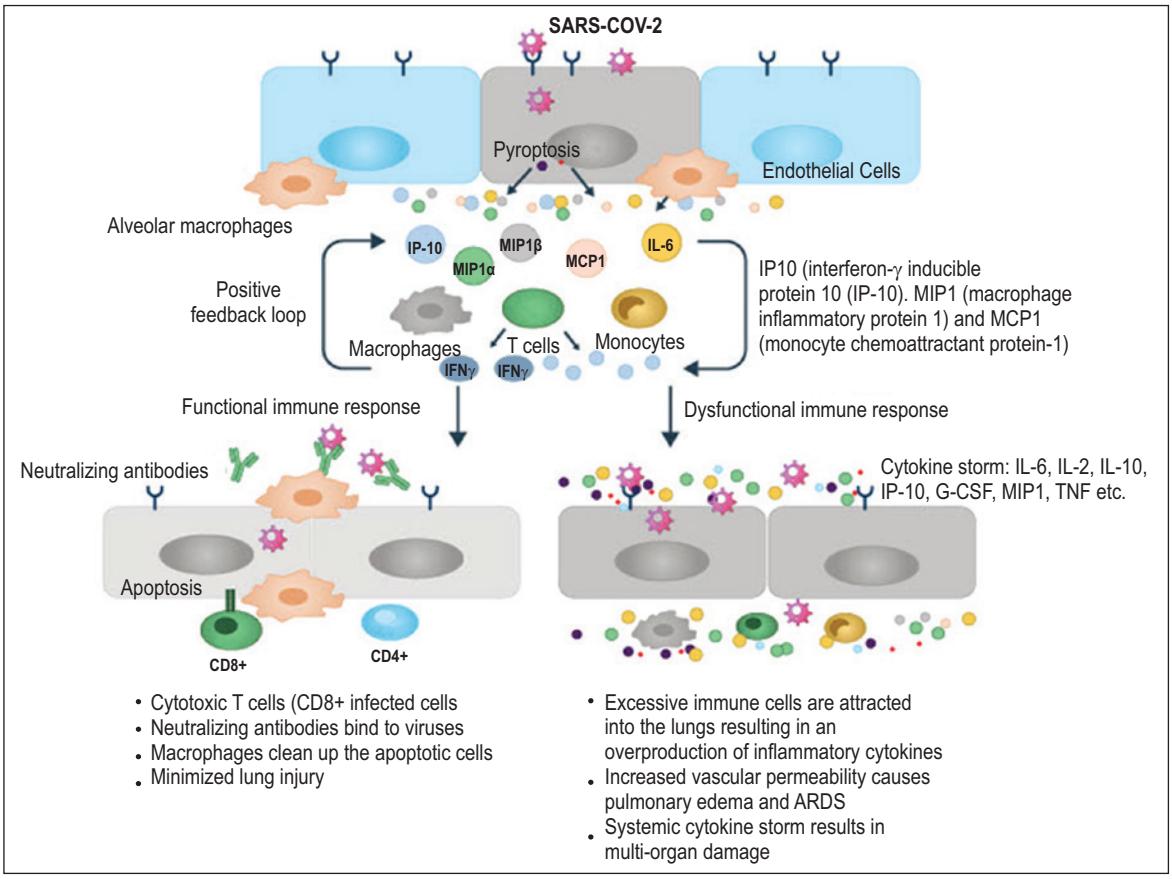
Source/Credit: Reproduced from the original work here [link to https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance) Permission obtained from © The European Society of Cardiology 2020. All rights reserved. [10].

Figure 2. SARS-CoV-2 (COVID-19)-mediated organ injury.



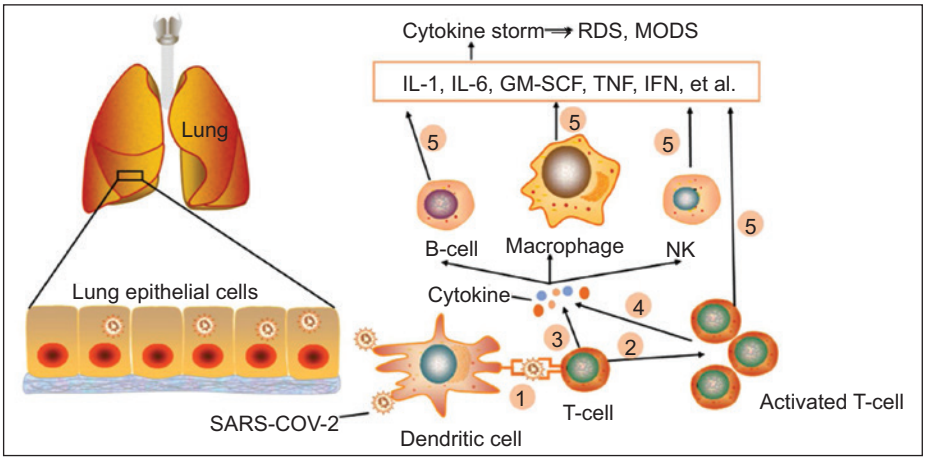
Source/Credit: Kazory and colleagues [14].

Figure 3. Immunopathogenesis of cytokine storm in COVID-19.



Source/Credit: Li [25].

Figure 4. Inflammatory storm mechanism.



1.Antigen presenting. 2. T cells activate and start reproducing. 3. A large amount of cytokine are secreted during T cell activation. B cells, macrophage and NK cells will be activated by these cytokine. 4. Activated T cells release cytokine and activate more B cells, macrophage and NK cells. 5. Cytokine secreted. The figure shows the mechanism of cytokine cascade, also known as an inflammatory cascade. Pathogen infection triggers an intense immune response and inflammatory response and rapid release of a large number of cytokines (such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, and interferon-γ (IFN-γ). In this context, patients with viral infection are particularly susceptible to acute respiratory distress syndrome and multiple organ failure. Cytokine cascades and low lymphocytes are also specific in other severe coronavirus diseases (such as SARS and MERS) and are positively related to disease progression and severity [26-28]. Recent studies have confirmed this conclusion, showing low lymphocytes and elevated inflammatory cytokines in most SARS-CoV-2 cases [29, 30]. Once triggered, the cytokine cascade may cause rapid failure of one or more organs with extremely adverse prognosis if not treated promptly.
Source/Credit: Zhang and colleagues [31].

lymphopenia) in severe COVID-19 patients [22,23]. The intense immune response causes damage to the lungs and other vital organs. Li and colleagues [24] observed that, also in other body systems, the systemic cytokine storm and the microcirculation dysfunctions together lead to viral sepsis.

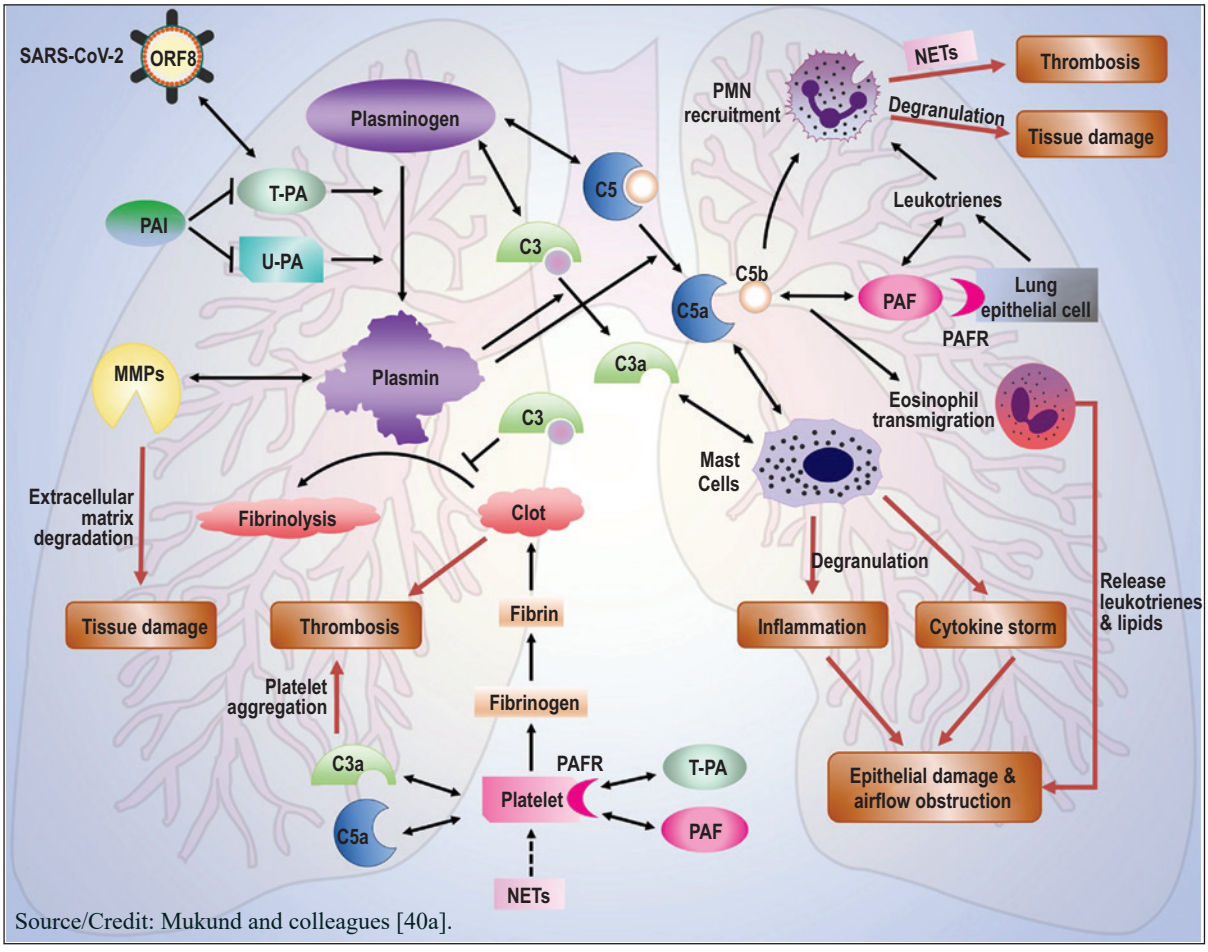
Hyperfibrinolysis

According to Ji and colleagues, four viral proteins are essential for the pathogenesis of COVID-19 [32]:

1. S proteins that bind to ACE2 receptors after being cleaved by furin-like proteases;
2. RNA-dependent RNA polymerase (RdRp, which is responsible for replicating SARS-CoV-2 RNA genome);
3. 3C-like and papain-like proteases that cleave two polyproteins, which are important for the packing new virions;
4. Plasmin and other host proteases cleave additional viral proteins that are not known.

The SARS-COV-2 has a similar receptor-binding domain in the spike (S) protein for host ACE2 (angiotensin-converting enzyme 2) proteins [33-35]. So, the S protein of SARS-CoV-2 binds to human ACE2 receptors with higher affinity and this might be a furin-like cleavage site (682RRAR/S686) inserted in the S1/S2 protease (S1 region of the spike protein is responsible for binding to the host cell ACE2 receptor, where the S2 region is responsible for fusion of the viral RNA and cellular membranes) of the SARS-CoV-2 virus (Figure 5) [36]. The expression of furin-like proteases could increase SARS-CoV-2 cell and

Figure 5. The role of plasmin in the increase of SARS-CoV-2 cell and tissue tropism due to the expression of furin-like proteases.



Source/Credit: Mukund and colleagues [40a].

tissue tropism and transmissibility, and enhance its pathogenicity, as well as possibly increasing the virus' ability to attach and invade human cells expressing ACE2 and CD147 receptors [37-39].

The presence of significant increases in the fibrin degradation products (FDPs) elevates the serum D-dimer levels, prolongs prothrombin time, and decreases the platelets, which are consistent with the presence of hyperfibrinolysis and coagulation activation in patients with severe COVID-19 infection [29, 40-44].

The Role of Plasmin(ogen)

Plasmin is an important key in fibrinolysis, improving the virulence and pathogenicity of viruses carrying a furin-site such as SARS-CoV-2 [40]. According to Ji and colleagues [40], elevated plasmin(ogen) is a common characteristic in people with comorbidities such as hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and chronic renal illness. These groups are especially susceptible to SARS-CoV-2 infection since the plasmin raises the virulence and infectivity of the SARS-CoV-2 virus by cleaving its spike proteins. And highly increased D-dimer in COVID-19 patients is the result of plasmin-associated hyperactive fibrinolysis. So, D-dimer and viral load are independent risk factors of disease severity and mortality.

Clinical Disease Course of COVID-19

Figure 6 summarizes the clinical course of COVID-19 infected patients according to survivors and non-survivors, related to the stage of the disease [45].

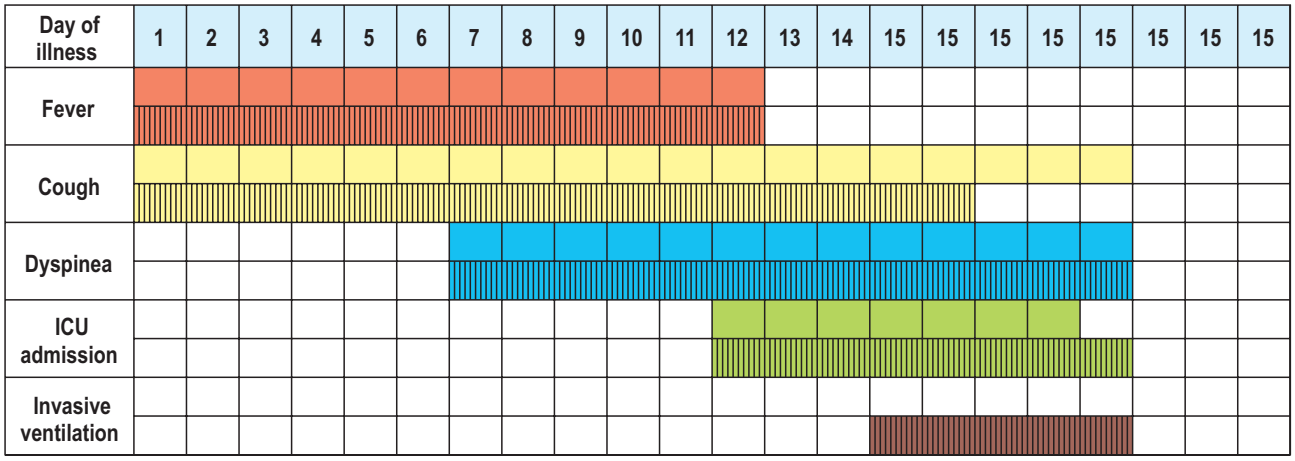
Clinical Manifestations and Symptoms of COVID-19 Infection

In our review, we found several studies with clinical manifestations of COVID-19. We then chose the major authors and discussions about the symptoms, the stage of the disease in which they occur, the laboratory abnormalities, and the implications for the patients (Table 1 and Figure 7).

In a meta-analysis, Nascimento, and colleagues [46] present the most common symptoms in patients with SARS-CoV-19 infection:

- Fever (82%);
- Dry cough (61%);
- Muscle aches (myalgia) and/or fatigue (36%); and
- Dyspnea (26%); and
- Chest images abnormalities: bilateral opacities, multiple ground-glass shadows/ opacities, septal thickening, and parenchymal consolidation.

Figure 6. Summary of the clinical course and the main symptoms of COVID-19 patients.

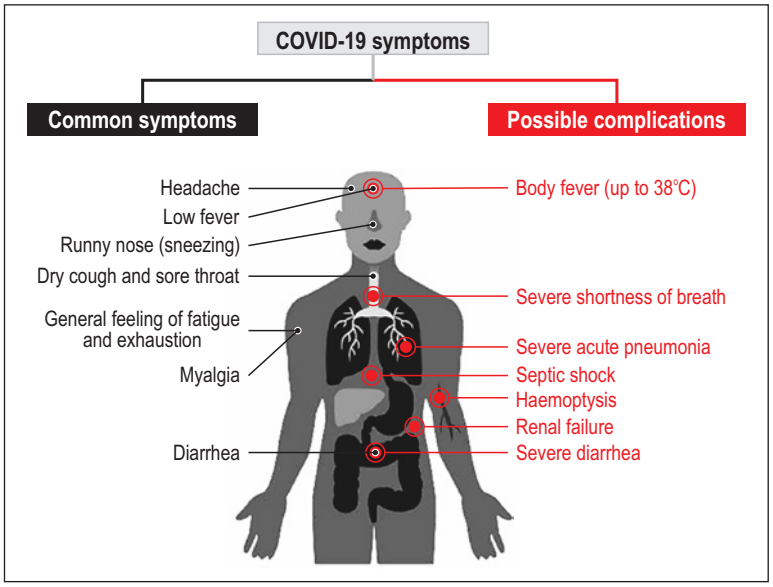


The solid colors and cross-hatched patterns indicate the survivors (n = 137) and non-survivors (n = 54), respectively.
Source/Credit: Kakodkar and colleagues [45].

Table 1. Clinical symptoms of patients with COVID-19 infection [66].

Study	Chen and colleagues [30]	Huang and colleagues [22]	Chung and colleagues [67]
Patient count	99	41	21
Age (mean, year)	55.5	49	51
Fever	83%	98%	67%
Cough	81%	76%	43%
Shortness of breath	31%	55%	-
Myalgia	11%	44%	3%
Haemoptysis	-	5%	-
Sputum production	-	28%	-
Confusion	9%	-	-
Sore throat	5%	-	-
Rhinorrhoea	4%	-	-
Chest pain	2%	-	-
Diarrhea	2%	1%	-

Figure 7. The most common symptoms of COVID-19 based on WHO.



McIntosh [47] and Wang and colleagues [29] also described the clinical features in COVID-19 infection:

- Pneumonia seems to be the most common and severe manifestations of COVID-19, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging]. Notwithstanding, there are no specific clinical features that can yet reliably distinguish pneumonia from COVID-19 to other viral pneumonia, the presence of dyspnea several days after the onset of initial symptoms is suggestive of COVID-19;
- Fever;
- Headache;
- Dry cough;
- Dyspnea;
- Sore throat, and rhinorrhea [30, 48];
- Myalgias and/or fatigue;
- Gastrointestinal symptoms (nausea and diarrhea, and abdominal pain in severe cases) [22, 29, 49-51];
- Smell or taste disorders (anosmia and dysgeusia) [52-54];
- Sputum production (uncommon; severity cases related the produce sputum due to the

opportunistic disease that could affect the severely ill patients) [22, 29, 55-57];
- Conjunctivitis (uncommon) [58];
- Dermatologic findings (more common in children) (maculopapular, urticarial, and vesicular eruptions and transient livedo reticularis [59-61]; reddish-purple nodules on the distal digits similar in appearance to pernio (chilblains – also called "COVID toes") have also been described, mainly in children and young adults [62-64].

According to El-Aziza and colleagues in a review study, present [65] the most common symptoms of COVID-19 based on the World Health Organization (WHO) report:
- Fever (88%);
- Dry cough (72%);
- Sore throat (68%),
- Fatigue (38%); and
- Diarrhea (4%);
- Severe shortness of breath (20%) (severity cases);
- Severe headache (13%) (severity cases).

Less common symptoms include headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting [22, 29].

Pulmonary Manifestations

Gulati and colleagues [68] described the studies that researched the pulmonary manifestations caused by COVID-19 and showed the clinical features and important discoveries as follow:
a. A dry cough is a common symptom, present in 68% of infected patients [29].
b. Sore throat and sputum production are uncommon (<5%) [48].
c. The presence of dyspnea is predictive of ICU admission [48].
d. Hospitalized patients had an abnormal chest computed tomography: ground-glass opacities with a peripheral lung distribution, followed by consolidation and interstitial abnormalities [22, 29, 48].
e. Lung histopathology presents diffuse alveolar damage, denuded alveolar lining cells, and interstitial fibrosis [69].
f. Higher incidence of thromboembolism with an association between elevated D-dimer levels and mortality [44].
g. Studies speculated that cytokine storms are responsible for lung injury [70,71].
h. COVID-19 uses angiotensin-converting enzyme 2 (ACE2) receptors to enter into cells [5, 72-74].

Specific Features of COVID-19-related SARS

According to the Task Force of Berlim definition, SARS is divided into three stages based on oxygenation index (PaO_2/FiO_2) on positive end-expiratory pressure (PEEP) ≥5 cmH2O:
a. Mild (200mmHg < PaO_2/FiO_2 ≤ 300mmHg);
b. Moderate (100 mmHg < PaO_2/FiO_2 ≤ 200mmHg); and
c. Severe (PaO_2/ FiO_2 ≤ 100mmHg) [75].

And also according to the same Task Force, there is a higher incidence of SARS-Cov-2 among hospitalized patients (29%) with higher mortality (15%) [75].

Nevertheless, although the presence of consolidation and exudation in SARS caused from many pathogens might be common, the image of SARS in COVID-19 is not as frequent as in other pneumonia since SARS is a condition associated with many disease processes, resulting in reduced lung compliance and severe hypoxemia (Box 1) [75, 76].

In the early exudative stage, the lungs present diffuse alveolar damage with the destruction of epithelial and endothelial cells, and present dry cough (59.4-82%) as the most common respiratory symptom [22, 29, 30, 44, 48, 76] The chest computed tomography (CT) scans usually showed multifocal bilateral patchy shadows and/or ground-glass opacities; and some patients showed a mixed pattern of ground-glass opacities and consolidation (Figures 8 and 9).

Pulmonary and Cardiac Injury Caused by COVID-19

SARS-CoV-2 is primarily a respiratory disease that causes fast pneumonia, and in severe cases can lead to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes [22]. Despite COVID-19 effecting primary the lungs, COVID-19 is being currently regarded as a systemic disease involving other vital organs, such as heart, liver, and kidneys [79]. We are aware of the role of ACE2 in the disease and how the ACE2 is expressed widely in many organs and tissues, including the cardiovascular, digestive, and urogenital systems besides the respiratory tract [80, 81]. However, it remains unclear if the organ and tissue injury in patients with COVID-19 is a direct or indirect consequence of the virus infection. Theoretically, the virus may target those organs and tissues with positive expression of ACE2. As we described in the cytokine storm, the viral infection induces an excessive immune reaction in the host, which leads to damage in the organ. Nonetheless, the pulmonary events can trigger the "Lung-Heart" syndromes with a combination of the respiratory and cardiovascular adverse events and conditions (Figure 10) [82, 83]. Seeing as many severe patients have cardiovascular disease (CVD), including hypertension, acute cardiac injury, and myocarditis, the cardiac damage may be secondary to the lung disease, since acute lung injury itself leads to increased cardiac workload. That can be problematic especially in patients with pre-existing hypertension or CVD, which may also be the important (patho)physiological role of the RAS/ACE2 in the cardiovascular system since ACE2 is expressed in the human heart, vascular cells and pericytes [84-87]. For instance, SARS-CoV-2 infection injures the myocardium, leading to elevated levels of myocardial biomarkers (e.g., troponin I > 28 pg/mL) and certain abnormalities

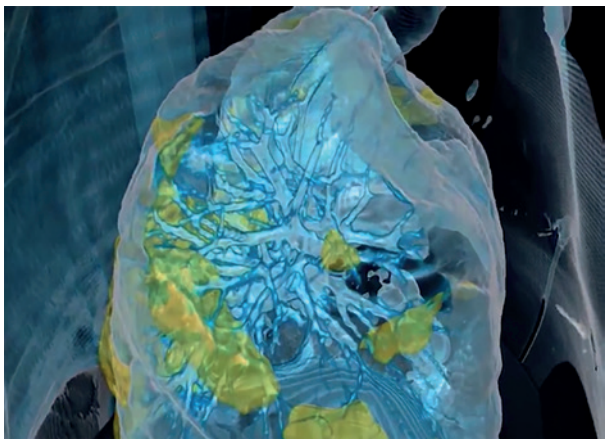
Box 1. Summary of characteristics of COVID-19-related ARDS.

Specific features of COVID-19-related ARDS	Differences from ARDS caused by other factors

• Injury site
  • Mainly respiratory system
  • Alveolar epithelial cells
• Specificity of clinical features
  • Clinical symptoms were inconsistent with the severity of laboratory and imaging findings
  • Clinical manifestations were relatively mild
	• Timing of onset
	  • 8-12 days
	• Respiratory system compliance
	  • Lung compliance might be relatively normal in some COVID-19-related ARDS patients
	• Severity based on oxygenation index
	  • Three categories (PEEP≥5cmH_2O)
	  • Mild (200mmHg≤PaO_2/FiO_2<300mmHg)
	  • Mild-moderate (150mmHg≤PaO_2/FiO_2<200 mmHg)
	  • Moderate-severe (PaO_2/FiO_2<150mmHg)
	• Management protocols
	  • HFNO
	  • HFNO can be safe even in some moderate-severe patients
	  • The timing of invasive mechanical ventilation is very important
	  • Corticosteroids
	  • The effects of corticosteroids were uncertain

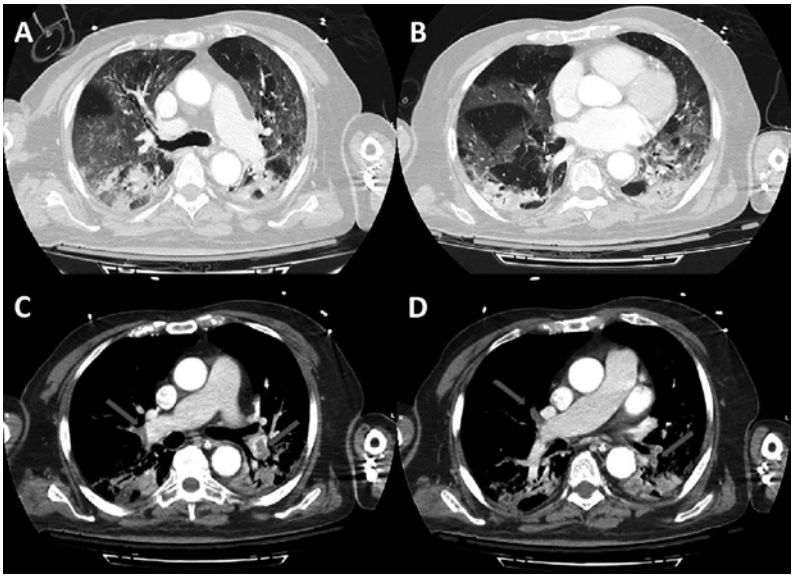
Source/Credit: Li and Ma [76].

Figure 8. 3D model based on computerized tomography scans presents extensive lung damage (yellow) in a patient with COVID-19.



Source/Credit: Wadman and colleagues [77].

Figure 9. Axial contrast-enhanced computer tomography (CT) of the chest.



A, B, Diffuse bilateral ground-glass opacities and small bibasilar consolidations compatible with COVID-19 pneumonia. C, D, Filling defects consistent with pulmonary emboli within the right upper lobe, right middle lobe, right lower lobe, and left lower lobe pulmonary arteries (arrows).
Source/Credit: Lushina and colleagues [78].

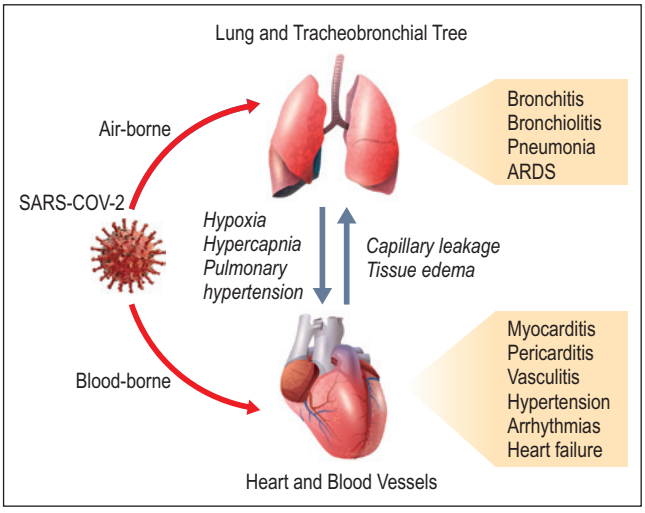
in electrocardiography and echocardiography, but the mechanisms still remain largely unclear (Figure 11).

Wu and colleagues [88] showed that the lung and cardiac tissues contain significant amounts of inflammatory infiltrations, indicating the inflammatory nature of tissue damage by SARS-CoV-2 infection. In autopsy reports, COVID-19-induced pulmonary and myocardial injury, and the lungs presented: edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells [88].

Cardiovascular Manifestations

Gulati and colleagues [68], as well as the European Society of Cardiology [10] summarized

Figure 10. Schematic demonstration of the viral injury to the lung and heart triggering the "Lung-Heart" syndromes.



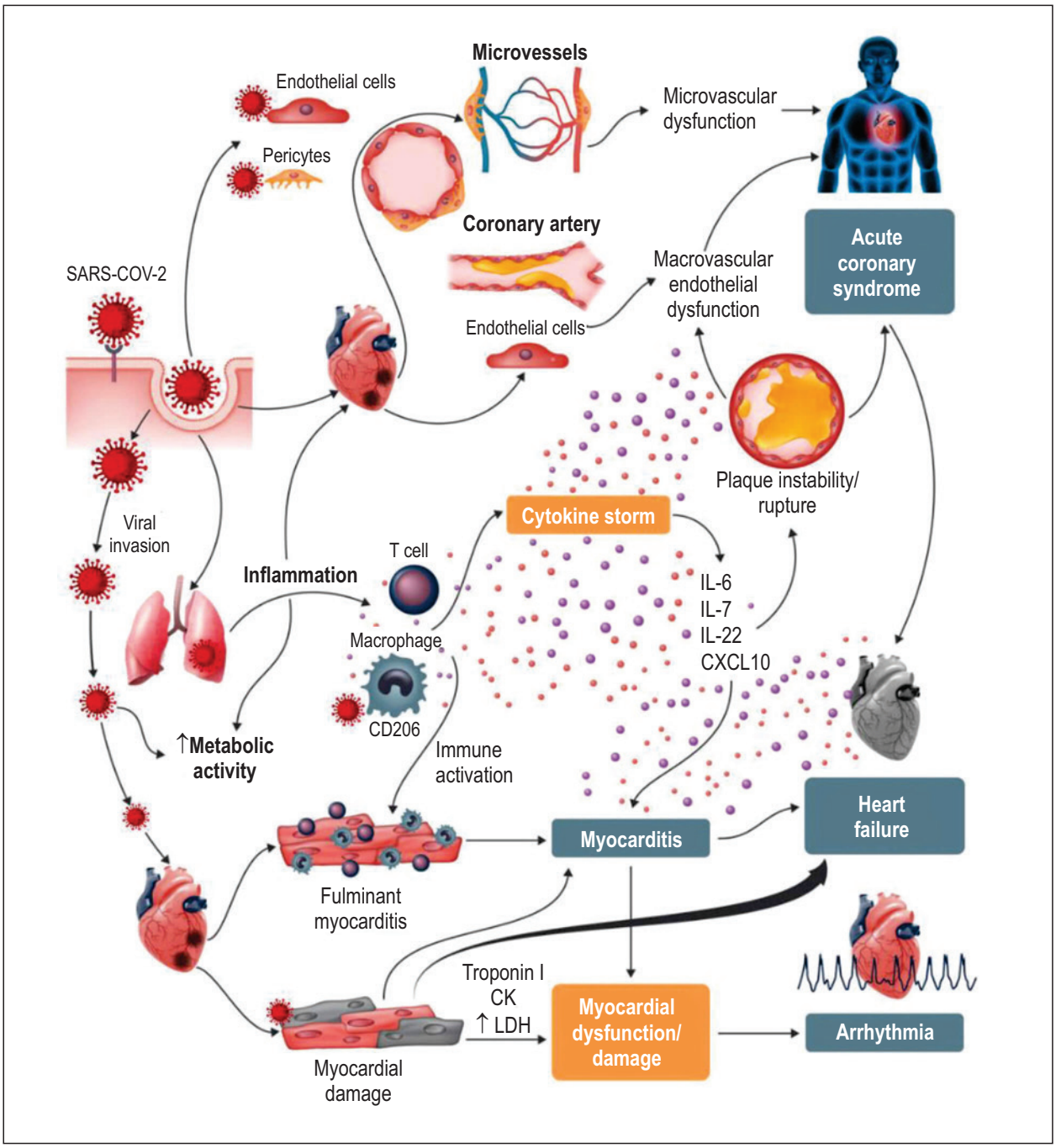
Source/Credit: Adapted from Geng and colleagues [89].

the cardiovascular manifestations and important issues related to COVID-19 and the cardiovascular system as follow:

a. The SARS-CoV-2 attaches to the host receptor ACE2 for mediate entry into cells. ACE2, which is expressed in the lungs, heart, and vessels, is an important member of the renin-angiotensin system (RAS), and critical in the pathophysiology of cardiovascular disease (CVD);
b. CVD and COVID-19 likely implicates in the dysregulation of the RAS/ACE2 system because of SARS-CoV 2 infection and the comorbidities, such as hypertension;
c. CVD may be the earliest aspect in COVID-19, but may be secondary to acute lung injury, which drives to improved cardiac workload, a critical problem in patients with pre-existing hypertension;
d. ACE2 (receptor of COVID-19) is expressed in the myocardium, which could head to myocardial damage;
e. Cytokine storm, which starts from an imbalance of T-cell activation with a dysregulated discharge of interleukin (IL)-6, IL-17, and other cytokines, may contribute to CVD in COVID-19;
f. Immune system overexpressed along with immunometabolism modifications may result in plaque vulnerability, contributing to acute coronary events;
g. COVID-19 also causes acute cardiac injury in patients with elevated high-sensitivity cardiac troponin-I (hscTnI) levels [22, 90].
h. CK-MB and hs-cTnI are high in severely ill patients in the intensive care unit (ICU), which suggests myocardial injury [85,91].
i. Higher cTnI level was also associated with higher complications and mortality [92];
j. Left ventricular dysfunction, persistent hypotension, acute myopericarditis, myocarditis, arrhythmia, and heart failure have also been reported in COVID-19 patients [29, 91, 93-95].
k. Interstitial mononuclear inflammatory infiltration in heart tissue also provides evidence of myocarditis in COVID-19 patients [96].
l. 7% of deaths in COVID-19 patients have been attributed to myocardial injury [97].
m. Other cardiac manifestations include acute myocardial infarction, fulminant heart failure, and dysrhythmias [98].
n. Arrhythmia with COVID-19 infection was >17% in some studies [29, 85].
o. Range from mild chest pain with preserved ejection fraction (EF) to profound cardiovascular collapse requiring extracorporeal membrane oxygenation (ECMO).
p. Echocardiography may show a regional wall motion abnormality or global hypokinesis with or without pericardial effusion [99, 100].
q. Initial electrocardiogram may show low voltage QRS complexes in the limb leads, ST-segment elevations in leads I, II, VL, V2-V6, and PR elevation and ST depressions in aVR [99, 100].

Also, Gulati and colleagues [68] proposed the mechanisms of cardiac injury in patients with COVID-19 that include overexpression of ACE2 in patients with chronic cardiovascular disease,

Figure 11. Cardiovascular damage in COVID-19.



SARS-COV-2 anchors on transmembrane ACE2 to enter the host cells including type-2 pneumocytes, macrophages, endothelial cells, pericytes and cardiac myocytes lead to inflammation and multi-organ failure. Infection of endothelial cells or pericytes is of particular importance because this could lead to severe microvascular and macrovascular dysfunction. In addition, immune over-reactivity can potentially destabilize atherosclerotic plaques and explain the development of acute coronary syndromes. Infection of the respiratory tract, particularly type-2 pneumocytes, by SARS-COV-2 is manifested by the progression of systemic inflammation and immune cell overactivation leading to "cytokine storm", resulting in increased levels of cytokines such as IL-6, IL-7, IL-22 and CXCL10. Subsequently, it is possible that activated T cell and macrophages may infiltrate infected myocardium resulting in the development of fulminant myocarditis and severe cardiac damage. This process may be further intensified by a cytokine storm. Similarly, the viral invasion may cause cardiac myocyte damage directly leading to myocardial dysfunction and contribute to the development of arrhythmias. From Guzik et al., COVID-19 and the Cardiovascular system - implications for risk assessment, diagnosis and treatment options. Cardiovasc Res., 2020, doi: 10.1093/cvr/cvaa106.

Source/Credit: Reproduced from the original work here [link to https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance) Permission obtained from © The European Society of Cardiology 2020. All rights reserved. [10].

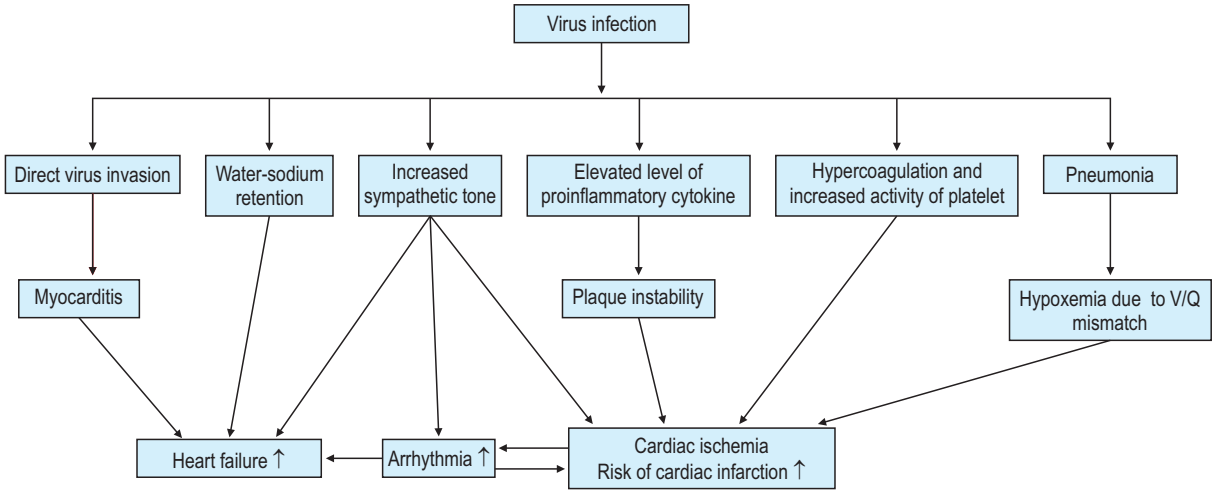
cytokine storm triggered by an imbalanced response by type 1 and type 2 helper cells, hypoxemia resulting in myocardial damage, plaque rupture, coronary vasospasm, or direct vascular injury [22, 85]. They also explained the possible complex interplay between the immunologic deregulation of the cytokines and T cells and the underlying cardiovascular or related metabolic conditions. Virally-induced systemic inflammation may also promote coronary plaque rupture and have a pro-coagulant effect necessitating the intensification of medical therapy [101].

As previously explained, cardiovascular cells also express ACE2 at high levels, which has a role in regulating blood pressure and cardiac contractility [102]. COVID-19 infection, therefore, might trigger a drastic immune response which leads to the "cytokine storm" and subsequently the injure of cardiac tissue [103, 104]. Cytokine storm is a clear contributor to COVID-19-related myocardial injury, demonstrated by Wu and colleagues in a study that showed the association of the increasing levels of IL-6 and high hs-TnI levels [88], a cardiac-selective biomarker of myocardial infarction and injury [105], which is significantly increased in severe or deceased COVID-19 patients when compared to patients with milder symptoms [22, 29, 92, 106, 107].

Also, elevated NT-proBNP levels had to be noticed since patients with elevated cTnI were more likely to have elevated levels of NT-proBNP2 [92]. All these findings suggest the relationship between cardiac injury, cardiac dysfunction, and poor outcome, and monitoring cardiac troponin I during hospitalization may help predict the progression of the disease [107].

The mechanism of cardiac complications is not completely defined, however, the systemic and overexpressed inflammatory responses due to pneumonia, which is a highly pro-inflammatory disease [95], and elevated levels of cytokines (C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), procalcitonin, interleukin-1beta (IL-1β), Tumor necrosis factor-alpha (TNF-α), Interleukin-10 (IL-10) [22, 30, 108], the direct damage by the virus [96, 102], the instability of coronary plaque and hypoxia (The instability of coronary atherosclerotic plaques [109], the increased coagulation activation and platelet-aggregating activity [110], and hypoxemia due to abnormal ventilation/perfusion(V/Q) lead to decreased myocardial oxygen supply and myocardial ischemia [92] (Figure 12). According to Ma and colleagues [111] cytokines have an important role in infection control, but they can also lead to tissue

Figure 12. Possible mechanisms of cardiac complications in patients with COVID-19.



Source/Credit: Ma and colleagues [111].

damage and dysfunction. The level of cTnI was positively associated with plasma high-sensitivity CRP2, which suggested the possible role of an inflammatory storm in the development of cardiac injury. TNF-α had been detected in patients with heart failure [112] and the positive correlation between TNF-α expression and the severity of heart failure, left ventricular dilation/hypertrophy and dysfunction was confirmed [113-115]. Increased level of IL-1β was found in patients with acute myocarditis [96] and elevated concentration of IL-6 was detected in patients with acute myocardial infarction and heart failure [96]. The level of IL-6 predicted the adverse cardiovascular events following acute coronary syndrome and chronic heart failure [116, 117]. Serum IL-8 level elevated in patients with acute myocardial infarction is associated with mortality in patients with acute coronary syndrome [119]. IL-10 was increased in patients with acute myocarditis [120] and it predicted the poor outcome of Takotsubo cardiomyopathy [121]. So the virus triggers a series of immune responses and the production of cytokines storm may contribute to the systemic presentation and multiple organ dysfunctions.

Thromboembolic Manifestations

The lungs are unequivocally the most affected organ in COVID-19, followed by heart, liver, kidney, and brain. But even though COVID-19 is characterized by hyperfibrinolysis, as evidenced by elevated levels of D-dimer, systemic microthrombi in the circulatory system and hemorrhages that affect the organs have been recorded to happen as a result of noncoordinated responses between the coagulation and fibrinolysis systems [40].

Coagulopathy

Coagulopathy usually increases the D-dimer concentration in patients with COVID-19, a moderate decrease in platelets, and a prolongation of the prothrombin time [122]. Coagulopathy in COVID-19 cases seems to be a combination of disseminated intravascular dissemination (DIC) and localized pulmonary thrombotic microangiopathy, which in severe patients can have a considerable impact on organ dysfunctions. Proinflammatory cytokinesis, such as tumor necrosis factor-α (TNF-α) and interleukins (IL), including IL-1 and IL-6, [122], IL-6, are also commonly found in severe Covid cases, and can induce tissue factor expression on mononuclear cells, which in turn activates coagulation and thrombin generation.TNF-α and IL-1 are the principal mediators stimulating the suppression of endogenous anticoagulant pathways. According to Levi and colleagues, as well as other previously mentioned authors, the patients most severely affected by COVID-19 can present a cytokine storm profile characterized by high concentrations of proinflammatory cytokines and chemokines [123, 124]. COVID-19 infections are also known to cause the activation of the fibrinolytic system. Researches in urokinase-type plasminogen activator knock-out mice showed a urokinase-driven pathway stimulating fibrinolysis as a critical factor in lethality. Additionally, patients infected with human severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) had plasma concentrations of tissue-type plasminogen activator (t-PA) 6-times higher than patients with no infection (appendix).

Inflammation-induced endothelial cell injury could result in a large release of plasminogen activators, which could justify the high concentrations of D-dimer and fibrin degradation products in patients with severe COVID-19 [122]. Thrombotic microangiopathy is typically caused by pathologically enhanced platelet-vessel wall interaction due to ultra-large von Willebrand factor multimers. The coagulation abnormalities seen in COVID-19 propose a hypercoagulable state and are compatible with an enhanced risk of venous thromboembolism/ thromboinflammation or COVID-19-associated coagulopathy (CAC) [78, 125-129]. Elevated levels of D-dimer (D-dimer is a degradation product of cross-linked fibrin indicating increased

thrombin generation and fibrin dissolution by plasmin) are one of the major contributors to clot formation in severe COVID-19 infection [128], and can lead to pulmonary embolism and acute stroke (even in patients younger than 50 years of age without risk factors), as well as the formation of microthrombi and limb ischemia [124, 125, 130-132].

Clinical Features

VTE — Venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), is very common in ICU patients.

Arterial events — There are also reports of arterial thrombosis, including in the central nervous system (CNS) (Figure 13).

CNS – acute ischemic stroke associated with COVID-19 over a two-week period, with symptoms suggesting large-vessel occlusion [133].

Limbs –limb ischemia [134].

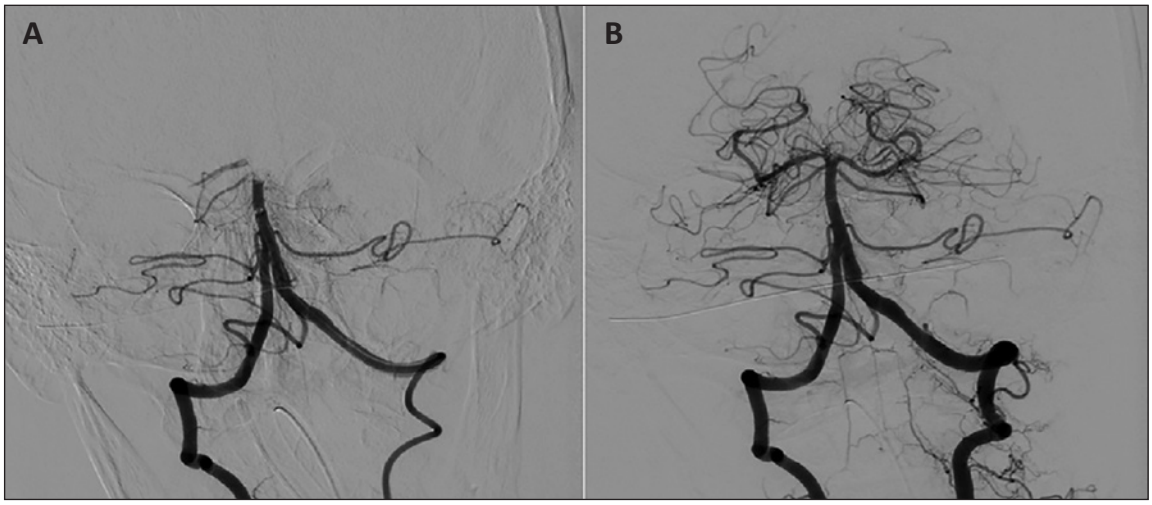
Microvascular thrombosis —microvascular thrombosis in the lungs [129, 135].

Bleeding — Bleeding is less common than clotting in patients with COVID-19, but it may occur, especially in the setting of anticoagulation.

The laboratory findings for coagulation abnormalities in COVID-19 are [136]:

- Prothrombin time (PT) and aPTT normal or slightly prolonged;
- Platelet counts normal or increased (mean, 348,000/microL);
- Fibrinogen increased (mean, 680 mg/dL; range 234 to 1344);
- D-dimer increased (mean, 4877 ng/mL; range, 1197 to 16,954);
- Factor VIII activity increased (mean, 297 units/dL);
- VWF antigen greatly increased (mean, 529; range 210 to 863), consistent with endothelial injury or perturbation;
- Minor changes in natural anticoagulants: small decreases in antithrombin and free protein S; a small increase in protein C;
- Reaction time (R) shortened, consistent with increased early thrombin burst, in 50 percent of patients;
- Clot formation time (K) shortened, consistent with increased fibrin generation, in 83 percent;

Figure 13. Catheter-directed cerebral angiography.



A Pre-thrombectomy angiogram demonstrates an occluded distal basilar artery (arrow). B, Postthrombectomy angiogram demonstrates successful restoration of the posterior circulation.
Source/Credit: Lushina and colleagues [78].

- Maximum amplitude (MA) increased, consistent with greater clot strength, in 83 percent;
- Clot lysis at 30 minutes (LY30) reduced, consistent with reduced fibrinolysis, in 100 percent;
- Circulating prothrombotic microparticles;
- Neutrophil extracellular traps (NETs).

Hematology Manifestations

Gulati and colleagues [68], reported in their study the common hematology manifestations as follow:

a. Lymphopenia is a frequent finding [48, 137].
b. Neutrophilia may help to predict intensive care unit (ICU) admissions.
c. Hemoglobin seems to be mostly unaffected by COVID-19 infection.
d. DIC is a rare complication [48].
e. Mild thrombocytopenia is present in one-third of patients [48].
f. Higher levels of D-dimer for patients admitted in ICU [138].
g. Thromboembolic events in severe patients with higher PT and d-dimer levels, which indicate the disseminated intravascular coagulation (DIC) or a highly inflammatory state [139].
h. Increased levels of circulatory cytokines, ferritin, C-reactive protein, and procalcitonin also seem to correlate with the severity of the disease [15, 140].

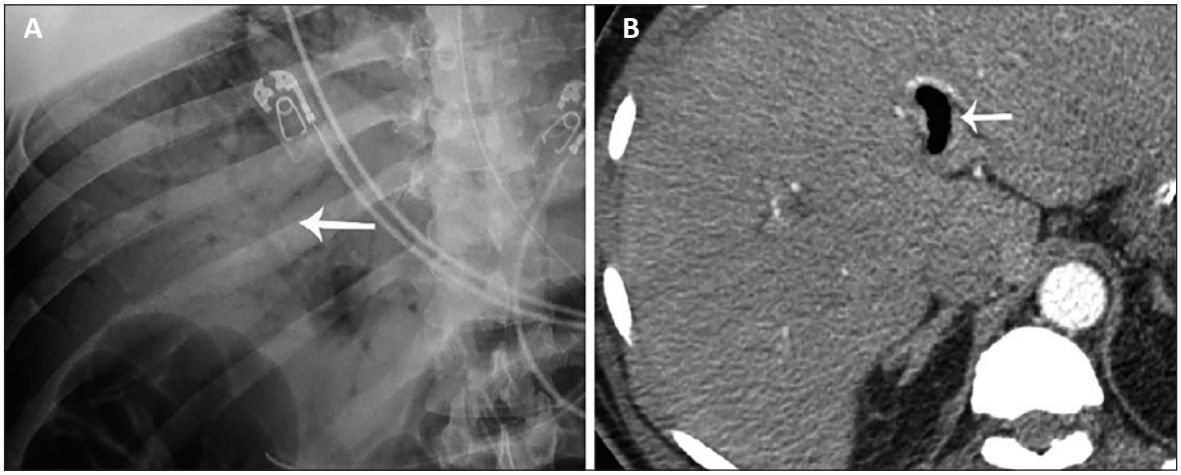
Gastrointestinal Manifestations

The symptoms of SARS-CoV-2 infection could vary, and in addition to affecting respiratory epithelial cells and alveolar cells, there is evidence that the virus could affect the digestive system [31]. In the intestines, ACE2 plays an important role in maintaining amino acid balance and regulating the expression of antimicrobial peptides and the equilibrium of the intestinal flora. The evidence shows the viral nucleic acid detected in stool specimens of patients with COVID-19, which explains the occurrence of diarrhea in coronavirus infection. Wong and colleagues [141] showed that SARS-CoV-2 encodes and expresses the spike (S) glycoproteins which bind to ACE2. So, the expression of viral nucleocapsid protein in the gastric, duodenal, and rectal epithelium is visualized in COVID-19 [142]. It might explain diarrhea in infected-COVID-19 patients. The SARS-CoV-2 binds the cell-surface receptor ACE2, which regulates the intestinal inflammatory response, and enters into the cell. They also showed that ACE2 expression is high in epithelial cells in proximal and distal intestines, and because the intestinal epithelium is in direct contact with exogenous pathogens, the cells there could be the first affected by the virus after the consumption of SARS-CoV-2–infected wild animals. That is why diarrhea can be an important sign of infection and clinical manifestation [31, 143].

Studies pointed to the increased recognition of gastrointestinal symptoms in COVID-19 patients (> 50%) [144], and sometimes this is the only symptom of the patients [29, 144]. Loss of appetite and diarrhea are the usually reported symptom, with vomiting and abdominal pain being less frequent [22, 29, 48, 144]. The gastrointestinal symptoms may delay seeking medical care [8x] because patients do not correlate GI with COVID-19. The virus is detectable in stool in more than 50% of COVID-19 patients [22], and the feces remains positive for as long as four weeks [145]. It is not clear if the fecal-oral route is a significant manner of transmission.

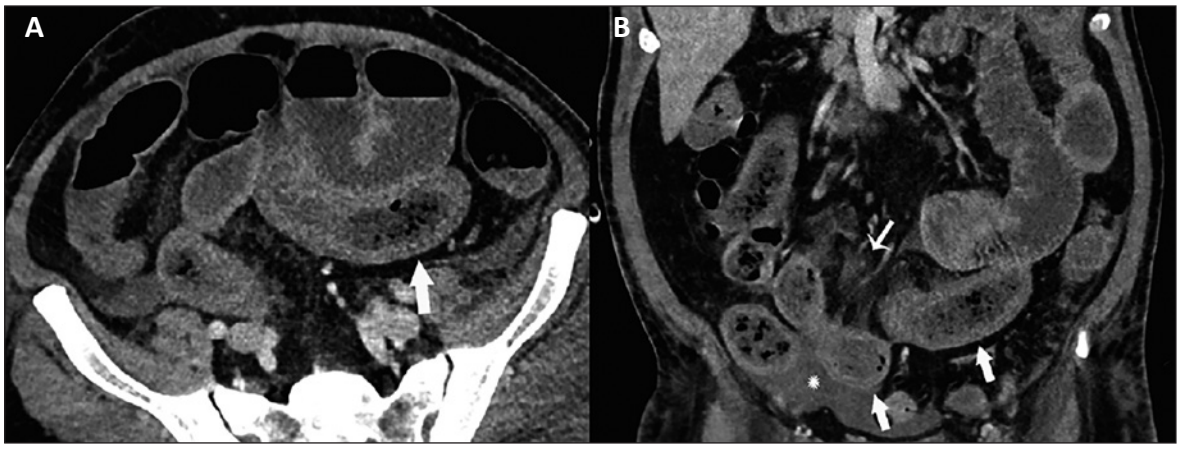
Bhayana and colleagues [146] reported in a study with 412 patients, of which 34% had gastrointestinal symptoms, similar to recent reports [49, 147]. CT was the most commonly performed exam for abdominal pain or sepsis, and for elevated liver enzymes, the ultrasound. Such were the findings: bowel wall thickening, pneumatosis, and portal venous gas (Figures 14 and 15). Pneumatosis and portal venous gas were frequently present in patients with mesenteric ischemia [148]. All the findings suggest that SARS-CoV-2 has a direct inflammatory effect on vascular endothelium [149, 150], and systemic coagulopathy is common in critically ill patients

Figure 14. Abdominal radiograph (A) in a 52-year-old man demonstrates portal venous gas (thin arrow in A), suggestive of bowel infarction. Post-operative CT (B) also demonstrates portal venous gas (thin arrow in B).



Source/Credit: Bhayana and colleagues [146].

Figure 15. Axial (A) and coronal (B) CT of the abdomen and pelvis with IV contrast in a 57-year-old man with a high clinical suspicion for bowel ischemia. There was generalized small bowel distension and segmental thickening (arrows), with adjacent mesenteric congestion (thin arrow in B), and a small volume of ascites (* in B).



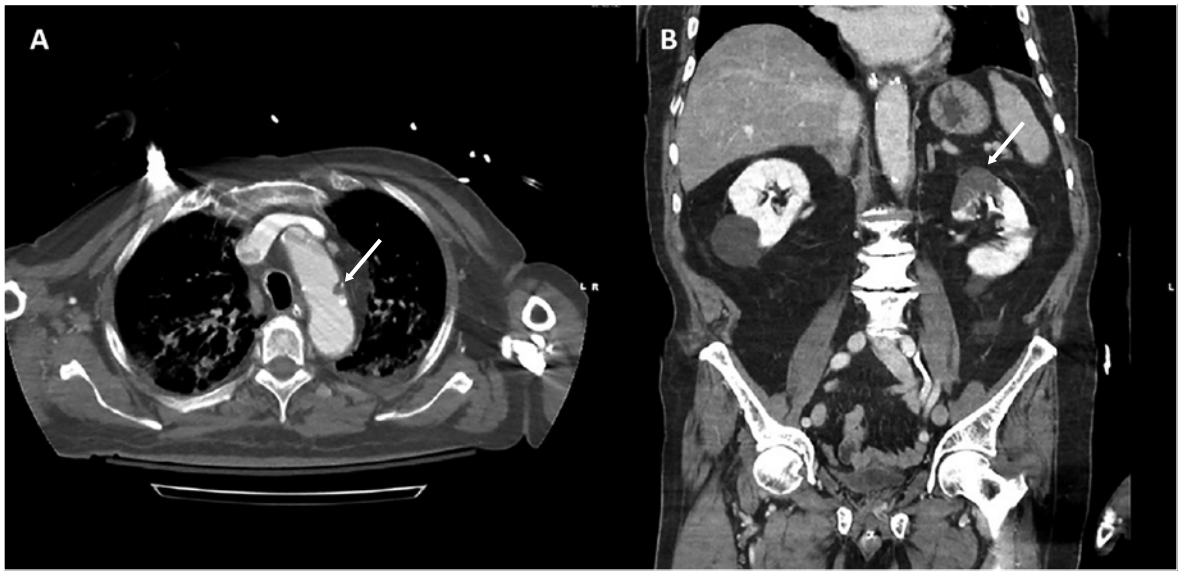
Source/Credit: Bhayana and colleagues [146].

with COVID-19 [41]. This can be supported by descriptions of microvascular injury and vascular imaging abnormalities [146].

Renal Manifestations

According to Gulati and colleagues [68], acute renal dysfunction in COVID-19 in early stages is not uncommon [151, 152]. The incidence of acute kidney injury is around 15% with a high mortality rate of 60%-90% [30, 44]. Other clinical manifestations have been reported such as albuminuria or proteinuria on admission (44%-63%), hematuria (27%), elevated urea (13%-27%), and creatinine (14%-19%), and low eGFR (13%) [152]. Images evidence present active renal edema and inflammation, and renal infarct (Figure 16) [152]. Renal involvement is associated with a worse prognosis [30, 44, 153]. The SARS-COV-2 has been detected in renal tissue and the urine

Figure 16. Renal infarct.



A, Axial contrast-enhanced CT of the chest demonstrates a filling defect in the aortic arch (arrow) consistent with thrombus. B, Coronal contrast-enhanced CT of the abdomen and pelvis demonstrates a wedge-shaped low-attenuation region in the superior pole of the left kidney (arrow) consistent with renal infarct.
Source/Credit: Lushina and colleagues [78].

[154], and the presence of ACE2 receptors in the Leydig cells and seminiferous tubules, it could lead to a testicular injury [155].

Li and colleagues [156] reported in a retrospective analysis that the proportion of patients with acute renal insufficiency (ARI) was low, although the mortality rate was high (>90 %). Also, Fan and colleagues in another study reported that besides severe respiratory dysfunction, 3% - 10% of the patients showed renal insufficiency, and 7 % had acute kidney injury, and had ACE2 highly expressed in renal tubular cells, mesenchymal cells, and testicular and vas deferens cells [155]. The viral nucleic acid was isolated from the urine samples of SARS-CoV-2 patients, which indicate that the kidney's injury is high or occurs after the SARS-CoV-2 infection. Both viral infection and antiviral therapy have potential nephrotoxicity and may cause kidney injury, according to Zhang and colleagues [31].

Hepatic Manifestations

Zhang and colleagues also analyzed the effects of the virus Cov (SARS-COV-1, MERS, and SARS-COV-2) on the liver and concluded that this VIRUS can alter liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 14%-53% of the cases, and in patients with SARS-CoV-2 and it is present hepatic pathologies disorders (chronic viral hepatitis, nonalcoholic fatty liver disease, alcoholic hepatitis, immune-mediated liver disease) in 2%-11% of the cases [31].

Gulati and colleagues [68] analyzed studies available for hepatic manifestation in COVID-19, and calculated 51% of patients with COVID-19 as having an abnormal liver function on admission (elevated liver enzymes, bilirubin, and LDH levels) [157], and the liver dysfunction may be related to damage to the cholangiocytes lining the biliary epithelium, due to the higher expression of ACE2 receptors [15]. They also reported that patients with fatty liver disease have been seen to have about a 6-fold higher chance of severe disease in the presence of coexisting obesity [48].

Pathogenetic Hypothesis

The hepatic involvement seems to have a multifactorial origin [158]:

a. Direct damage: caused by the binding of the virus to ACE2 receptors expressed in lung, kidney, and gastrointestinal tract, and endothelial cells of the liver [12, 159, 160];
b. Intestinal translocation: In the patients that have diarrhea (2%-10%), SARS-CoV-2 RNA has been detected in blood and stool samples, which demonstrates how its RNA could "translocate" from the intestinal lumen [154, 161-163].
c. Drug hepatotoxicity: Zhang and colleagues [161] observed that liver function tended to alter during and after the infection with COVID-19. They have a hypothesis that it could be a "residual effect" due to the drugs taken during the infection, as a side effect of the therapies used against the infection. This theory is also reinforced by Rismanbaf and colleagues [164]. Liu and colleagues [165] analyzed 32 patients and observed that liver damage was prominent in severe patients under medical therapy; and
d. Immune-mediated inflammation: the "cytokine storm", especially, in severe forms of COVID-19 may cause liver damage [123] due to increased levels of interleukin (IL)-2, IL-7, IL-6, interferon-γ, and tumor necrosis factor-α [166].

Wang and Chai [167] performed RNA sequencing and found specific ACE2 expression in bile duct cells, suggesting that it is important to monitor the liver function of SARS-CoV-2 patients, especially liver indicators involving bile duct function. In the case of liver dysfunction, targeted treatment and care should be given promptly [31,168]. According to Zhang and colleagues [31], ACE2 expression in the lungs reduces SARS-CoV-2 spike protein-induced lung injury via the renin-angiotensin system. Wang and colleagues presented RNA sequencing analysis in patients with inflammatory bowel disease (IBD) or colitis and showed that ACE2 expression in colon cells was positively correlated with the regulation of viral infection and congenital cellular immunity and was negatively correlated with viral transcription, protein translation, phagocytosis, and complement activation [15x]. So, ACE2- mediated SARS-CoV-2 infection may be a double-edged sword concerning susceptibility and immunity [31].

Neurologic Manifestations

The neurological symptoms of COVID-19 include dizziness, headache, nausea, vomiting, and hypoesthesia (hyposmia, hypogeusia, and hypopsia), which may indicate that the virus enters the CNS and causes injury in nuclei or neural circuits. This is confirmed by postmortem studies of COVID-19 patients with neurological symptoms [169, 170]. The development of hyposmia, hypogeusia, and hypopsia could be a sign of the presence of the virus in CNS via intranasal and oral routes [171].

Gulati and colleagues [68], summarized the neurologic manifestations of COVID-19:

a. Anosmia
b. Dysgeusia [172].
c. Acute cerebrovascular accidents, altered mental status, and myopathy occurred in approximately one-third of patients.
d. Confusion and agitation (most common neurologic symptoms)
e. Corticospinal tract signs: increased deep tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes [173].
f. Acute hemorrhagic necrotizing encephalopathy [174].
g. Guillain-Barré syndrome: lower-limb weakness and paresthesia as well as facial diplegia and ataxia [171].
h. Neurological involvement affected more patients with severe COVID-19, and patients with central neurologic symptoms also had severe lymphopenia, thrombocytopenia, and uremia [171].
i. The magnetic resonance imaging (MRI) currently presents leptomeningeal enhancement with bilateral frontotemporal hypoperfusion [173].

j. Electroencephalography showed mostly nonspecific changes with findings consistent with encephalopathy.
k. Cerebral spinal fluid (CSF) analysis may show oligoclonal bands or elevated IgG levels, however, the significance of these findings is uncertain.
l. Ocular manifestations of COVID-19 need attention. Studies with animals demonstrated that ACE2 and TMPRSS2 (Transmembrane Serine Protease 2) are also expressed in the conjunctiva [91]. The conjunctivitis is present in 31.6% of COVID-19 patients but is common in patients with severe disease or as an initial presentation of the disease [97].
m. SARS CoV-2 has been isolated from conjunctival swabs [91].

The pathology of severe viral infections is closely associated with the development of a systemic inflammatory response syndrome (SIRS) [175].

Viral Encephalitis

Encephalitis is inflammatory lesions in the brain parenchyma caused by pathogens, including neuronal damage and nerve tissue lesions [175], characterized by symptoms such as headache, fever, vomiting, convulsions, and consciousness disorders [176]. SARS-CoV- 2 can cause encephalitis as described in the Xiang and colleagues study [177]. Also, patients with severe COVID-19 infection often suffer from hypoxia and viremia [178], which has the potential to cause toxic encephalopathy, characterized by headache, dysphoria, mental disorder, and delirium, loss of consciousness, coma, and paralysis [179-181]. Moreover, patients with COVID-19 (40%) have headaches, disturbed consciousness, and other brain dysfunction manifestations [132].

Acute Cerebrovascular Disease

The infection by SARS-CoV-2 has been widely reported to lead to an acute cerebrovascular disease due to the cytokine storm syndromes, [123, 182]. Also, critically ill patients with severe SARS-CoV-2 infections often show elevated levels of D-dimer and severe platelet reduction, which may render these patients prone to acute cerebrovascular events [183].

Mechanisms of CoV Infections on the Nervous System Damage (Figures 17 and 18)

Direct Infection Injury

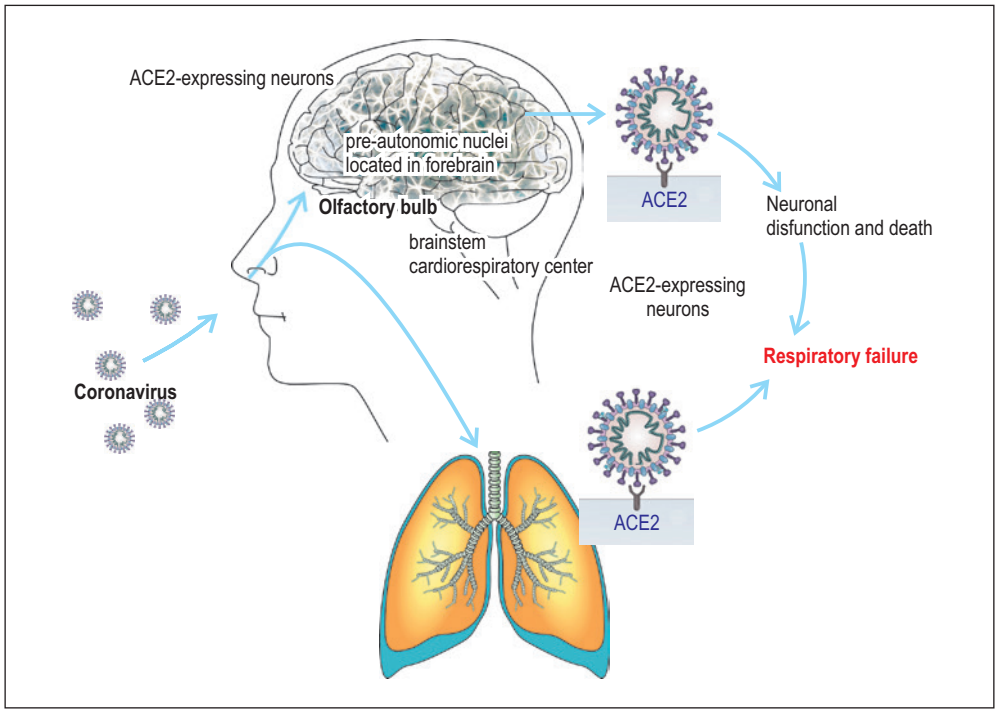
The genetic material of SARS-COV-2 has been detected in nervous system tissue samples (such as cerebrospinal fluid or brain), suggesting the virus invasion in the nervous system, which can cause nerve damage [184, 185].

Blood Circulation Pathway

Although there is rare evidence that SARS-CoV-2 invades the nervous system via the blood circulation pathway [185, 186], however, further studies are needed.

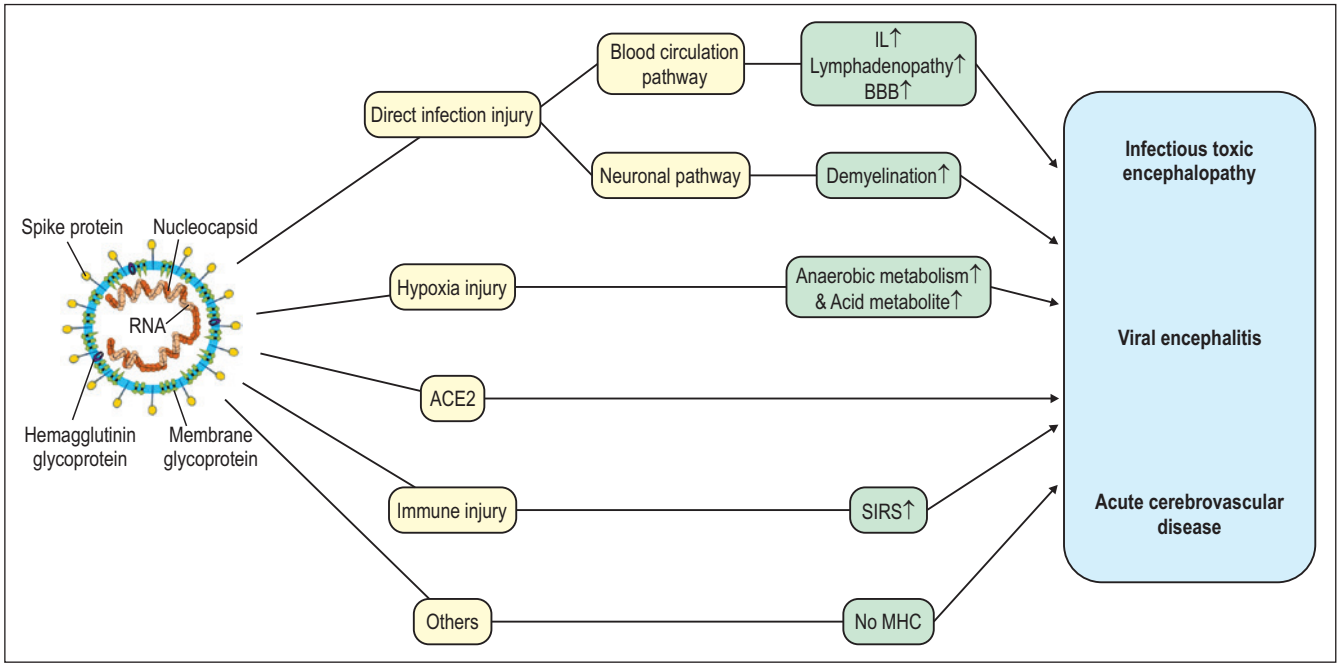
According to Netland and colleagues [187], for penetrating the nervous systems by the hematogenous pathway, the virus must infect the endothelial cells of the blood-brain-barrier (BBB), and then invades the CNS. The entrance of SARS-CoV-2 into human cells is propitiated by ACE2 [9]. Notwithstanding the neural pathway is by the olfactory nerve, there are many infected sites indirectly related to the olfactory bulb that indicate non-neuronal routes for viral infection, such as the hematogenous route. This pathway is following: SARS-CoV-2 encodes the surface glycoprotein spike that binds to ACE2 and mediates viral entry [188]; the spike protein is cleaved by proteases and releases a signal peptide to promote virus entry into host cells [189]. The virus infects the epithelial cells and also the resident, infiltrating, and circulating immune cells, which carry the virus to other systems, causing the extrapulmonary symptoms, including fever, myalgia, fatigue and kidney dysfunctions [151], acute myocardial injury [120], CNS and pulmonary symptoms [77, 132, 142].

Figure 17. The mechanisms of coronaviruses infections and neurological damage caused by coronaviruses.



Source/Credit: Adapted from Wu and colleagues [175].

Figure 18. Pathogenesis of nervous system injury caused by coronaviruses.



ACE2: angiotensin-converting enzyme 2; BBB: blood brain barrier; IL: interleukin; MHC: major histocompa-tibility complexes; SIRS: systemic inflammatory response syndrome.
Source/Credit: Adapted from Wu amd colleagues [175].

Digestive Tract Route

Single-cell RNA sequencing data show a positive correlation between the expression of ACE2 in colon cells with genes controlling virus infection, and innate and cellular immunity [171], but a negative correlation with virus transcription, protein translation, humoral immunity, phagocytosis, and complement activation [190]. Based on these conclusions, Li and colleagues [171] consider SARS-CoV-2 may bind with ACE2 in the gastrointestinal tract and destroy the barrier of gastrointestinal epithelial cells, rise the production of inflammatory cytokines, reduce gastrointestinal absorptive ability, and enhance secretion through the gastrointestinal mucosa. The disorder caused by SARS-CoV-2 infection generates the production of many inflammatory agents, which lead to a cytokine storm. The spike protein of SARS-CoV- 2 is different from SARS-CoV-1. In SARS-CoV-2, the spike has a site that is activated by furin, a host cell enzyme that is located in many human tissues, including intestine and lung. The virus gets into the intestines and attaches to specific host-cell receptors in order to enter and infect host cells to produce more virions. When there are sufficient virions expanded, they are released into the enclosing environment where they can infect more resident host cells.

Enteroviruses (poliovirus, coxsackievirus, and echovirus) reproduce in the intestine and can penetrate intestinal epithelial cells [191]. The inflammatory reply to host cell death can reduce the expression of the intestinal barrier proteins ZO-1, occludin, or claudin 3, and disrupts the intestinal barrier [192, 193]. Besides, the inflammatory response can also begin intestinal microbiota disturbance, which aggregates the injury of the intestinal mucosa barrier structure. So, the virus can simply access the blood circulation through the broken intestinal barrier, while viruses in lymphoid tissue can affect distant organs through the lymphatic pathway. The virus can also penetrate local peripheral nerves and after replication can proceed along their axons to the CNS.

However, there is no immediate evidence to prove that SARS-CoV-2 can enter the CNS retrogradely via the intestinal branch of the vagus nerve. The broken gastrointestinal environment may affect the integrity of the BBB through immune, neural, and humoral pathways, thus aiding the passage of the peripheral virus into the CNS [171].

Neuronal Pathway

The neuronal pathway is an important channel for neurotropic viruses to access the CNS. Viruses can move by infecting sensory or motor nerve endings, reaching retrograde or anterograde neuronal transport through the motor proteins, dynein, and kinesins [184, 187]. An example of a neuronal pathway is the olfactory neuron transport. The anatomical organization of olfactory nerves and the olfactory bulb in the nasal cavity and forebrain is a channel between the nasal epithelium and the CNS. It has been proposed that the neural pathway happens after the droplets carrying SARS-CoV-2 land in the nasal cavity and adheres to the nasal mucosa, pharynx, cavum larynges, or trachea. If the virus adheres to the nasal mucosa, it may directly infect olfactory sensory neurons in the olfactory epithelium and then could be moved into the CNS through the olfactory nerve [187, 195]. As a result, the SARS-COV-2 can enter the brain through the olfactory region in the early stages of infection [195, 196] and then cause injuries such as inflammation and demyelinating reaction in the brainin the brain.

About hypogeusia, three cranial nerves are responsible for the sense of the taste: the facial nerve (VII), the glossopharyngeal nerve (IX), and the vagus nerve (X). So, the hypogeusia caused by SARS-COV-2 could result from damage to any of these three nerves (VIII, IX, and X). For hypopsia, there is limited data that supporting direct infection of the optic nerve by SARS-CoV-2, according to research carried out by Shunbun University in Japan [195, 196]. SARS-CoV- 2 may cause a neurogenic refractory dyspnea [197, 198]. Also, viruses in neurons “escape from immune

surveillance" and can, therefore, replicate when the immunity of the host is impaired or weakened, which is similar to the varicella-zoster virus [199, 200].

Smell and Taste Dysfunction in Patients with COVID-19

The American Academy of Otolaryngology-Head and Neck Surgery and the British Association of Otorhinolaryngology recommend that these symptoms be added to the list of primary screening symptoms for COVID-19. The conclusion of the lost or reduced ability to smell or taste, resulting from a neurotropic or neurovirulent viral infection targeting the olfactory system, remains incomplete but could be an explanation of neuronal pathway [201].

Hypoxia Injury

The proliferation of SARS-COV-2 in lung cells causes diffuse alveolar and interstitial inflammatory exudation, edema, and the formation of transparent membranes and these events compromise the gas exchange disorders causing hypoxia in the CNS, increasing anaerobic metabolism in the mitochondria of brain cells [202]. The accumulation of acid can cause cerebral vasodilation, swelling of brain cells, interstitial edema, obstruction of cerebral blood flow, and even headache due to ischemia and congestion [202]. If the hypoxia continues, it could lead to intracranial hypertension, and brain function deterioration, drowsiness, bulbar conjunctival edema, and even coma [202]. Hypoxia may also induce the occurrence of acute cerebrovascular disease such as acute ischemic stroke.

Immune Injury

According to Wu [175], nervous system damage caused by viral infection may be mediated by the immune system [203]. An over immunity response by the body could be abnormally initiated in severe pneumonia caused by CoV infection [123, 204]. The CoV infections and its ability to infect macrophages, microglia, and astrocytes in the CNS is important. A neurotropic virus can activate glial cells and induce a pro-inflammatory state [197], such as interleukin (IL)-6, which has an important member of the cytokine storm that is positively correlated with the severity of COVID-2019 symptoms [17]. Additionally, researches have proved that primary glial cells cultured in vitro secrete many inflammatory factors such as IL-6, IL-12, IL-15, and TNF-α after being infected with CoV [205]. Moreover, activation of immune cells in the brain causes chronic inflammation and brain injury.

Still according to Wu, Angiotensin-converting enzyme 2 Angiotensin-converting enzyme 2 (ACE2) is a cardio-cerebral vascular protection factor existing in a variety of organs, including the nervous system and skeletal muscles, playing a major role in regulating blood pressure and anti-atherosclerosis mechanisms [206]. SARS-COV-2 may cause abnormally raised blood pressure and enhance the risk of a cerebral hemorrhage. Besides, as the spike protein of SARS-CoV-2 binds with ACE2 expressed in the capillary endothelium, the virus may also break the blood-brain barrier and enter the CNS by affecting the vascular system [198].

SARS-CoV-2 was detected in patient's cerebrospinal fluid and brain tissue from autopsy. However, the route of the virus to central nervous system needs further studies. In this Zhang and colleagues' study, they suggested that the virus can migrate after infecting sensory or motor nerve endings. Under the action of motor proteins, dynein and kinesins, the viruses can achieve neuronal transport in a way of retrograde or anterograde. Based on the unique anatomical structure of olfactory nerves and olfactory bulb, it becomes a channel between the nasal epithelium and the CNS [31]. So, in the early stages of SARS-CoV-2 infection of the respiratory system, olfactory tract becomes an important channel for virus transmission to brain. Several studies also presented that coronavirus can invade the CNS from the periphery through neural pathways [175]. In addition, studies have shown that

some coronaviruses can invade brainstem via a synapse-connected route from the lungs and airways. Zhang and colleagues suggest that the infection of CNS by SARS-COV-2 might be one reason for the acute respiratory failure due to the specific neurological symptoms such as headache, epilepsy, and confusion, is similar to symptoms of intracranial infection, and in some cases, intracranial infection–related symptoms have been the initial symptoms, coming before the symptoms of pulmonary infection, such as cough, fever, and dyspnea [175].

As SARS-CoV-2 binds to ACE2, some patients with underlying hypertension may have unusually high blood pressure and increased risk of intracranial hemorrhage after SARS-CoV-2 infection [175] due to angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may increase the expression of ACE2. It is therefore important to adjust antihypertensive drug dosages in SARS-CoV-2 patients with underlying hypertension.

Musculous Manifestions

Patients with myopathy have a higher inflammatory response and a higher association with hepatic and renal disease. Gulati and colleagues [68] listed some musculous manifestations such as:

a. Myalgia is a common presenting symptom of COVID-19 infection.
b. 36% of patients develop muscle pain during the illness [130].
c. High creatinine kinase (CK) levels present in 14%-33% of patients [22, 41, 106, 131].
d. Rhabdomyolosis has been reported in patients with COVID-19 with MYO levels >12,000 ug/L and CK levels >11,000 U/L [132].

Skin Manifestations

Cutaneous manifestations of COVID-19 increased since they might be useful in the early diagnosis triage of COVID-19-positive patients and their risk stratification (Table 2). Wollina and colleagues [207] reported chilblain-like acral eruptions, purpuric and erythema multiforme-like lesions associated to children and young adult patients who are either asymptomatic or develop a mild disease. In contrast, acro-ischemic lesion and maculopapular rash are often seen among adult patients who run a more severe course. Urticaria with pyrexia has diagnostic significance since this

Table 2. Cutaneous sign of COVID-19 disease.

Vascular complications	Acro-ischemia
	Livedo-like
	Necrosis
	Chilblain-like eruptions
Maculopapular eruption	Morbiliform
	Plaques
	Pityriasis rosea-like eruptions
Urticarial rash	
Vesicular eruption	Vesicle
	Bullous eruption
	Chickenpox-like rash
Petechiae/ Purpuric eruptions	
Erythema multiforme-like rash	
Palmar erythema	
Perifollicular eruption	
Pruritus	
Mucosal lesions	Enanthema
Androgenetic alopecia	

combination is an early symptom of an otherwise not confirmed SARS-CoV-2 infection. Careful registration of possible cutaneous manifestations of the COVID-19 pandemic is warranted.

Gulati and colleagues [68] noted in their study that common cutaneous manifestations present as follow:

a. Erythematous rash, widespread urticaria, and chickenpox like vesicles [59].
b. Pruritis is uncommon.
c. Several recent case series have reported a viral exanthum similar to chilblains disease in patients with COVID-19 [62].

Other Manifestations

Guillain-Barré syndrome has also been reported, with onset 5 to 10 days after initial symptoms [208].

A multisystem inflammatory syndrome possibly associated with COVID-19, with clinical features similar to those of toxic shock syndrome and Kawasaki disease, has also been described in children [47].

Figure 19 summarizes the main injuries caused by SARS-COV-2 in the human body.

Comorbidities, Symptoms, and Risk

The spectrum of symptomatic infection ranges from mild to critical, however, most infections are not severe [22 29, 30, 47, 72, 74, 77, 210, 211]. The critical cases can occur in healthy individuals of any age, but it predominantly occurred in patients with advanced age or underlying medical comorbidities such as [44, 212-214]:

- Immunocompromising conditions [215]
- Male over 65 [216];
- Smoking patients [216];
- Hypertension [217];
- Diabetes mellitus [217];
- Chronic obstruction pulmonary disease (COPD) [217];
- Cardiovascular disease [217];
- Cerebrovascular disease [217];
- Chronic lung disease [217];
- Cancer (in particular hematologic malignancies, lung cancer, and metastatic disease) (in particular hematologic malignancies, lung cancer, and metastatic disease) [218];
- Chronic kidney disease [217];
- Obesity [217];
- Liver disease [219], although specific data regarding risks associated with these conditions are limited [40, 220].

Laboratory Findings

Diagnostic Tests - RT-PCR

The diagnosis of COVID-19 is performed by detection of SARS-CoV-2 RNA by nucleic acid amplification tests (NAATs), primarily reverse transcription-polymerase chain reaction (RT-PCR) [47]. Numerous RT-PCR assays are used around the world to detect SARS-CoV-2; and different assays amplify and detect different regions of the SARS-CoV-2 genome. Common gene targets include nucleocapsid (N), envelope (E), spike (S), and RNA-dependent RNA polymerase (RdRp), as well as regions in the first open reading frame [221].

Reverse transcription PCR (RT-PCR) is positive in 59%-78.2% of cases, and is the gold standard method to detect COVID-19 [222, 223]. This method, however, is time-consuming and expensive. Often times it can present a false-negative result due to the low specificity of the RT-PCR when compared to the sensibility of the test, especially if the sample is collected from the upper respiratory tract. In this case, if the clinic is consistent with COVID-19, it is important to admit the patient as a positive case [224, 225].

Serological Methods (IgM and IgG)

Serologic tests detect antibodies to SARS-CoV-2 in the blood, and those that have been adequately validated can help identify patients who have had COVID-19 [47]. Serologic tests are

less likely to be reactive in the first several days to weeks of infection, and thus may have less utility for diagnosis in the acute setting [226-230]. This assay requires 15 min to generate results and can be used for rapid screening in clinics however has a very low specificity [230].

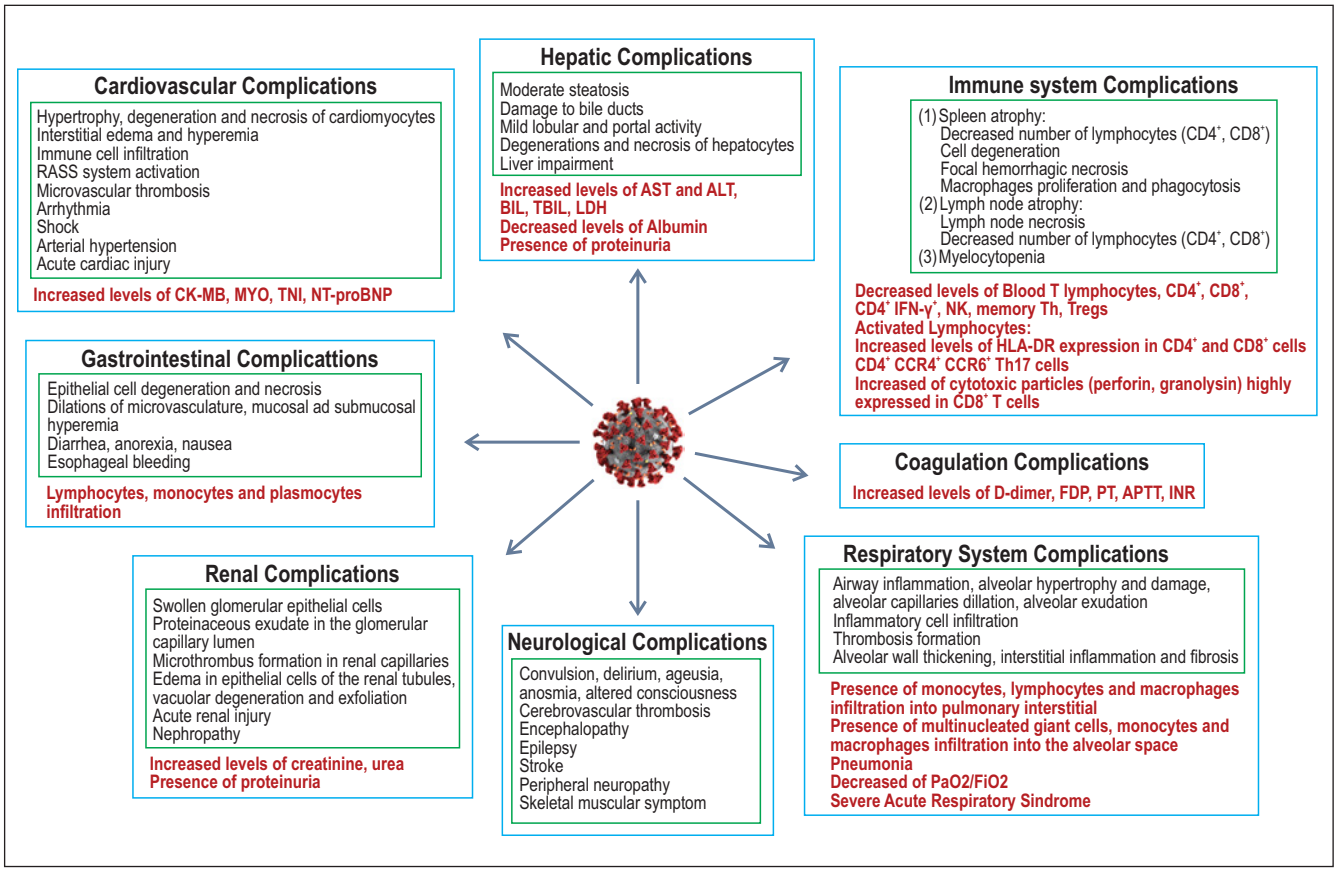
Routine Tests

The laboratory exams such as WBC, AST, Cr, hs-cTnI, PCT, LDH, and D-dimer could show the progress of the disease, but it is not a specific biomarker for COVID-19 [216].

Commonly, the exams of COVID-19 infection presents: [22, 29, 30, 47, 48, 50, 72, 210, 211, 231]:

- Lymphopenia (83.2%);
- Increased inflammatory markers (eg, ferritin, C-reactive protein, and erythrocyte sedimentation rate);
- Elevated aminotransaminase levels (usually hospitalized patients);
- Changes in albumin;
- Elevated lactate dehydrogenase;
- Elevetade neutrophils (severity cases);
- Elevated D-dimer (>1 mcg/mL) (severity disease);

Figure 19. SARS-CoV-2 infection-induced impairment of multiple organ function.



Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; CNS, central nervous system; FDP, fibrinogen degradation products; HLA-DR, human leukocyte antigen DR; INR, international normalized ratio; LDH, lactate dehydrogenase; MYO, myoglobin; NK, natural killer cell; NT-proBNP, N terminal pro-B-type natriuretic peptide; PaO2/FiO2, oxygenation index; PNS, peripheral nervous system; PT, prothrombin time; RAAS, renin-angiotensin-aldosterone system; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; TBIL, total bilirubin; Th, helper T cell; TNI, troponin I.
Source/Credit: Adapted from Zhang and colleagues [209].

- Higher levels of D-dimer, CRP, and procalcitonin are associated with severity disease;
- Prothrombin time and D-dimer levels on admission were higher in the intensive care unit (ICU) patients than in non- ICU patients;
- Plasma concentrations of IL-2, IL-7, IL-10, and TNF-α were higher in ICU patients;
- Higher white blood cell and neutrophil counts (severe patients);
- Eosinopenia (severe patients);
- Elevated in procalcitonin levels (ICU patients);
- Elevated prothrombin time (PT);
- Elevated troponin;
- Elevated creatine phosphokinase (CPK);
- Progressive decline in the lymphocyte count and rise in the D-dimer over time were observed in nonsurvivors compared with more stable levels in survivors [29];
- Elevated proinflammatory cytokines; these laboratory abnormalities have been associated with critical and fatal illnesses [22].
- Notably, decreases in CD8+ T cells and B cells in adults have been associated with severe COVID-19 and poor response to therapy [232];
- CD8+ T cell and B cell recovery has been associated with moderate disease [233];
- Decreasing in regulatory T cells also have been associated with a hyperinflammatory response in adults [234];
- The high hs-cTnI act is one of the specific biomarkers of myocardial injury [105].
- Elevation of creatine kinase (CK), creatine kinase MB isoenzyme (CK-MB), and lactate dehydrogenase (LDH) could indicate a cardiovascular injury.

Imaging Findings

In early or mild cases, Chest radiographs might be regular. Current abnormal radiograph findings were consolidations and ground-glass opacities, with bilateral, peripheral, and lower lung zone distributions [235].

Chest CTs in COVID-19 patients have a tendency of showing ground-glass opacification with or without consolidative abnormalities, peripheral distribution, and involve the lower lobes. Other findings, although less frequent, are pleural thickening, pleural effusion, and lymphadenopathy. Abnormalities have been identified in Chest CTs even before patients develop symptoms and viral RNA has been detected in upper respiratory specimens [47].

Conclusion

Since the outbreak, the development of supportive drugs, vaccines, and targeted antiviral drugs is underway. At the beginning of the outbreak, studies revealed that the SARS-COV-2 affected the lungs with of manifestation of respiratory symptoms. Because the virus' mechanisms take over the cells, binding with the ACE2 receptor, other symptoms were noticed by physicians and health care workers. As a result, news studies have emerged and confirmed new symptoms and probable route of the virus. These studies have demonstrated that the virus could affect and damage the respiratory system, circulatory system, digestive system, urogenital system, and central nervous system. This complicates potential clinical manifestations and makes it harder to treat such cases. We might be just beginning to understand this new virus and the effect in patients it has on patients during and after infections. A deeper understanding of this virus from biomedical research and epidemiological observation will provide important clues to etiologic research, diagnosis, differential diagnosis, treatment, and prognostic assessment regarding COVID-19.

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The Radiological Images and the Diagnostic of COVID-19

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The gold-standard method to identify the presence of COVID-19 is the RT-PCR. However, the imaging diagnostic has been requested when there is suspicion of disease's presence and/or the inflammatory phase of the disease begins. Ths artices described the most common manifestations and patterns of lung abnormality on computed X-Ray (CXR), computer tomography (CT) and Ultrasound of the chest in COVID-19. Notwithstanding the RT-PCR is the gold-standard diagnostic method for COVID-19, the CT has been shown an essential tool to identify pneumonia and the complications of COVID-19 in a patient. This review article aimed to summarize the radiological findings of COVID-19 researches for the following three principal areas: (1) radiological performance in the detection of COVID-19; (2) radiological role in the diagnosis of COVID-19; and (3) radiological function in the monitoring of COVID-19. We searched the articles in the main database (PubMed/Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Exerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), in the high-impact international scientific Journals (Scimago Journal and Country Rank - SJR - and Journal Citation Reports - JCR), such as The Lancet, Science, Nature, The New England Journal of Medicine, Physiological Reviews, Journal of the American Medical Association, Plos One, Journal of Clinical Investigation, and in the data from Center for Disease Control (CDC), National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO). We prior selected meta-analysis, systematic reviews, article reviews and original articles in this order. We reviewed 121 articles and used 57 for this paper from March to May 2020, using the terms coronavirus, SARS-CoV-2, novel coronavirus, Wuhan coronavirus, severe acute respiratory syndrome, 2019-nCoV, 2019 novel coronavirus, n-CoV-2, covid, n-Sars-2, COVID-19, corona virus, coronaviruses, diagnostic, radiology, imaging, computed tomography, chest, CT, X-Ray, with the tools MeSH (Medical Subject Headings), AND, OR, and characters [,",; /., to ensure the best review topics. We concluded that the imaging method to detect the features of COVID-19 plays an important role in the diagnosis and follow up of the patient with COVID-19 pneumonia. Despite CT has a better sensitivity when compared to CRX and ultrasound, the portable CRX and portable ultrasound could be a new tool with minimal risk of contamination and with good sensitivity.

Keywords: COVID-19. SARS-COV-2. Diagnostic. CT. X-Ray. Lungs. Groud-Glass Opacity.

Introduction

Since the spread of COVID-19 last December, chest imaging has been of great importance for the diagnosis and management of patients with COVID-19 infection [1], since the infection can lead to severe acute respiratory syndrome (SARS) and death in a short amount of time. Some image methods are currently being used to detect the abnormalities of pneumonia caused by COVID-19, such as computed tomography (CT) or high resolution computed tomography (HRCT), computed X-Ray (CRX) and ultrasound (US), to help in the diagnosis and in the management of the patient [2]. Moreover, it also important to know how it manifests in the lungs, the location of the lesions, the progression of the disease and the abnormalities that can be present in the lungs [3]. A deep understanding of image methods is essential in order to determine which are good options to use, and how to look for the abnormalities found in infected patients with COVID-19. That is one of the key components in the diagnosis of patients with suspected infection so as to secure the best possible outcome for them [4,5].

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The objective of this review is to present the main image methods for COVID-19 detection and the pulmonary findings observed in the disease through the images of the reviewed studies.

Main Findings in Chest Images of COVID-19

The typical radiological characteristics in COVID-19 pneumonia involve bilateral, multifocal, multilobar ground-glass opacity (GGO) with patchy consolidations, a peripheral/subpleural, or posterior distribution (or both), principally in the lower lobes (Figure 1) [1-25]. GGO occurs in multiple interstitial and alveolar processes maintaining the bronchial and vascular margins [26], while consolidation is a region of opacification, which obscures the bronchial and vascular margins [27]. GGO or GGO with consolidation was the most frequent radiological features in COVID-19 pneumonia. Other typical radiological characteristics incorporate interlobular septal thickening, crazy-paving pattern, air bronchogram/traction bronchiectasis, halo sign/reverse halo sign, peripheral/subpleural involvement, and pleural thickening [1, 2, 5, 7-9, 12, 14, 17, 19-21, 24, 26]. In the literature, tuncommon findings are: pulmonary emphysema, pneumothorax, pleural effusion, pericardial effusion, lymphadenopathy, cavitation, and are uncommon findings [1, 5, 8].

Li and colleagues [28], summarized the findings in chest computer tomography (CT) as following:

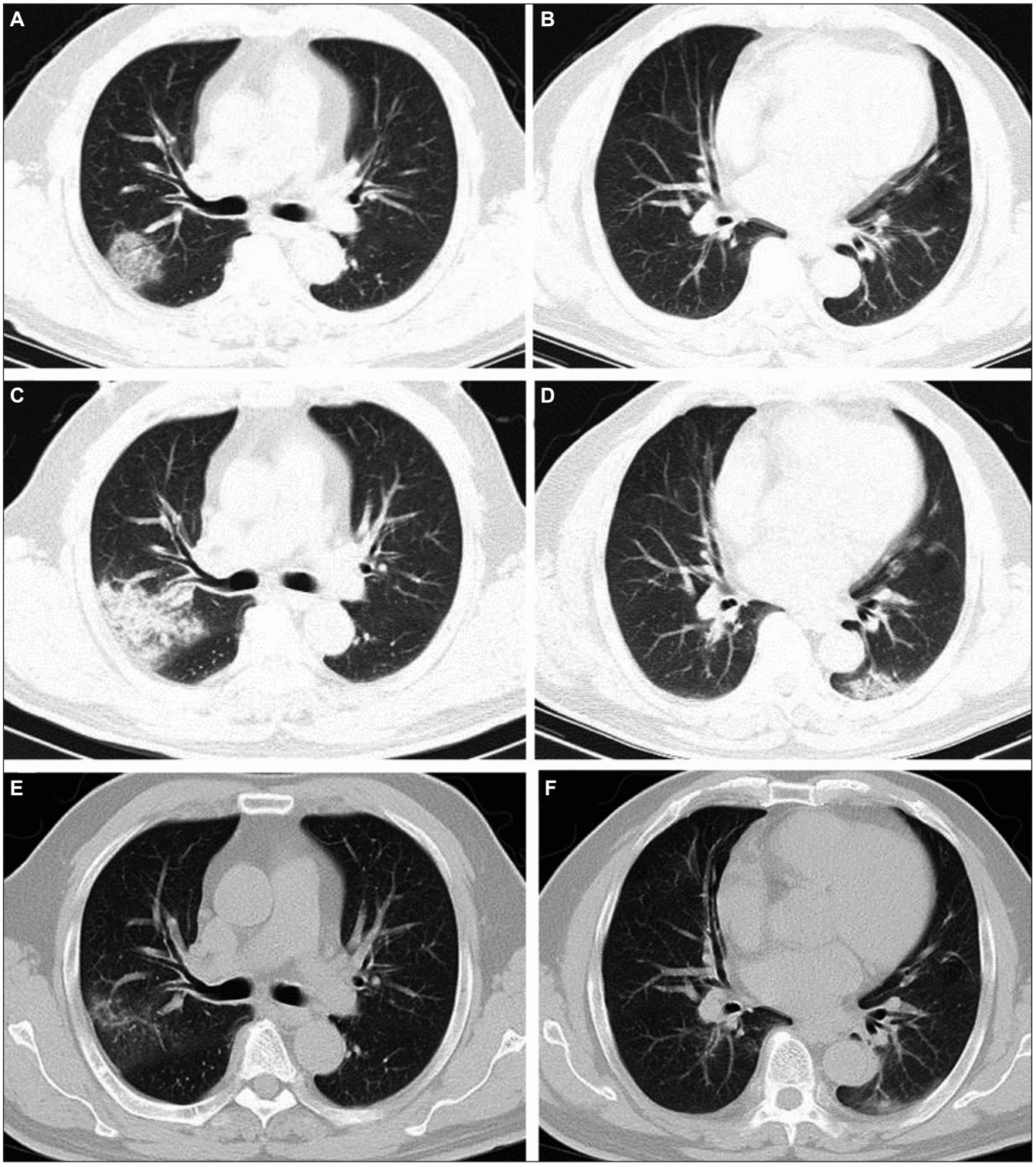
1. Ground-glass opacities (GGO) (100% of the cases);
2. GGO pattern;
3. GGO location;
4. Consolidation;
5. Multilobe involvement;
6. Bilateral distribution;
7. Location of consolidation or GGO;
8. Pulmonary nodules surrounded by GGO;
9. Interlobular septal thickening;
10. Air bronchogram;
11. Halo sign;
12. Presence of cavitation;
13. Bronchial wall thickening;
14. Bronchiectasis;
15. Perilesional vessel diameter;
16. Lymphadenopathy (defined as lymph node with short-axis > 10mm);
17. Pleural effusion; and
18. Pericardial effusion.

Based on a several images studies, the American College of Radiology, Society of Thoracic Radiology, and Radiological Society of North America Radiology categorized the main findings of COVID-19 chest CT images as typical, indeterminate and atypical features, and negative for pneumonia) [29,30]. The typical features are peripheral bilateral GGOs, rounded GGOs, and reverse halo sign of organizing pneumonia. Indeterminate features diffuse, perihilar, or unilateral GGOs with nonrounded, nonperipheral distribution. Atypical features include isolated consolidations, treein-bud opacities, cavitation, and smooth interlobular septal thickening with pleural effusion (Table 1). Regarding the phase of the disease, Pan and colleagues [4] divided the progression of chest abnormalities/disease in 4 phases: early phase, progressive phase, severe phase, and dissipative phase (Table 2). Additionally, there are specific placements for abnormalities on the chest that can common occur in COVID-19 patients (Table 3) [31]. Zhang (2020) [32] observed 95.40% of the lesions caused by COVID-19 are in the middle and lower part of the lung, while 4.60% is in the upper part of the lung. The same author introduced a CT imaging score system to quantify the pathological changes in the lungs of patients with COVID-19 (Table 4).

Computer Tomography (CT) High Resolution

In addition to computed X-Rays, computed tomography (CT) is also able to show the main finding (GGO) in COVID-19 pneumonia. High-resolution CT (HR-CT) especially plays an important role in the early diagnosis of COVID-19 disease infection [28, 37, 38] due to a higher

Figure 1. CT scans in a patient with COVID-19 pneumonia.



A, B, Scan obtained on illness days 2 showed ground-glass opacity with intralobular septal thickening (crazy-paving pattern) that affected posterior segment of right upper lobe. C, D, Scan obtained on illness days 8 showed increased consolidative opacities. Note that patchy ground-glass opacity newly developed in left lower lobe. E, F, Scan obtained on illness days 13 showed absorption of abnormalities, with pure ground-glass opacity left in the posterior segment of right upper lobe and posterior basal segment of left lower lobe.
Source/Credit: Wu and Wang [1].

Table 1. Chest CT findings related to COVID-19 (expert consensus by Society of Thoracic Radiology, and Radiological Society of North America Radiology [30].

Classification	Rationale	CT findings	Suggested reported language
Typical	Commonly reported imaging features of greater for specificity for COVID-19 pneumonia	Peripheral, bilateral (multilobar) GGO*, consolidation, or visible intralobular lines	Commonly reported imaging features of COVID-19 pneumonia are present
Indeterminate	Nonspecific imaging features of COVID-19 pneumonia	Multifocal, perihilar, unilateral GGO or nonrounded or nonperipheral	Imaging features can be seen with COVID-19 pneumonia
Atypical	Uncommonly or not reported features of COVID-19 pneumonia	Isolated lobar or segmental consolidation, discrete small nodules, cavitation or interlobular septal thickening, pleural effusion	Imaging features are atypical or uncommonly reported for COVID-19 pneumonia, an alternative diagnosis should be considered
Negative	No features of pneumonia	No CT features to suggest pneumonia	No CT findings indicate pneumonia

*GGO: Ground-glass opacities.
Source/Credit: Akçay and colleagues [30].

Table 2. Phase and findings in Chest CT-COVID-19 patients.

Phase	CT Finding	Figure
Early (0-4 days)	Single or multiple lesions distributed along with the subpleural areas or bronchi [33, 34]. Presence of nodular or patchy GGOs [30], with the blood vessels seen thickening and passing through the GGO [12, 35].	Figure 2
Progressive (5-8 days)	The number of lesions increased significantly. Original lesions are partially absorpted and new lesions with GGOs and the consolidations coexisted [7, 36]. Presence of distortion of local lung structures, bronchodilation, and focal atelectasis.	Figure 3
Severe (9-13 days)	Bilateral lesions with diffuse infiltration of all segments of the lungs, and manifesting as "white lung." Air bronchograms suggested a large amount of cellular exudation in the alveolar cavity. Subsegmental atelectasis or reduction of lung volume was sometimes noted, and a small amount of pleural fluid could be seen bilaterally. Currently appears around 14 days after the onset of the disease, but in some cases developed rapidly [37, 38].	Figure 4
Dissipate (≥14 days after the onset of the initial symptom)	Gradual absorption of the lesions, leaving a few cord-like high-density shadows, indicative of fibrosis. This phase happens commonly after 14 days [28].	Figure 5

Source/Credit: Li and colleagues (adapted) [28].

sensitivity (98%) [39] compared with other images methods.

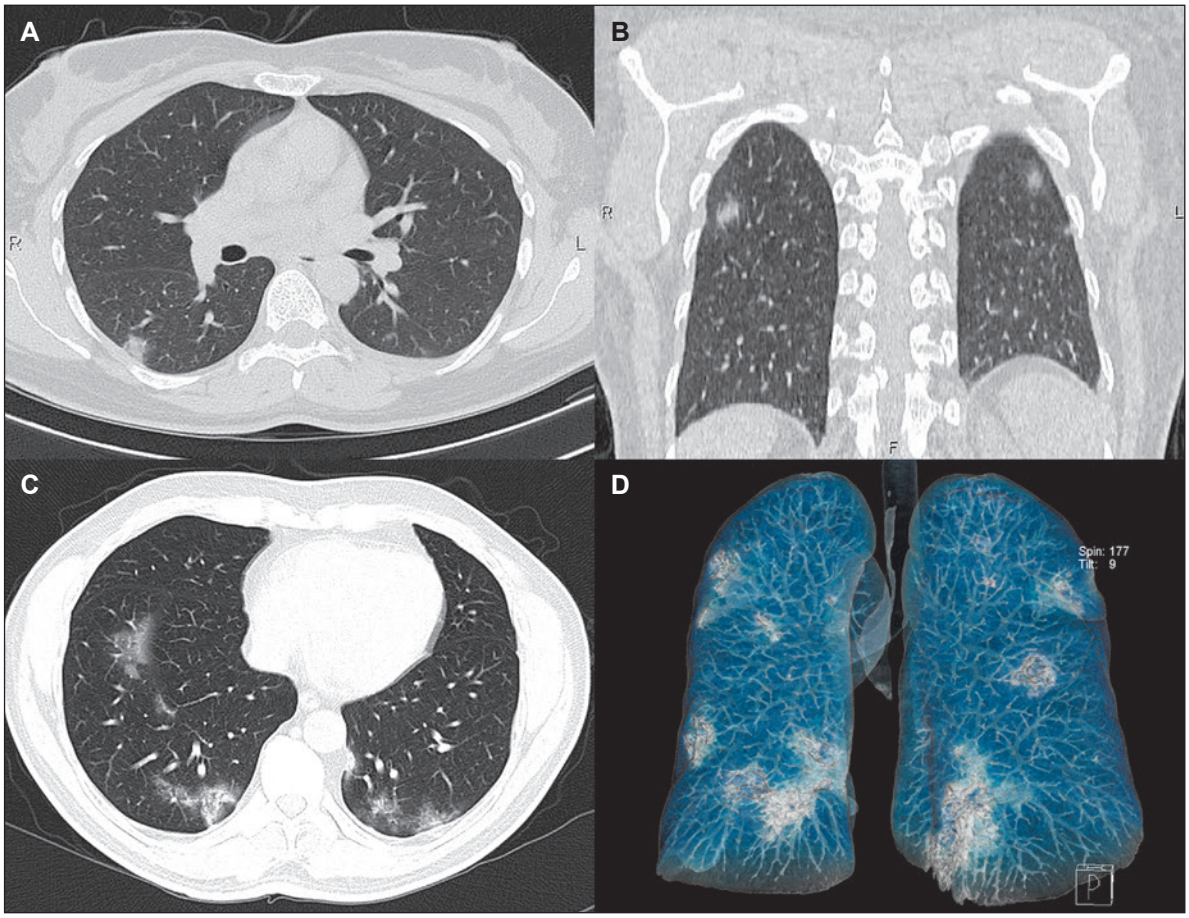
The HR-CT allows for an evaluation of lesions in the lungs, and, combined with clinical manifestations and laboratory diagnosis, such as RT-PCR, can confirm COVID-19 diagnosis and instruct the management of the patient in the early stage of the disease. In cases when the laboratory test is negative but the physician is suspicious of COVID-19 infection, the performance of an HR-CT is important because abnormalities in the lungs are present in the early stage of the disease sometimes [40, 41]. However, it is important to be aware of the radiation of CT. If the patient

Table 3. Main location findings in the chest of COVID-19 patient [31].

Phase	AbnL	GGO	Co	CPP	PE	Ca	L
Early	Lower lobes unilaterally or bilaterally	Yes	Sometimes	No	No	No	No
Progressive	Bilateral multilobe distribution	Yes	Sometimes	Yes	Sometimes	No	No
Severe*	Bilateral multilobe distribution	Yes	Yes	Yes	Yes	Sometimes	Sometimes
Dissipate/ Absorption	Bilateral	Sometimes (as a demonstration of the absorption)	Sometimes	No	No	No	No

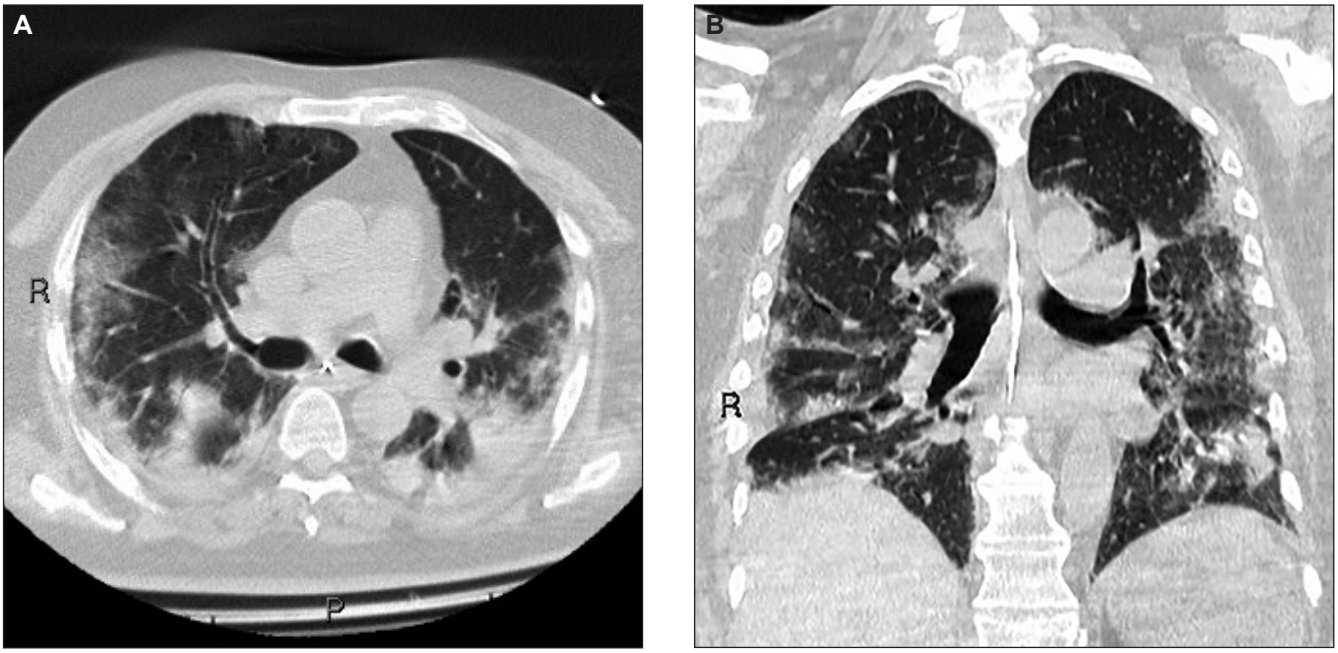
AbnL: abnormalities location; GGO: groud-glass opacity; Co: consolidation; CPP: crazy-paving pattern; PE: pleural effusion; Ca: cavitation; L: lymphadenopathy. *Presence of residual parenchymal bands.

Figure 2. Patient with coronavirus disease (COVID-19) pneumonia in the early stage.



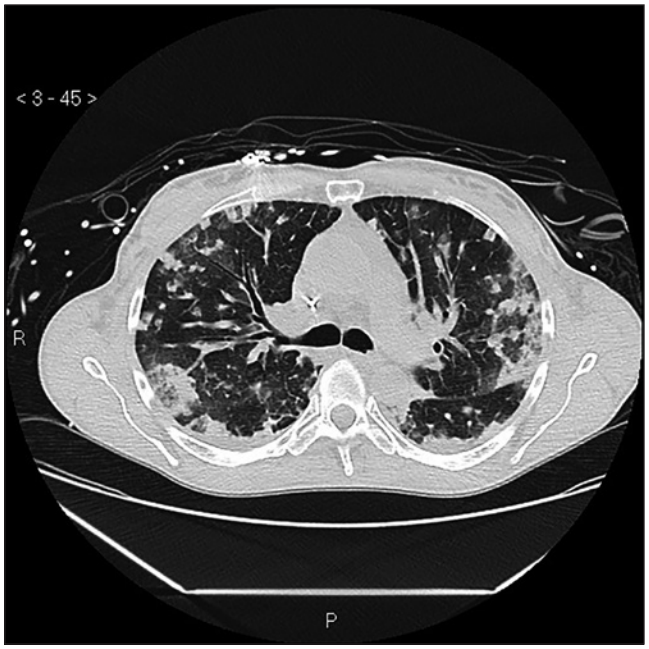
A. Axual reconstruction. B. Coronal reconstruction. Several small patchy ground glass opacities and consolidations are scattered at both lungs more prominent at subpleural regions (CT images). C. Axial reconstruction. B. Coronal reconstruction. CT demonstrates multilobar and bilateral ground-glass opacities with rounded morphology, mostly in the periphery of both lungs. Source/Credit: A-B: Radiopaedia - Case courtesy of Dr Mohammad Taghi Niknejad, Radiopaedia.org. From the case rID: 75829. C-D: Case courtesy of Dr Antonio Rodrigues de Aguiar Neto, Radiopaedia.org. From the case rID: 77010

Figure 3. Patient with COVID-19 pneumonia (progressive phase).



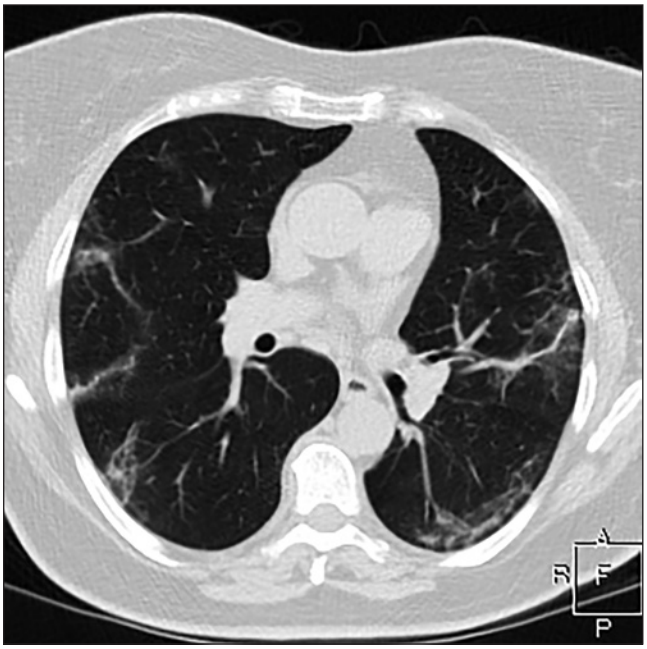
A. Axial reconstruction. Multifocal regions of consolidation and ground-glass opacifications. These have a peripheral and basal predominance. No pleural or pericardial effusion. B. Coronal reconstruction.
Source/Credit: Li and colleagues [28].

Figure 4. Patient with coronavirus disease (COVID-19) pneumonia (severe phase).



Axial reconstruction. Diffuse bilateral coalescent opacities and groundglas opacities, mediastinal lymphadenomatosis.
Source/Credit: Case courtesy of Dr Sajoscha Sorrentino, Radiopaedia.org. From the case rID: 16290.

Figure 5. Patient with coronavirus disease (COVID-19) pneumonia in dissipative phase.



Transforming ground-glass opacity to subpleural fibrous stripes.
Source/Credit: Case courtesy of Dr Vitalii Rogalskyi, Radiopaedia.org. From the case rID: 76319.

Table 4. CT imaging score system to quantify the severity of pneumonia in the COVID-19 patients.

Number	Performance	Score
1	Unbilateral patchy shadow or ground-glass opacity	5
2	Bilateral patchy shadow or ground-glass opacity	7
3	Diffuse changes for (1) or (2)	2
4	Unbilateral solid shadow, striped shadow	2
5	Bilateral solid shadow, striped shadow	4
6	Unbilateral pleural effusion	2
7	Bilateral pleural effusion	4
8	Increased or enlarged mediastinal lymph nodes	1

Source/Credit: Zhang Z. (2020) [32].

does not show clinical symptoms or has an RT-PCR negative but the physician suspects it is a COVID-19 case, an initial X-Ray could be satisfactory [32, 40, 41].

Imaging Phases of COVID-19

In the early phase of COVID-19, when the patient exhibits moderate clinical symptoms or no clinical symptom (Table 3), the chest CT could show nodular-shape-lesions (single or multiple) or patchy GGOs, indicating the spread of the disease with the invasion of the bronchioles and alveolar epithelium of the cortical lung tissues [5]. It could be followed by the thickening of interlobular and intralobular septa, and the appearance of halo signs around the nodules. The pathological basis may be congestion of alveolar septal capillaries, exudation of fluid into the alveoli, and interstitial edema of the interlobular septum [5, 4, 41]

In the progressive phase, the number of lesions increased, the GGOs and the consolidations coexisted due to the amount of cellular exudate accumulated in the alveolar cavity, which cause interstitial vasodilation and exudation, and fusion of alveoli. The "crazy paving appearance" is presented reflecting interstitial lesions [28].

In the severe phase, the lesions are bilateral with diffuse infiltration of all lungs' segments, with the apparency of "white lung." A large amount of cellular exudation suggests air bronchograms in the alveolar cavity. Also, subsegmental atelectasis or decrease of lung volume, as well as a small quantity of pleural fluid could be seen bilaterally. The clinical symptoms were compatible with the severe nature of clinical manifestations. Nevertheless, unlike SARS, the appearance of both pneumomediastinum and subcutaneous gas was uncommon [5, 37, 38]. The dissipative phase is similar early phase or presents gradual absorption of the lesions, leaving a few cord-like high-density shadows [5].

The dissipative phase is like the early phase or shows gradual absorption of the lesions, leaving a few cord-like high-density shadows [5].

The Role of Chest X-Rays in COVID-19

Bhat and colleagues [31] demonstrated that the value of computed chest X-Ray (CRX) is relatively low (30%-60%) in COVID-19 pneumonia [42], indicating that a normal chest X-Ray cannot exclude the presence of abnormalities in lung patients of COVID-19, especially in the early stages (Figure 6) [31, 42, 43]. For this reason, non-contrast chest CT is considered best for early diagnosis of viral disease in suspected patients with normal chest X-Ray [11, 44]. However, CXRs remain the initial imaging tool of choice but have a limited role in the diagnosis of the disease [31].

About the main findings, Wong and colleagues [45] found that consolidation was the most common finding on CXRs in COVID-19 patients with a peripheral, lower zone predominance.

Despite CT's higher sensitivity when compared to other imaging methods, the issue lies in the transportation of the patient to the CT room. It is especially difficult for Intensive Care Unit (ICU) patients, for children and pregnant women due to the ionizing radiation, not to mention the risk of contamination to healthcare workers during the transportation and management of the infected patient. So, since infection control

issues associated with patient transportation to CT rooms, the difficulties concerning CT room decontamination, and the absence of CT available in parts of the world, the portable chest radiography (CXR) is a possible method for identification and follow up of lung abnormalities [31].

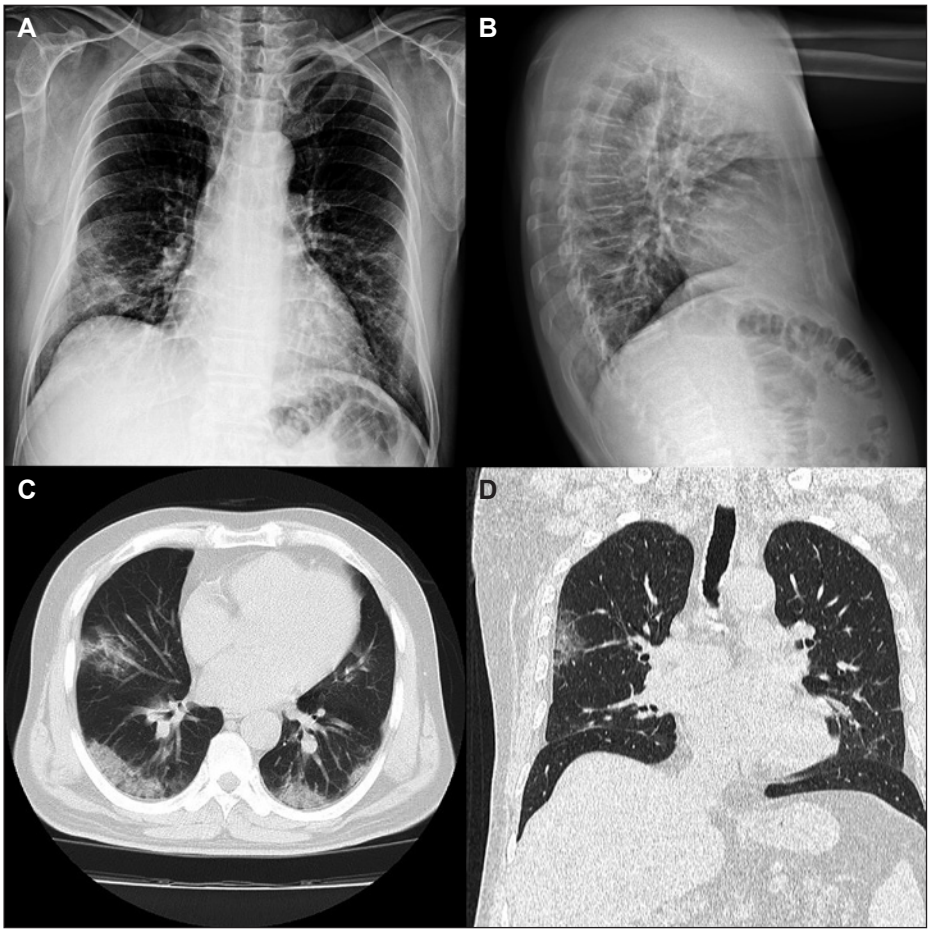
Portable CXR

According to Jacobi and colleagues [46], patterns of COVID-19 lung disease can be identified by conventional chest radiography, besides the gold-standard image methods is the chest CT. The grade of the disease's severity is based on the percentage of lung involvement. So portable CXR will widespread availability and reduced infection control issues that currently limit CT utilization [46, 47].

Also, groud-glass densities observed on CT may often have a correlation that is difficult to detect on portable CXR (Figure 7). Often, reticular opacities following regions of ground-glass attenuation are more easily detectable on standard CXR (Figure 8). The obscure pulmonary opacities on CXR can sometimes be diffuse, causing the identification of the features a challenge for some clinicians (Figure 9) [46, 47].

Neri and colleagues [48] in a study about CT and artificial intelligence presented the

Figure 6. Patient with COVID-19 pneumonia (CRX and CT images).



A. CXR Frontal. B. Lateral. Patchy peripheral opacities are seen at the lung fields mid to lower zones. C. CT Axial. D. Coronal. Bilateral multi-lobar peripheral ground-glass and consolidative opacities are seen in both lungs, mostly mid to lower zones. Non-specific mediastinal lymph nodes. Source/ Credit: Case courtesy of Dr Bahman Rasuli, <a href="https://radiopaedia.org/">Radiopaedia.org</ a>. From the case rID: 75330.

recommendations of the Italian Association of Ultrasonography in Medicine and Biology, and the Italian Association of Scientific Medical Societies and the Italian Image Society of Medical Radiology (SIRM, in Italian) about the use of radiological methods for COVID-19 as follow:

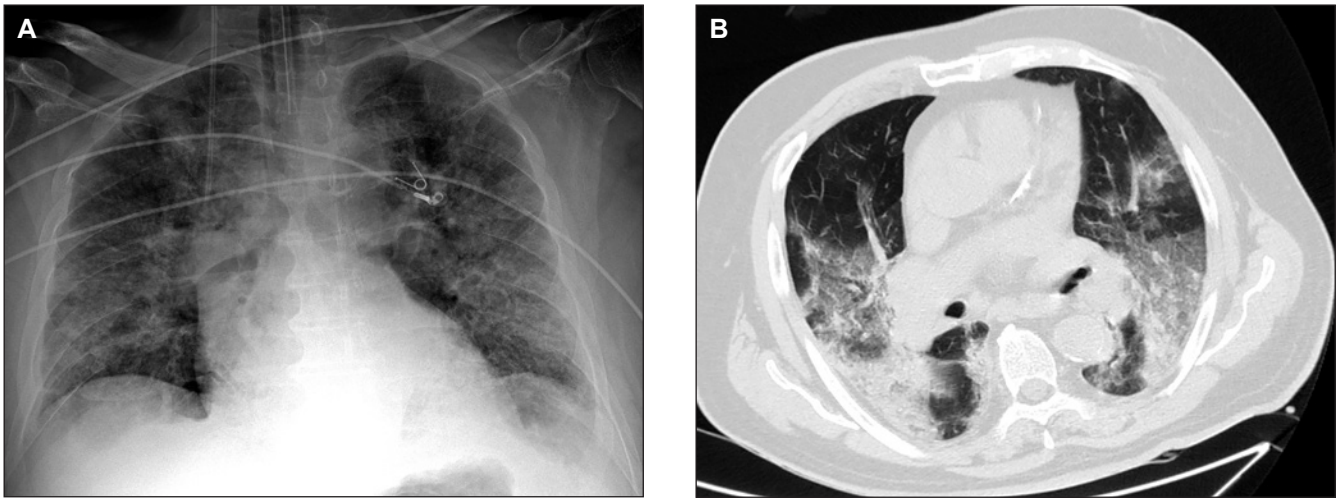
1. Chest X-Ray could be a first-line imaging tool that permits the first assessment of patients, especially in the emergency room, and in regions that CT does not exist. Also, it could differ the diagnosis toward other possible causes of pulmonary parenchymal involvement than COVID-19 infection [49].
2. CT as an additional tool that shows typical features of COVID pneumonia, which the most common is bilateral ground-glass opacities involving mainly the lower lobes [50].
3. Ultrasound of the lungs as a monitoring tool also to evaluate the effectiveness of prone-supination maneuvers [51].
4. SIRM recommends as high priority, to ensure appropriate sanitation procedures on the scanning equipment after detecting any suspected or positive COVID-19 patients, since the risk of spreading the infection into the CT room.

The Point-of-Care Ultrasound (POCUS) Use

In addition to the CRX and CT, the most effective imaging methods used for COVID-19 also include the portable ultrasound (US), which has been tested and showed good results, especially for mitigating the risk of care takers contagion from Intensive Care Unit (ICU) patients. Ultrasound imaging can be an alternative method for chest imaging to follow up on COVID-19 pneumonia [52], as demonstrated in the case report from Italy [53]. Ultrasound can also distinguish between cardiogenic and noncardiogenic pulmonary edema [54] and can be deployed rapidly to exclude alternative causes of hypoxia in intensive care [55]. For consolidation, ultrasound has an accuracy of 97% (sensitivity 93%; specificity 93%), compared with 75% for chest radiography (sensitivity 68%; specificity 95%) and 36% for auscultation (sensitivity 8%; specificity 100%) [54].

There are advantages in the use of US: the test is cheap, involves no ionizing radiation, and the results are available instantly. Compared to a portable X-Ray or CT machine, ultrasound

Figure 7. Portable CXR x CT in a patient with COVID-19 pneumonia.



A. Portable CRX shows the presence of extensive bilateral ground-glass opacities as demonstrated on the recent CT. Also right IJV catheter and ETT noted. B. There are bilateral large areas of ground-glass opacities with crazy paving and, more evident at both bases, areas of consolidation. Enlarged mediastinal lymph nodes.

Source/Credit: Case courtesy of Dr Fabio Macori, Radiopaedia.org. From the case rID: 74867.

machines are faster to decontaminate due to their small size. POCUS has a high sensitivity for the pulmonary manifestations of COVID-19, such as ARDS and consolidation. Furthermore, POCUS can be used to monitor treatment response. US is professional dependent, which means more training to have US as a method of choice especially in ICU [56, 57]. Indeed, the main choice of POCUS is about the risk of contamination of healthcare staff, patients, and visitors when the patient is transferred to CT or CRX room.

Conclusion

Imaging methods to recognize indications of COVID-19 performs a critical role in the diagnosis and follow up of the patient with COVID-19 pneumonia. Despite CT having a better sensitivity when compared to CRX and ultrasound, the method brings a high risk of contamination to health professionals, visitors, room service, and staff of the hospital, as well as more ionization radiation for the patient. So, portable CRX and portable ultrasound could be a new tool with minimal risk of contamination and with good sensitivity. Currently, adding to the recommendation of CRX in the early stage, the CT is still preferable in the protocols to managing and diagnosing the patient with COVID-19 pneumonia.

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COVID-19 Photos' Gallery

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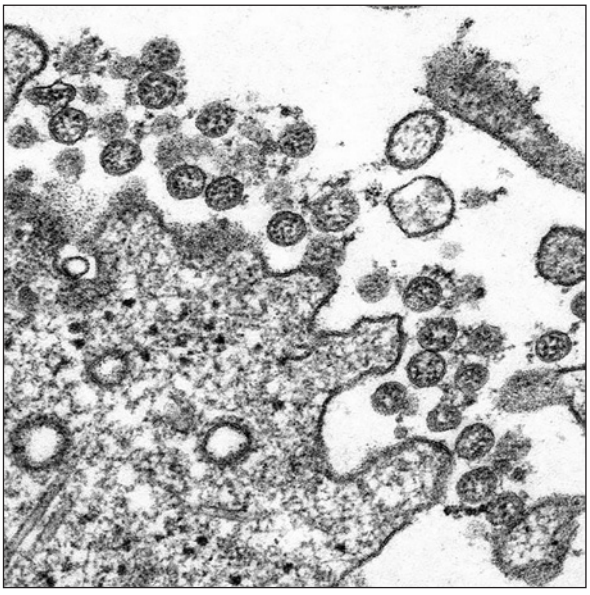
The images available below is part of our research from March to June 2020, to present a gallery photo of the SARS-CoV-2, the virus that causes COVID-19. We aimed to show with high-resolution images of the viral structures, proteins, how the virus attacks the cells, and the face of the virus that is causing the highest and severe pandemic of the last 100 years, which led a huge impact in public health systems, the way of life of the society and the negative perspective for the global economy for next future. Our Group searched yhe images in the main database (PubMed/Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Exerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), in the high-impact international scientific Journals (Scimago Journal and Country Rank - SJR - and Journal Citation Reports - JCR), such as The Lancet, Science, Nature, The New England Journal of Medicine, Physiological Reviews, Journal of the American Medical Association, Plos One, Journal of Clinical Investigation, and in data from Center for Disease Control (CDC), National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO), using the terms Coronavirus, SARS-CoV-2, severe acute respiratory syndrome coronavirus, 2019-nCoV, 2019 novel coronavirus, Wuhan coronavirus, n-CoV-2, n-Covid-2, Covid, n-Sars-2, COVID-19, coronavirus, corona virus, coronaviruses, images and photos, from March to June 2020. We used the tools MeSH (Medical Subject Headings), AND, OR, and characters [,",; /. However, the Center for Disease Control (Figures 1, 2, and 3) and the gallery photo of the National Institute of Allergy and Infectious Diseases (NIAID) (Figures 5 to 30), both from the USA, presented the best images.
Keywords: COVID-19. Images. CDC. NIAID. Database. SARS-CoV-2. 2019-nCoV.

Figure 1. Transmission electron microscopic image of an isolate from the first U.S. case of COVID-19, formerly known as 2019-nCoV. The spherical extracellular viral particles contain cross-sections through the viral genome, seen as black dots.



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J Bioeng. Tech. Appl. Health 2020;3(1):91-97. DOI 10.34178/jbth.v3i1.117.

Figure 2. Transmission electron microscopic image of an isolate from the first U.S. case of COVID-19, formerly known as 2019-nCoV. The spherical viral particles, colorized blue, contain cross-section through the viral genome, seen as black dots.

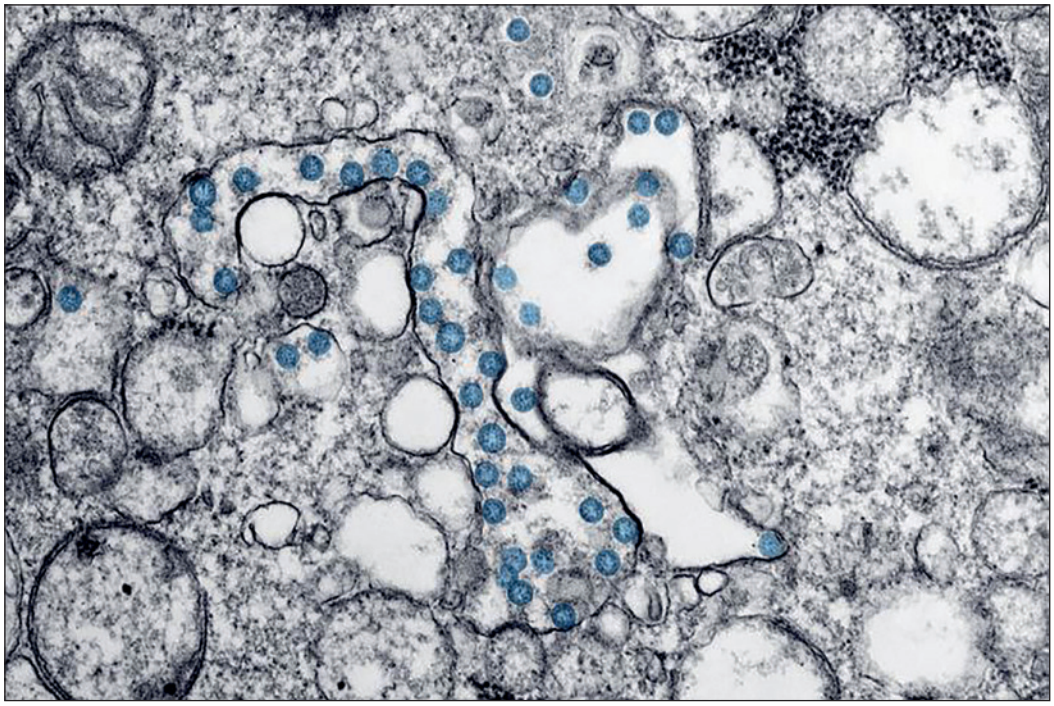


Figure 3. A. This illustration, created at the Centers for Disease Control and Prevention (CDC), reveals ultrastructural morphology exhibited by coronaviruses. Note the spikes that adorn the outer surface of the virus, which impart the look of a corona surrounding the virion, when viewed electron microscopically. In this view, the protein particles E, S, and M, also located on the outer surface of the particle, have all been labeled as well. A novel coronavirus, named Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of an outbreak of respiratory illness first detected in Wuhan, China in 2019. The illness caused by this virus has been named coronavirus disease 2019 (COVID-19). B. Structure of protein domains of COVID-19.

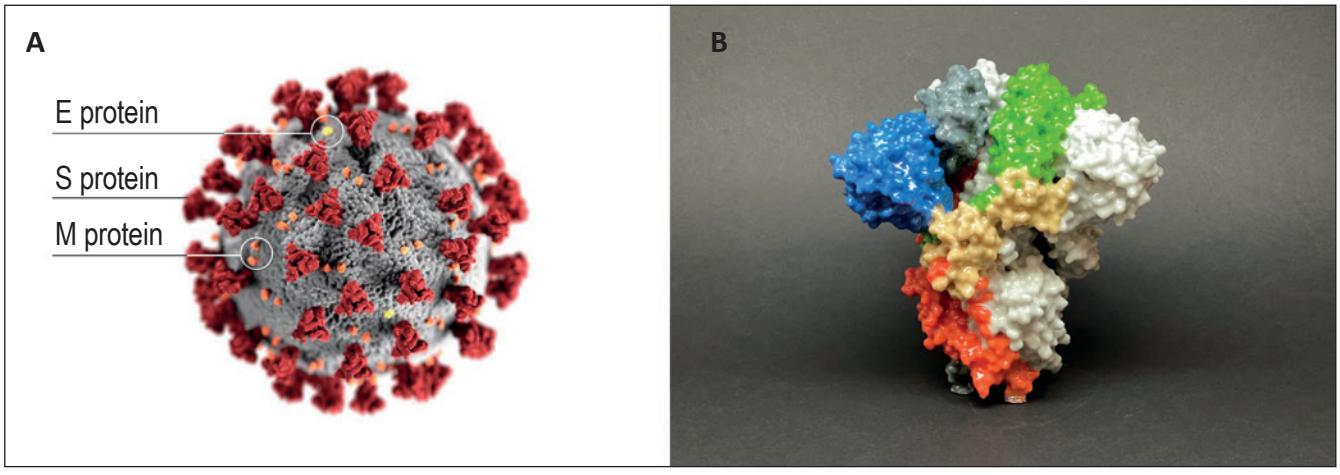


Figure 4. Transmission electron microscope image reveals the virus particles emerging from the surface of cells grown in the laboratory - the peaks on the outer edge of the virus particles give the names of the coronaviruses, in the form of a crown.

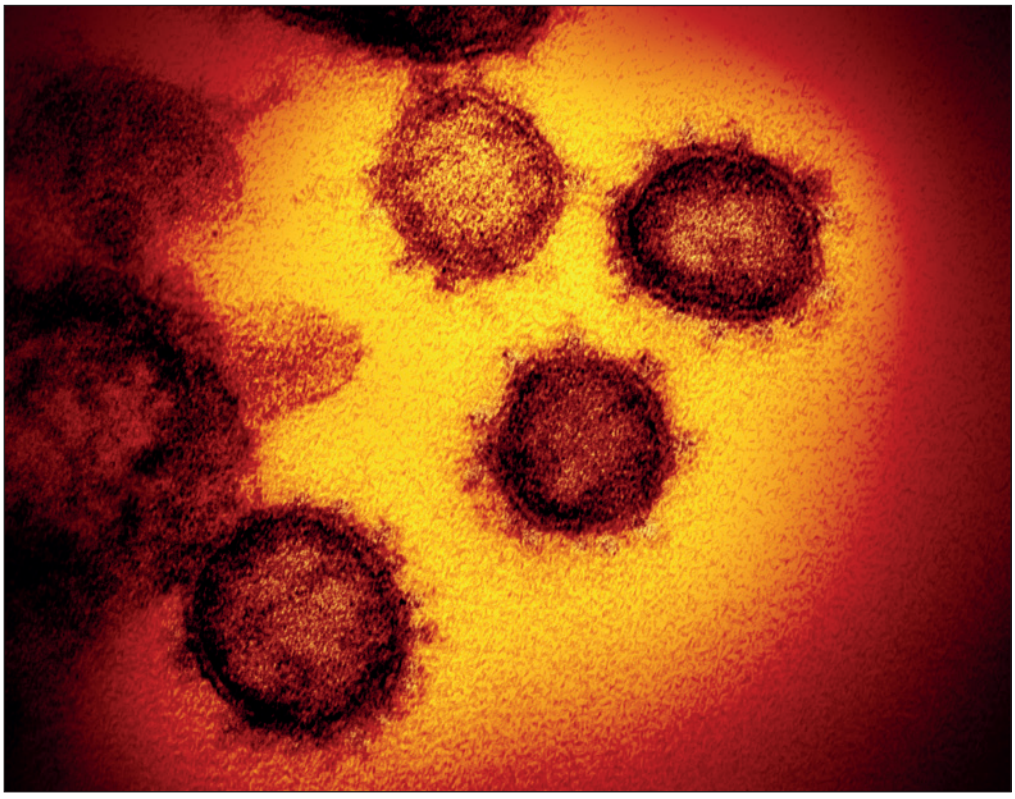
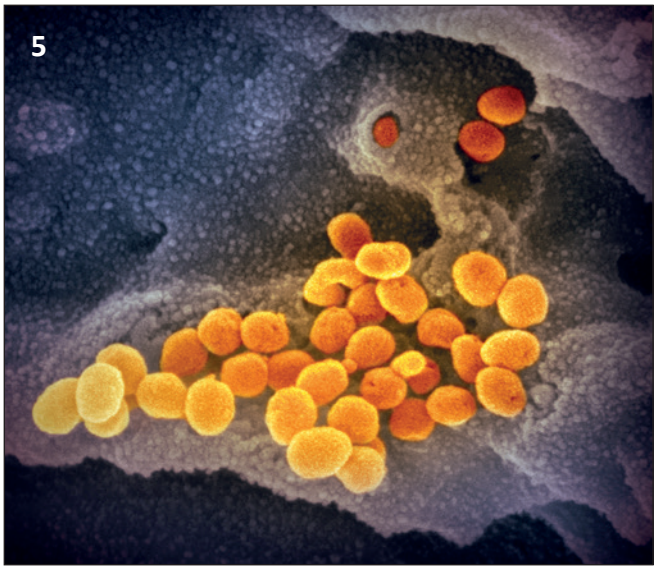
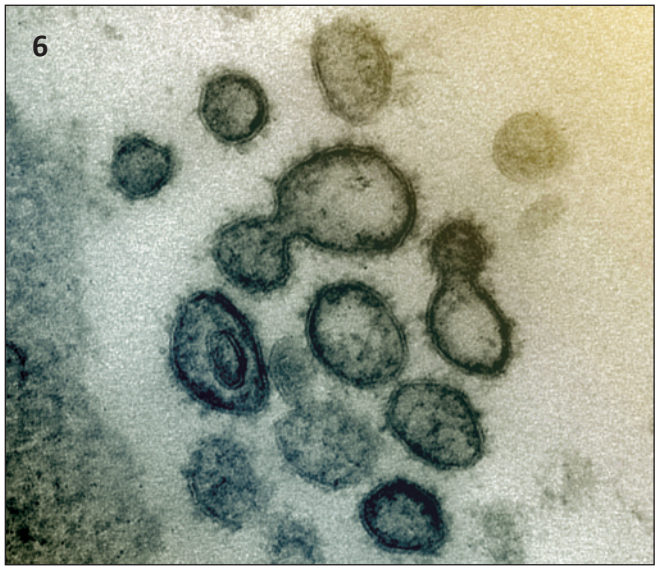
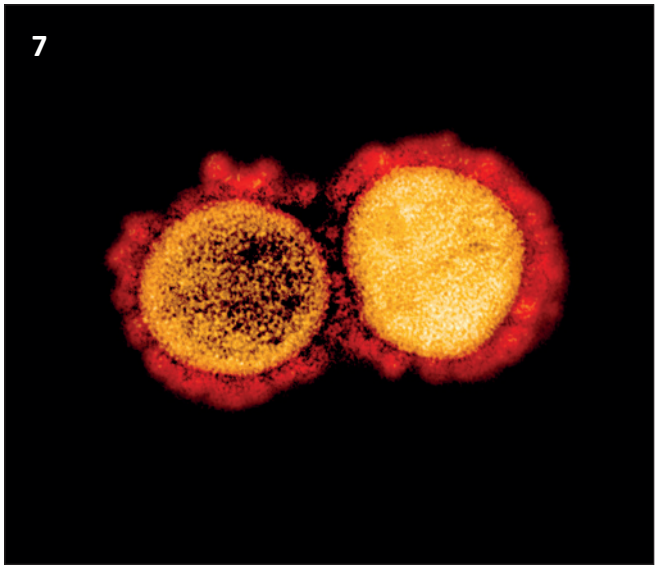


Figure 5 to 30. Transmission electron microscope image and the drawings of COVID-19, presenting the COVID-19 isolated and cells' infection by the virus.



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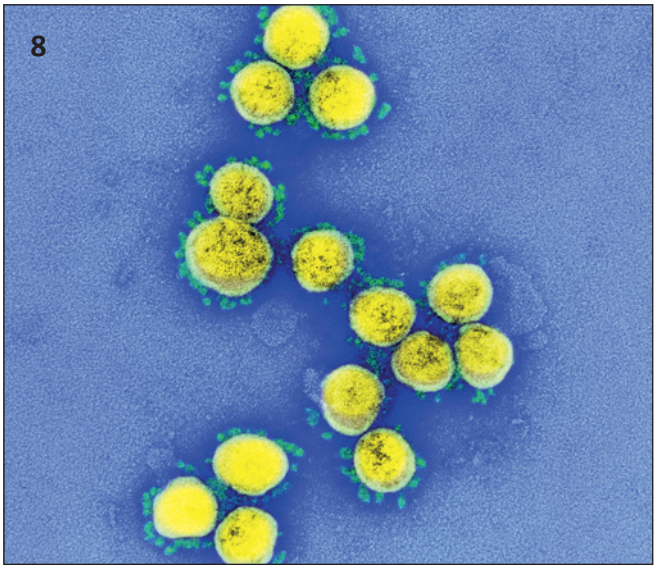
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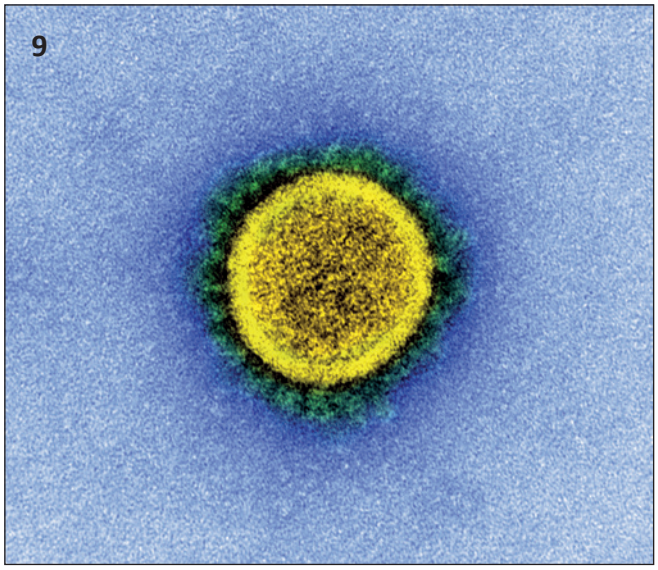
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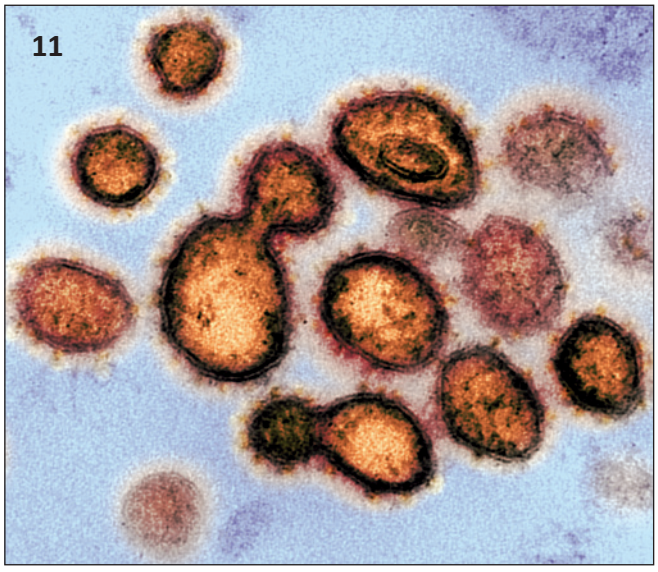
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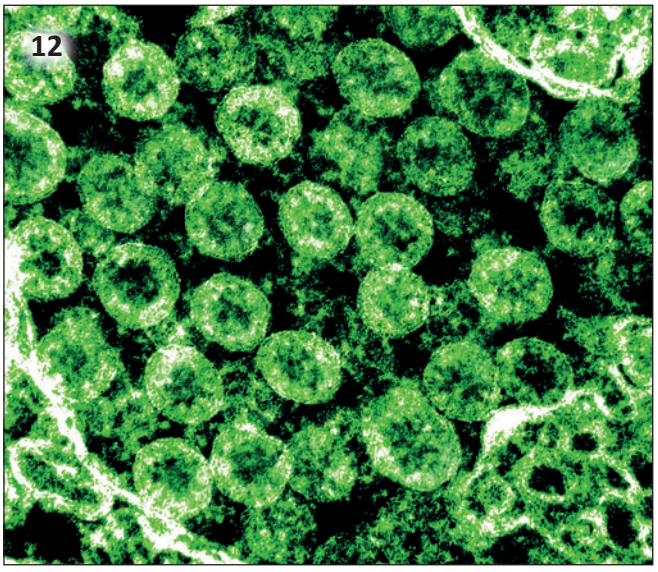
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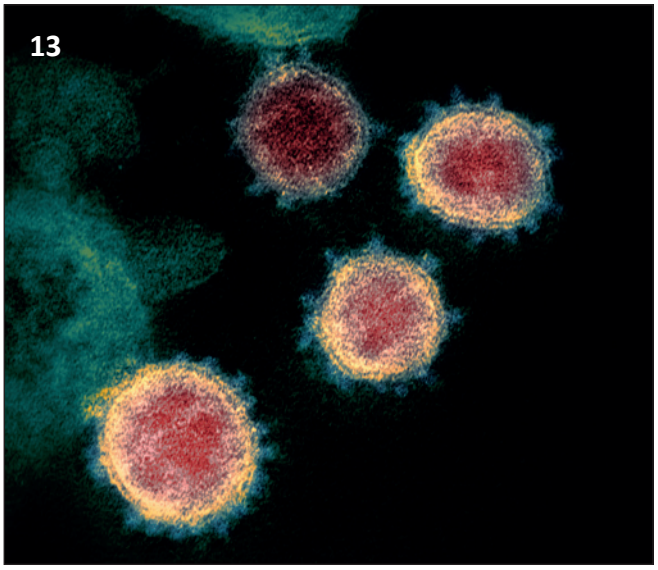
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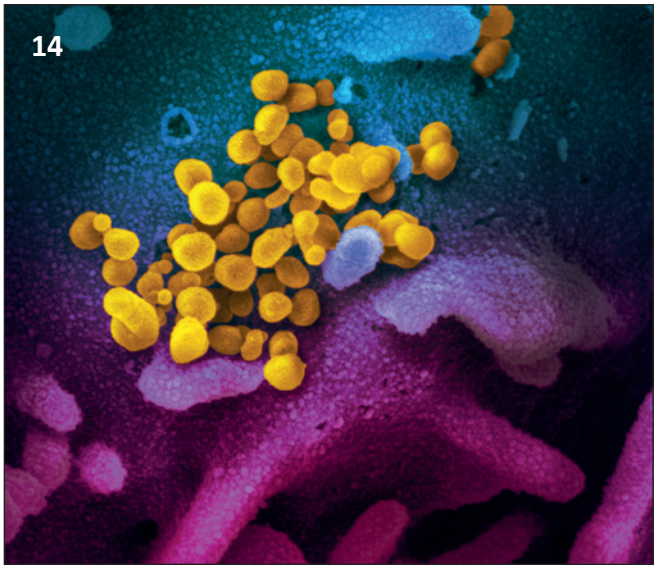
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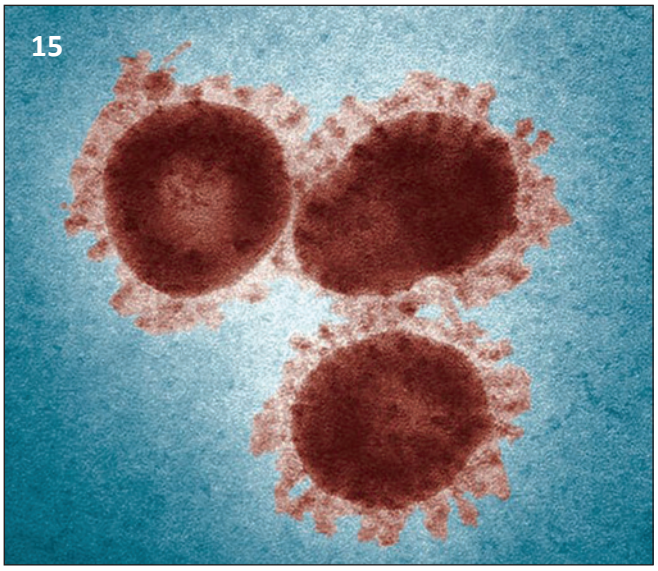
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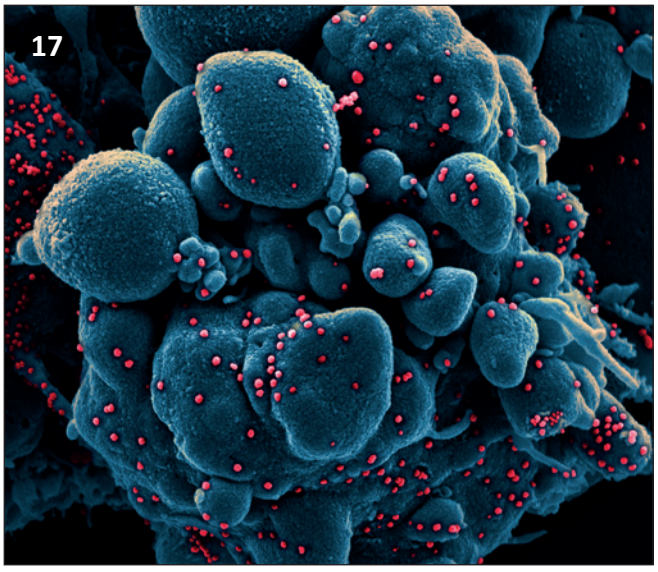
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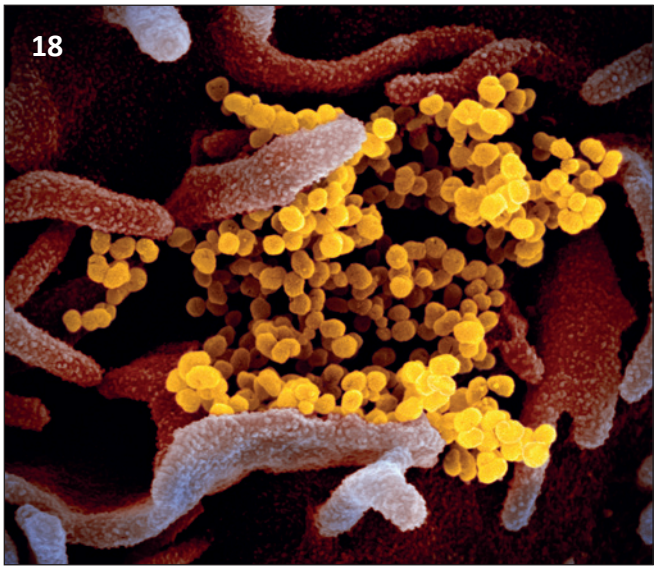
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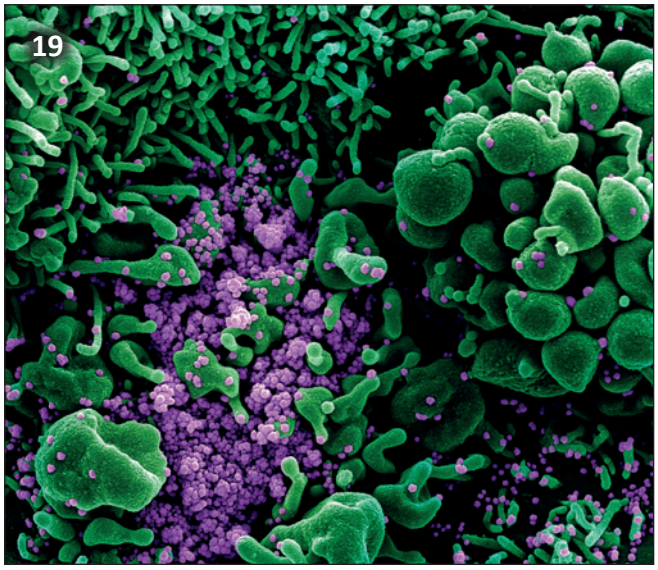
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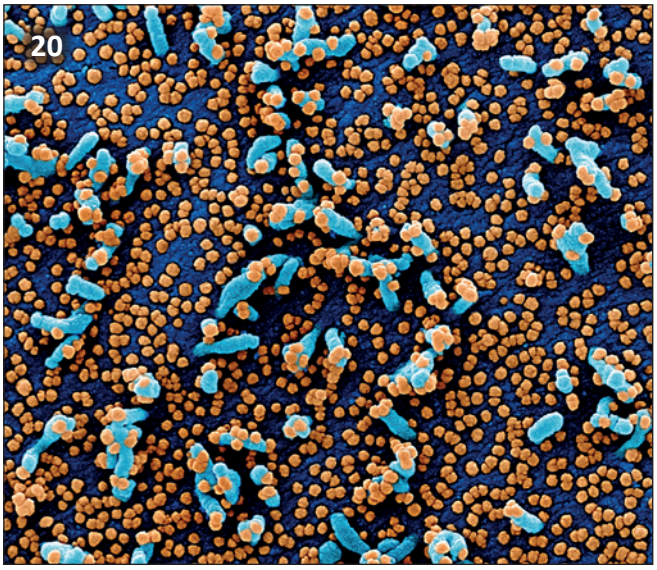
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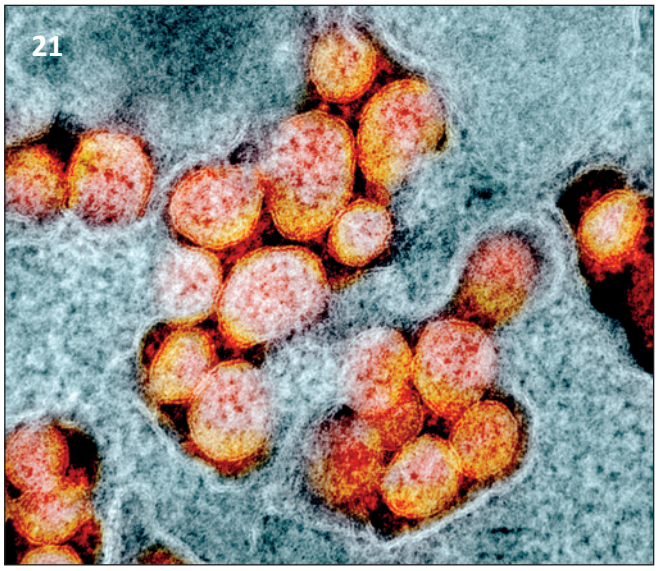
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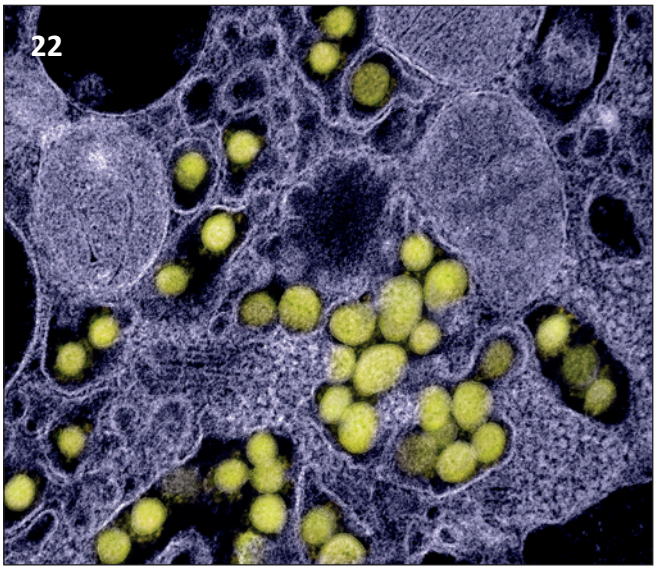
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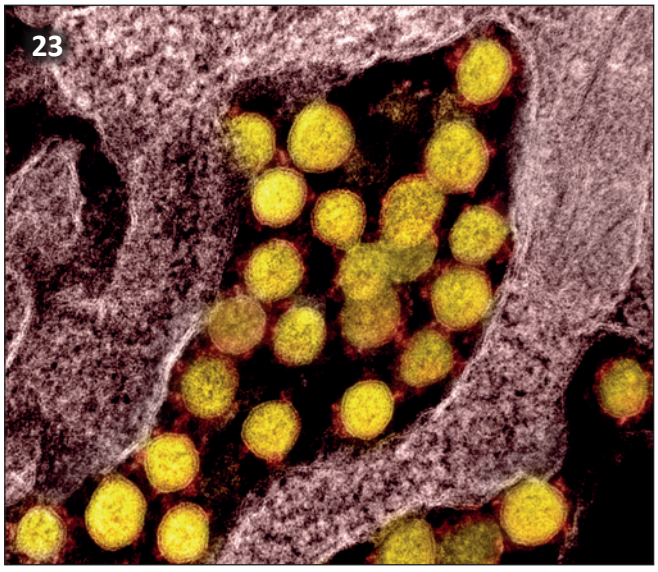
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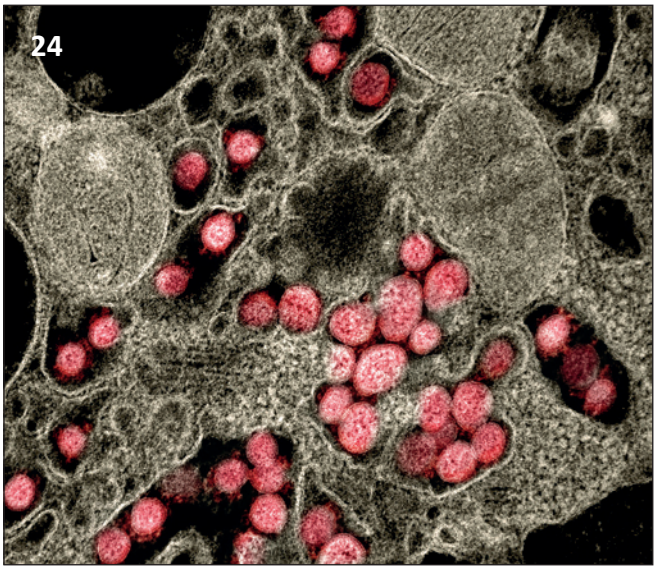
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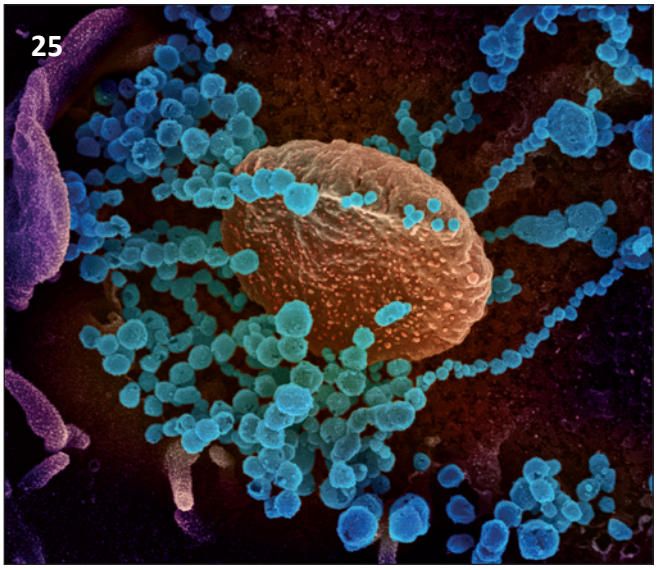
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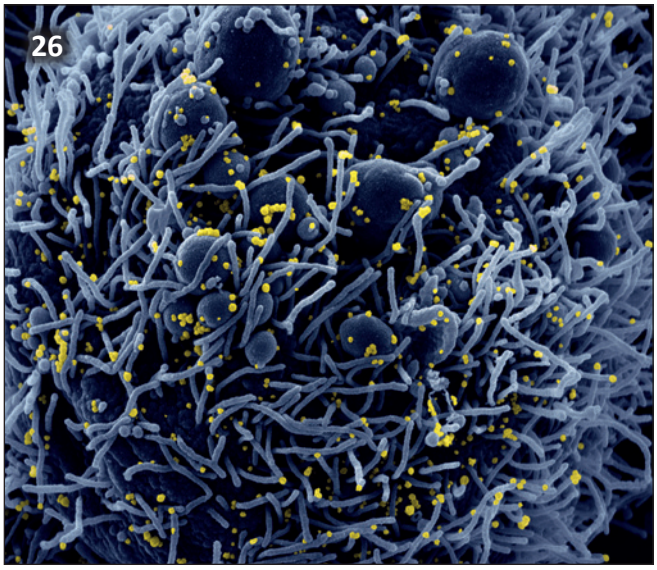
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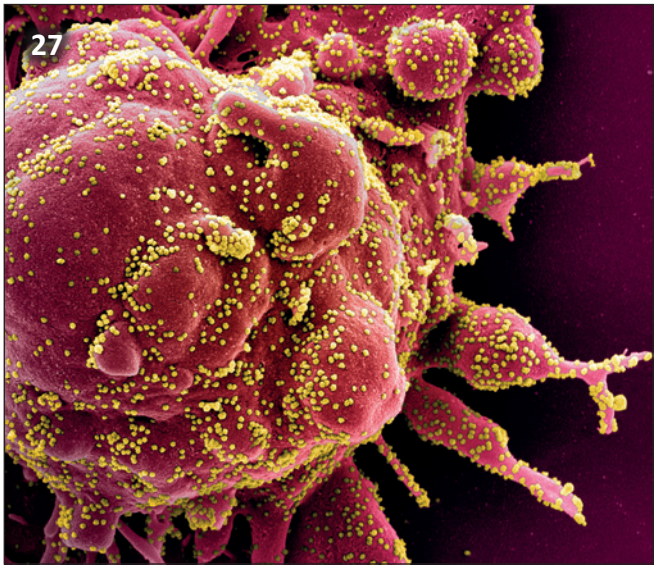
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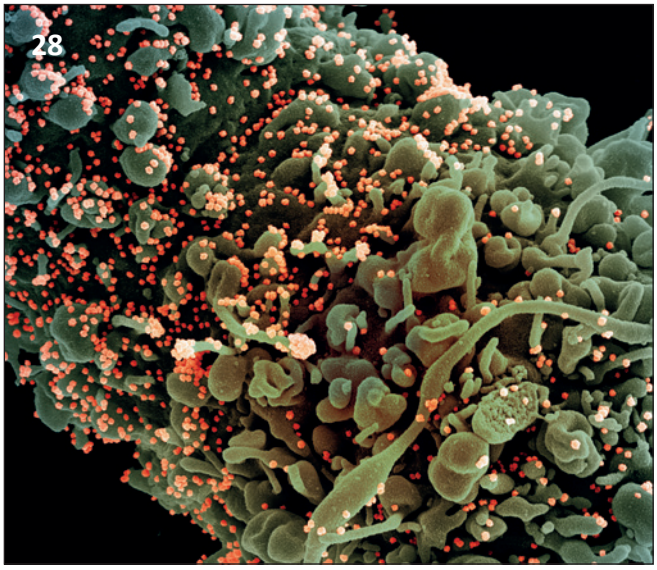
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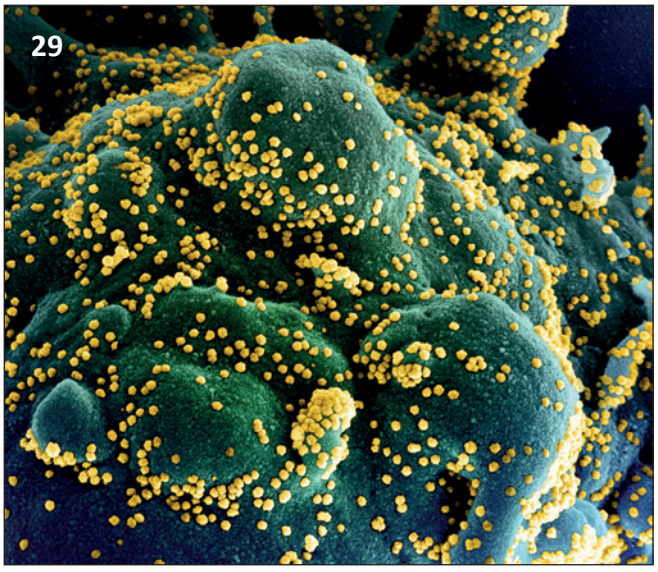
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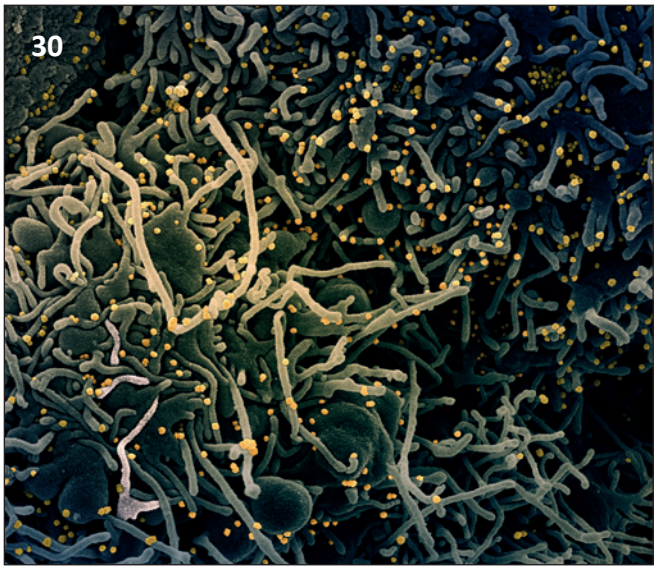
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Clinical Trials for COVID-19 – An Urgent Response

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In this article, we listed databases, guidance, protocols, guidelines, and similar resources that have been produced to help in the tracking and identification of trials and studies about COVID-19. We focused the clinical trials with antiviral drugs, inflammatory cascade (cytokine storm) / target-receptors / blokers, antibiotics, complement system, antibodies, breathing support, testing methods, healthcare workers, impact on other conditions, and vaccines. We used four database to reproduce the clinical trials and to present some of the most promising therapeutic approaches from March to May, 2020: clinicaltrials.gov (clincial trials around the word and in the USA – 1,833 clinical trials in May 30, 2020), the data from Brazil (Rebec), EU Clinical Trials Register (European Union – 37,503 clinical trials with a EudraCT protocol), and the list of the International Clinical Trials Registry Platform (ICTRP) from World Health Organization (WHO). We also prepared an Appendix with the main promise clinical trials evidences against COVID-19 until May 10, 2020.
Keywords: SARS-CoV-2. COVID-19. Clinical Trials. EU. CDC. WHO. Rebec. Database.

Introduction

Since COVID-19 spread to over 190 countries, it has become the greatest challenge worldwide. There have been pandemics before in the history of human race, yet this specific pandemic has reached not only individuals but all of society as a whole, becoming not only a health issue but an economic and social problem. Henceforth, fast development and approval of effective and safe treatments is essential to minimize losses of lives during the pandemic. The world teamed up to identify effective strategies, drugs, therapies, and vaccines that are effective and safe to combat COVID-19. There has been exceptional progress, with multiple agents in late-stage clinical trials [1]. We used three databases to reproduce the clinical trials and to present some of the most promising therapeutic approaches. We used the site clinicaltrials.gov (clinical trials around the word and in the USA – 1833 clinical trials in May 30, 2020), the data from Brazil (Rebec), EU Clinical Trials Register (European Union – 37,503 clinical trials with a EudraCT protocol, of which 6,153 are clinical trials conducted with subjects less than 18 years old, and information on 18,700 older pediatric trials – in scope of Article 45 of the Pediatric Regulation (EC) No 1901/2006), and a list from International Clinical Trials Registry Platform (ICTRP) from World Health Organization (WHO) that does not include those from clinicaltrials.gov [1-3]. In order to track the ever growing number of clinical trials (with information and findings emerging at an unprecedented pace), the Global Coronavirus COVID-19 Clinical Trial Tracker has been created, gathering and classifying all trials in order to avoid waste of time and efforts [5].

This article aims to present the clinical trials database and the main promising clinical trials evidences in the treatment for COVID-19 (Appenix 1 – The appendix was listed on May 10,2020).

Promising Clinical Trials

Antiviral Drugs

There were no promising results in the first trials with traditional antiviral drugs [6, 7]. Nevertheless, due to the possibility that multiple small trials might not generate enough evidence to determine the effectiveness of treatments, WHO

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put together the international SOLIDARITY study. The purpose was to compare untested treatments for COVID-19, and it is made up of over dozens of countries studying four possible treatments: a combination of HIV protease inhibitors ritonavir and lopinavir, the RNA polymerase inhibitor remdesivir, and lopinavir associated with ritonavir in combination with the immunomodulatory agent interferon beta-1ª [8][4].

The RECOVERY trial (UK) is ordering together similar selections of possible treatments at several hospitals. Because of the adaptive nature of its design, new treatments are being joined to the trial as evidence emerges. As of the month of May of 2020, RECOVERY is currently the world's biggest trial of drugs to treat COVID-19 patients [9]. Another clinical trial that appears to be encouraging is the antiviral agent ribavirin (Virazole®, Bausch Health Companies Inc., Laval, Canada) - a nucleoside that restrains syncytial virus (RSV) replication, approved in several countries for the treatment of infants and young children with severe lower respiratory tract infections. So, this trial is evaluating the safety and efficacy of hospitalized adult patients with COVID-19 with critical respiratory distress [10]. A similar antiviral drug, favipiravir (Avigan®, FUJIFILM Toyama Chemical Co., Ltd., Tokyo, Japan), is currently in phase II development (NCT04358549) [11].

Currently, there are many clinical trials about ribavirin, its dose and the effectiveness of the drug. Ribavirin was approved by FDA to be used in severe patients with COVID-19 in intensive care units (ICU) due to the efficacy of the drug in reducing petients'time in ventilators and in reducing mortality.

Antibiotics

The preclinical and clinical data infers that the antibiotic azithromycin (Zithromax®, Pfizer Inc., New York, NY, USA) has antiviral characteristics and this is being investigated in patients with COVID-19 [12].

Inflammatory Cascade (Cytokine Storm) / Target-Receptors / Blockers

Recent data propose that patients with COVID-19 have high serum levels of pro-inflammatory cytokines, such as interferon-gamma (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which drive a cytokine storm [13]. So, other proposals include targeting the inflammatory response to the virus. The same study, carried out by a group of several Chinese medical institutions, shows that infiltration of immune cells in COVID-19 patients' lungs due to the aggravated immune response leads to lung damage, which results in acute respiratory distress syndrome (ARDS). "Preventing the cytokine storm has therefore become an important investigational strategy in the development of COVID-19 therapeutics", says medical writer Katrina Mountfort.

One of the over expressed cytokines produced by activated macrophages in COVID-19 infections is Interleukin (IL)-6[14]. That is why some of the first agents to be assessed in patients with COVID-19 infection are antibodies such as sarilumab (Kevzara®, Sanofi, New York, NY, USA and Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) and tocilizumab (Actemra/RoActemra®, F. Hochmann-La Roche AG, Basel, Switzerland), which are effective in blocking IL-6 signal transduction.

Phase II of the investigation regarding sarilumab, in Sanofi's trial (NCT04327388), revealed fast lowering of C-reactive protein, a key marker of inflammation[4]. Sarilumab showed no evidence of benefits when combining the severe and critical groups *versus* placebo, but the clinical trial has been amended, and enrollment to receive treatment became solely for critical patients. It occurs because negative outcomes were reported for most of those in the "severe" group, while there were positive inclinations for outcomes in the critical group [15].

Studies with tocilizumab seem to have more promising results, although the Roche global,

randomized, double-blind, placebo-controlled phase II COVACTA trial (NCT04320615) will be sure to provide a more definitive answer [16]. In the interim, Novartis released plans for phase III the clinical trial that studies Canakinumab, an IL-1β blocker, in COVID-19 patients that developed pneumonia, after evidence of elevated levels of IL-1β in COVID-19 patients [17].

Other conclusions by Dr. Mountfort concerning current clinical trials for COVID-19 treatments involve the possible therapeutic approach in the regulation of overactive signaling through the janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway during a cytokine storm. Ruxolitinib (Jakafi®, Incyte Corporation, Wilmington, DE, USA) is a JAK1/JAK2 inhibitor approved for polycythaemia vera, myelofibrosis and graft-versus-host disease. A global phase III study, RUX-COVID (NCT04331665), is evaluating the safety and efficacy of ruxolitinib, together with the current standard of care for COVID-19 [18]. Also, Barcitinib JAK1/JAK2 inhibitor) (Olumiant®, Eli Lilly and Company, Indianapolis, IN, USA), approved in many countries as a treatment for adults with moderately-to severely-active rheumatoid arthritis, has been studied as a treatment possible in the National Institute of Allergy and Infectious Diseases (NIAID) against COVID-19 (NCT04280705) [19]. Tofacitinib (Xeljanz®, Pfizer Inc., New York, NY, USA), another JAK1/JAK3 inhibitor, used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, is also being reviewed in a phase II study (NCT04332042). Still, specialists have revealed safety concerns around the proposition, since the antiviral effects of interferons are largely mediated by the JAK–STAT signaling pathway [4, 20].

After the results that evidence the performance of BTK pathway in the production of inflammatory cytokines and promoting early clinical data, Astrazeneca is looking to placate the inflammatory cascade with an extremely selective Bruton's tyrosine kinase (BTK) inhibitor currently used to treat chronic lymphocytic leukemia, the Acalabrutinib (Calquence®, AstraZeneca, Cambridge, UK), which is in the phase II CALAVI trial (NCT04346199) [21]. Furthermore, Medicinova is studying ibudilast (MN-166, Medicinova, Inc., La Jolla, CA, USA), a small-molecule inhibitor of macrophage migration inhibitory factor (MIF) and phosphodiesterase (PDE) -4 and -10, which is recognized to suppress the production of pro-inflammatory cytokines and promote neurotrophic factors [22].

Tradipitant (Vanda Pharmaceuticals Inc., Washington, DC, USA), an investigative neurokinin-1 receptor (NK-1R - the principal receptor for substance P, a pivotal component of the neuroinflammatory processes that guides to significant lung injury following a viral infection) antagonist in development for gastroparesis, motion sickness, and atopic dermatitis treatment, has also entered the ODYSSEY phase III clinical trial (NCT04326426) to attest how effective and safe it can be for critical cases of COVID-19 pneumonia [23].

Complement System

The activation of pro-inflammatory responses is connected to the complement system, which is another essential part of the natural immune response to viruses. There is evidence that suggests that complement inhibition might improve lung injury caused by COVID-19 infection, and it stems from animal models of viral pneumonia [24]. Such data and promising findings from compassionate-use cases, Alexion launched a global phase III trial to investigate the use of ravulizumab-cwvz (Ultomiris®, Alexion Pharmaceuticals, Boston, MA, USA) [25]. Alexion are also planning to further investigate a related drug, ecilizumab (Soliris®, Alexion Pharmaceuticals, Boston, MA, USA), in COVID-19.

Antibodies

Antibody-based therapies may also be a hopeful approach to COVID-19 treatment. An

introductory study on 10 Chinese patients infers that immunotherapy with neutralizing antibodies existing in convalescent plasma improved clinical symptoms, higher levels of blood oxygen and lymphocytes, lower C-reactive protein levels, and undetected viral loads; two patients were removed from ventilators. Treatment was particularly successful if the plasma was delivered within 14 days of symptom onset and no adverse effects were observed [4, 9]. This finding needs investigation in larger studies.

Kiniksa Pharmaceuticals (Bermuda) recently published introductory data of treatment response with mavrilimumab, an investigational fully-human monoclonal antibody that targets granulocyte-macrophage colony-stimulating factor receptor alpha (GM-CSFRα), in patients with severe pneumonia and hyperinflammation by COVID-19 infection (all patients presented an early resolution of fever and improvement in oxygenation within 1-3 days; none of these patients have advanced to require mechanical ventilation). However, the N of the study is low (six) and further studies are being started [4, 9].

Eli Lilly and Company initiated a phase II study (A study of LY3127804 in participants with COVID-19; NCT04342897) with LY3127804, a monoclonal antibody against angiopoietin 2 (Ang2), in hospitalized patients with COVID-19 pneumonia, who are at a higher risk of progressing to ARDS. Ang2 levels are known to be elevated in the alveolar components of patients with ARDS. It is hoped that inhibition of Ang2 will decrease the progression to ARDS or the necessity for mechanical ventilation in patients with COVID-19 [19].

Breathing Support

The RECOVERY Respiratory Support (Recovery-RS) study is testing treatments that intend to prevent people to go on a ventilator. They randomized patients and designated to receive oxygen either through a tight-fitting mask (continuous positive airway pressure [CPAP]) or blown up their nose by a machine (high-flow nasal oxygen [HFNO]), or through a normal oxygen mask. Both CPAP and HFNO are already used routinely in the National Health Service (UK) for other conditions [9].

Testing

A rapid bedside test's results for COVID-19 may concede doctors to distinguish infected patients more quickly and stop the virus from circulating in hospitals. Therefore, the CoV-19POC study aims to update the tests already existing and find out whether using a new rapid test for COVID-19 to an earlier decision to better management of the sick patients [9].

Healthcare Workers

The HEROs' study taking place at five hospitals in Canada intends to find out whether taking hydroxychloroquine before and during exposure to patients decreases their risk of COVID-19 infection. The COVVA study in Spain is looking at the effects on healthcare workers wearing personal protective equipment (PPE), such as N95 respirators and FFP2 face masks, to examine whether their working conditions can be improved. The healthcare workers are required about the presence of problems such as headaches and skin lesions after working in isolation areas [9].

Impact on Other Conditions

The COVER study is an international study intending to collect information on how the COVID-19 pandemic is affecting the medical care of patients with artery and vein (vascular) conditions. Also, UKOSS's study is collecting information about all pregnant women admitted to the hospital with COVID-19 in UK to study the effects of the infection and treatments on the mother and baby [9].

Vaccines

Despite all described clinical trials above, the vaccines are the principal target to clinical

trials currently, and the most cost-effective way of controlling outbreaks such as COVID-19. The COV001 and COV002 studies based in Oxford (UK) are testing a new vaccine on healthy volunteers to check if they can be protected from COVID-19. The first results attested to the safety of the vaccine and its capacity to generate good immune responses against the virus. Phase II was initiated in the last week (May 21) [4, 9].

Another promised vaccine is developing in China, which confers promise after early study in 100 people. The vaccine seemed safe and capable to generate an immune response after an early trial in more than 100 people, according to the new study. The Ad5 vectored COVID-19 vaccine, called Ad5-nCoV, being developed by the Chinese company CanSino Biologics, is tolerable and immunogenic at 28 days post-vaccination (almost all participants had developed antibodies that bound to SARS-CoV-2). The vaccine uses a weakened version of adenovírus, a common cold virus, which infects human cells but doesn't cause disease, to deliver a fragment of genetic material from SARS-CoV-2. This genetic material carries instructions for making the "spike protein" on the surface of SARS-CoV-2, leading a humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses from day 14 post-vaccination, The Ad5 vectored COVID-19 vaccine is now in Phae II (500 participants). warrants further investigation [26].

Several other coronavirus vaccine candidates published promising developments this week. On Monday (May 18), Biotech company Moderna announced that 45 volunteers who received doses of its vaccine candidate, called mRNA-1273, developed antibodies within 15 days and that the level of antibodies observed in their blood was similar to that seen in people who have recovered from COVID-19 [26].

Ongoing Trials

In Table 1, based on TranspariMED [33], we listed databases, trial trackers, and similar sources that have been developed to help in the tracking and identification of trials and studies involving COVID-19.

Discussion and Conclusion

There is an imperative demand for strategies, drugs, and vaccines against COVID-19. Since new clinical trials appear by the minute due to the battles to fight COVID-19, this review cannot present a comprehensive account of all the potential therapeutics in clinical development, considering the speed of progress and the gaps that exist in our knowledge of the immunopathology of COVID-19. We do have to be mindful of the safety of patients. The hydroxychloroquine and chloroquine case is a good example of the pitfalls of small and uncontrolled trials [27]. The early studies *in vitro* suggested that the drugs might be effective against SARS-CoV-2 [28], so clinical trials were launched around the world. But as there are many trials, the researchers did not have a clear answer to whether the drugs work against COVID-19 in people.

Despite this — and despite their known effects on the heart — the drugs entered the treatment protocol against Covid all over the world. Currently, the REMAP-CAP study (include participants from more than 160 sites across 14 countries), and several larger and controlled studies [29-32] have demonstrated that hydroxychloroquine and chloroquine, as they were being used, are not benefic for patients and they have no efficacy against COVID-19. In spite of this, novel studies are in course.

A pandemic emergency is a reason to work quicker, but the clinicians and researchers must not lose sight of the fact that experimental interventions carry an inherent risk to the patient. To consider this risk, clinical trials must be as robustly produced as possible. For this purpose, collaborative trials and collaborative efforts between pharmaceutical companies are important because they are the ones with a greater chance of showing what really works. Nevertheless, every

Table 1. Databases, trial trackers and similar resources that have been develped to aid in the tracking and identification of trials and studies concerning COVID-19 [33].

Resource	Description
Cytel COVID-19 Clinical Trial Tracker	Cytel has developed this COVID-19 trial dashboard to identify registered trials investigating the use of interventional strategies for the treatment of COVID-19, or COVID-19 related symptoms. Trials can be filtered by location, trial status and intervention, amongst other identifiers. The dashboard uses data from WHO International Clinical Trials Registry Platform, the European Clinical Trials Registry, clinicaltrials.gov, the Chinese Clinical Trial Registry, the German Clinical Trials registry, the Japan Primary Registries Network, the Iranian Clinical Trial Registry, and the Australian New Zealand Clinical Trials Registry.
COVID-19 TrialsTracker	Developed as part of TrialsTracker.net project run by The DataLab at the University of Oxford, the 'COVID-19 TrialsTracker' brings together structured, cleaned data from clinical trial registries on studies of COVID-19, and tracks the availability of their results.The tracker uses data from the ICTRP and may collect additional information directly from certain registries over time.
COVID-19 Vaccine Development Pipeline	This tracker, developed by the Vaccine Centre at the London School of Hygiene & Tropical Medicine, follows COVID-19 vaccine candidates as they progress through the development pipeline. The tracker is updated weekly. Users can filter developmental COVID-19 vaccines according to stage of development and vaccine type. An overview of the different vaccine types as well as the phases of clinical development is provided in the Summary tab.
GloPID-R/UKCDR COVID-19 Research Project Tracker	UKCDR and GloPID-R are maintaining a live database of funded research projects across the world related to the current COVID-19 pandemic. The database aims to support funders and researchers in delivering a more effective and coherent global research response to the pandemic by providing an overview of research projects mapped against the priorities identified in the WHO Coordinated Global Research Roadmap: 2019 Novel Coronavirus.It includes: new research projects funded to date from the dataset sources; heatmap of these projects against the research priorities set out in the WHO Coordinated Global Research Roadmap: 2019 Novel Coronavirus, March 2020; supporting information on funding calls; links to other sources of information.
GHTC COVID-19 R&D Tracker	The Global Health and Technologies Coalition (GHTC) is tracking research and development (R&D) efforts to combat SARS-CoV-2. Here they summarise the latest updates on: US government-supported R&D for SARS-CoV-2; efforts led by multilateral institutions; R&D being led by GHTC members; other efforts by GHTC members to respond to the pandemic
Milken Institute COVID-19 Treatment and Vaccine Tracker	This document, compiled by The Milken Institute, aims to list all treatments and vaccines currently in development for COVD-19. It contains an aggregation of publicly-available information from validated sources.
WHO International Clinical Trials Registry Platform	The main aim of the WHO ICTRP is to facilitate the prospective registration of the WHO Trial Registration Data Set on all clinical trials, and the public accessibility of that information. Users can download all COVID-19 trials from the ICTRP database.
ClinicalTrials.gov	ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. Users can See listed clinical studies related to the coronavirus disease (COVID-19). Alternatively, users can search 'COVID-19' or related terms.
EU Clinical Trials Register - COVID-19 Trials	The European Union Clinical Trials Register allows users to search for protocol and results information on: interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA); clinical trials conducted outside the EU / EEA that are linked to European paediatric-medicine development. This link shows the results for COVID-19 clinical trials from the EU Clinical Trials Register.

Table 1. Batabases, trial trackers and similar resources that have been develped to aid in the tracking and identification of trials and studies concerning COVID-19 [33].

Resource	Description
COVID-evidence Database	COVID-evidence, a non-profit initiative of the Department of Clinical Research at University of Basel and the Meta-Research Innovation Center at Stanford, are maintaining this database of available trial evidence on benefits and harms of interventions for COVID-19. As well as trial information, the database provides links to original sources such as study protocol documents, registry entries, and publications. In addition, COVID-evidence also aims to provide reliably extracted key trial information that would otherwise only be accessible by reading every manuscript in detail.
Cochrane COVID-19 Study Register	Cochrane's COVID-19 Study Register is a freely-available, continually-updated, annotated reference collection of human studies on COVID-19, including interventional, observational, diagnostic, prognostic, epidemiological, and economic designs. Please note: the register will not include in vitro study references. The three primary data sources for Cochrane's COVID-19 Study Register are ClinicalTrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) and PubMed
EPPI-Centre COVID-19: Living Map of the Evidence	EPPI-Centre (Evidence for Policy and Practice Information and Co-ordinating Centre) are maintaining an up-to-date map of the current evidence surrounding COVID-19 that is partitioned into broad domains for easy exploration. The map is updated weekly and consists of studies on COVID-19, identified in MEDLINE and Embase, and published in 2019 or later.
RAPS COVID-19 Vaccine Tracker	Compiled by the Regulatory Affairs Professionals Society (RAPS), this tracker lists the major vaccine candidates in development for prevention of COVID-19. The tracker is updated weekly.

possible effort must be made to halt the epidemic as soon as possible respecting all phases and ethics of clinical research to bring efficacy, tolerability, and security in the treatments against COVID-19.

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Early Guidelines and Protocols About COVID-19

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In just six months, the coronavirus changed the world very quickly. The protocols and guidelines to face and to manage the pandemic of COVID-19 is as fast as the changes in people's lives during this period. However, some policies, protocols and guidelines are established. This article compiled the global management strategies for COVID-19 infection pandemic preparedness, the issues about peaking of the outbreak, and "flattening the curve", and the guidelines and protocols by World Health Organization (WHO), Center for Disease Control (CDC), Brazil Ministry of Health, European Union guidelines, Panamerican Health Organization (PAHO), the protocols of China, Belgium, Italy, Netherlands, and Infectous Diseases Society of America (IDSA). We searched the data in the main database (PubMed/ Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Exerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), and in the health Organizations around the world, such as World Health Organization, Panamerican Health Organization (PAHO), Center for Disease Control, National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID). We prior selected meta-analysis, systematic reviews, article reviews and original articles in this order. We reviewed 41 articles and sites and used 20 from March to June 2020, adopting the terms coronavirus, SARS-CoV-2, novel coronavirus, Wuhan coronavirus, severe acute respiratory syndrome, 2019-nCoV, 2019 novel coronavirus, n-CoV-2, covid, n-Sars-2, COVID-19, corona virus, coronaviruses, protocols, guidelines, CDC, WHO, European Union, PAHO, China, Italy, IDSA, with the tools MeSH (Medical Subject Headings), AND, OR, and characters [,",; /., to ensure the best review topics. We concluded that all guidelines and protocols tend to use WHO as a reference with particular differences between countries. Also, the more the COVID-19 is known, the more the protocols and guidelines change.
Keywords: COVID-19. SARS-CoV-2. Guidelines. Protocols.

Introduction

The current knowledge about epidemiology, pathogenesis, treatments, protocols and guidelines of COVID-19 disease is updating quicly so that as we are writing this paper a novel information is being publishing. Nevertheless, there is some establishing knowledge and management about the disease that we could present here, however regarding protocols and guidelines, which are the aim of this review, the reports change all the time. The objective of this manuscript was to sumarize the updating protocols and guidelines against COVID-19 addopted from the main centers in the world (World Health Organization (WHO), Center for Disease and Preventing Control (USA), the European protocols, and Infectious Diseases Society of America) in order to present an overview about systematic procedures and actions established against the COVID-19 by full reproduce.

Pandemic Preparedness

WHO and other leading epidemiology organizations universally recognize the indispensable task of pandemic preparedness and a project at global and national levels to mitigate the public health emergency of COVID-19 or any future outbreaks. Pandemic preparation is an effort of the government and the society requiring inputs from each person susceptible to the infection agente as well as policy makers at national and international levels, frontline healthcare providers, infrastructure developers and maintenance personnel, pharmaceutical industry and researcher community, and so forth. Moreover, the pandemic

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preparedness project needs constant reviewing and improvisation [1, 2].

The magnitude of the COVID-19 pandemic requires worldwide action plans. The United States quickly created the United Nations' Strategic Preparedness and Response Plan (SPRS) to control the tramission of the virus in order to delaying the spread of COVID-19, provide optimal care for all patients, and minimize the impact on healthcare systems and socioeconomic activities. Several nations are well placed to implement this action plan with minimal support. However, each country has its own issues that the place authority has to adjust the guidelines and protocols for the reality of each country or district. Thus, all nation has to prepare a COVID-19 Country Preparedness and Response Plan (CPRP) against the COVID-19 [1]. These CPRPs need constant monitoring and reviewing using indicators shared by WHO and CDC, for example, updating as the situation evolves. Part of these plans is the protocols and guidelines adopted in each country [3].

Saxena [1] reported that the success against a pandemic is grounded in the following actions, which have to be included in the protocols and guidelines:

- Surveillance of the pathogen: characterization of the pathogen, epidemiology, transmission, symptoms, pathogenesis, diagnosis and detection, testings, infection, contact tracing, data from confirmed cases, predicting mass infection outbreak, keeping a count, and estimation of mortality.
- Response management: production and supply of protective/preventive pharmaceutical interventions or non-pharmaceutical interventions; extensive test the community, education of the Community about the disease and how it spreads, transmit and all information about the disease.
- Medical help: access to hospitals/healthcare providers, personal and public hygiene, disinfection, and quarantine services.
- Lesson from the present outbreak to facilitate future action strategies and preparedness.

Global Management Strategies for COVID-19 Infection

The authorities of worlwide and Health Organizations created strategies, which including protocols and guidelines, due to the exponential transmission of SARS-CoV-2 and social-economic impact of the pandemic [4-6], such as:

- Social distancing;
- Travel restrictions;
- Implementation of personal and public hygiene (non-pharmaceutical interventions);
- Implementation of diagnosis (clinical with symptoms and laboratorial);
- Extensive testing for community;
- Medicines interventions.

All these practices (Figure 1) delay the peaking of the outbreak, avoid burden on the healthcare infrastructure, "flattening the curve" of the infected patients (Figure 2) [7].

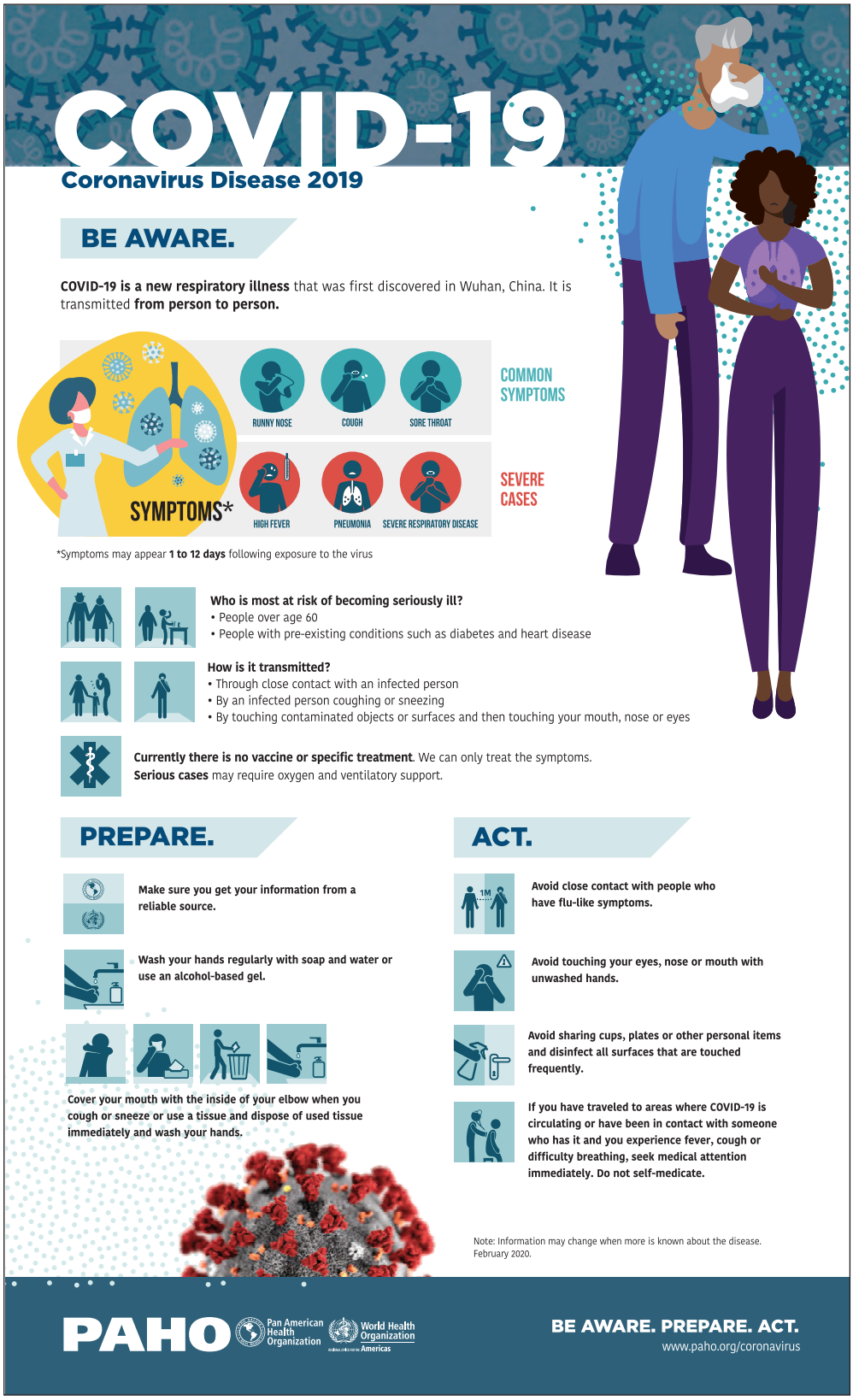
In the sections below, we presented the guidelines and some protocols from WHO and CDC in the combat against COVID-19.

World Health Organization (WHO) Guidelines

Individual protections against the transmission of COVID-19 between the the people is following [9]:

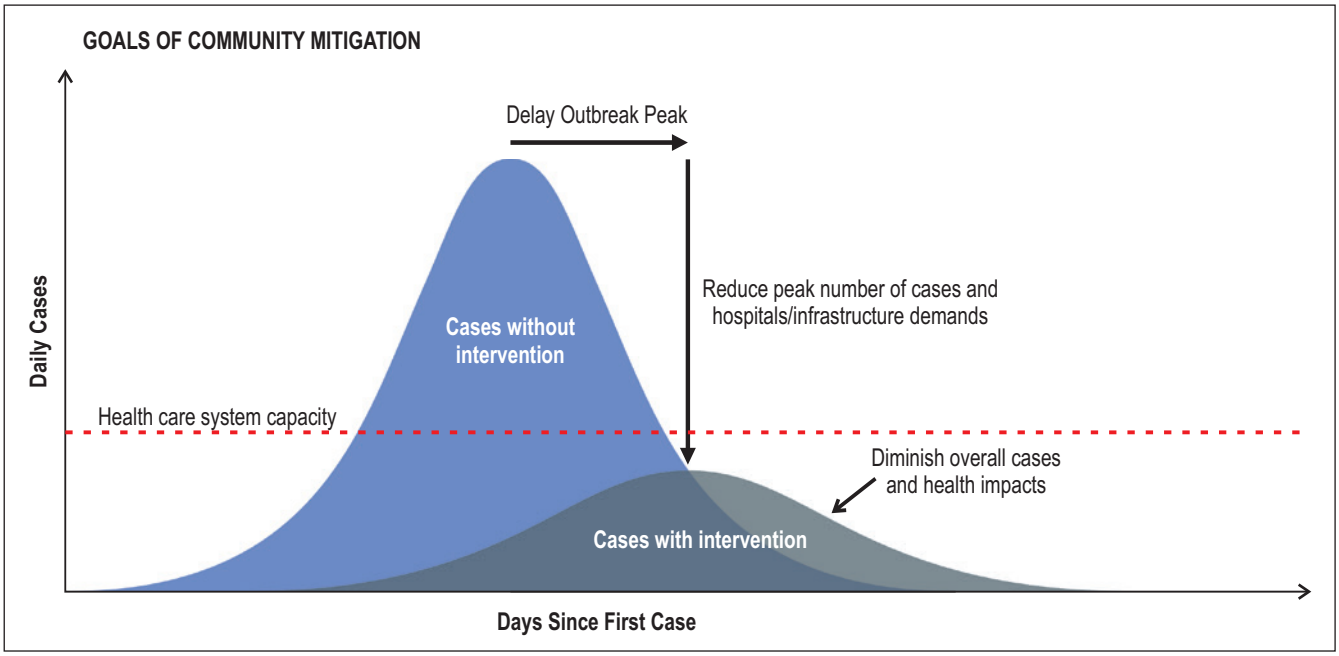
- Regularly and thoroughly clean your hands with an alcohol-based hand rub or wash them with soap and water. Why? Washing your hands with soap and water or using alcohol-based hand rub kills viruses that may be on your hands.
- Maintain at least 1 metre (3 feet) distance between yourself and others. Why? When someone coughs, sneezes, or speaks they spray small liquid droplets from their nose or mouth which may contain virus. If you are too close, you can breathe in the droplets, including the COVID-19 virus if the person has the disease.
- Avoid going to crowded places. Why? Where people come together in crowds, you are more

Figure 1. Tips to prevent coronavirus transmission and allert about symptoms.



ource: PAHO [8].

Figure 2. Flattering the curve.



likely to come into close contact with someone that has COIVD-19 and it is more difficult to maintain physical distance of 1 metre (3 feet).

- Avoid touching eyes, nose and mouth. Why? Hands touch many surfaces and can pick up viruses. Once contaminated, hands can transfer the virus to your eyes, nose or mouth. From there, the virus can enter your body and infect you.
- Make sure you, and the people around you, follow good respiratory hygiene. This means covering your mouth and nose with your bent elbow or tissue when you cough or sneeze. Then dispose of the used tissue immediately and wash your hands. Why? Droplets spread virus. By following good respiratory hygiene, you protect the people around you from viruses such as cold, flu and COVID-19.
- Stay home and self-isolate even with minor symptoms such as cough, headache, mild fever, until you recover. Have someone bring you supplies. If you need to leave your house, wear a mask to avoid infecting others. Why? Avoiding contact with others will protect them from possible COVID-19 and other viruses.
- If you have a fever, cough and difficulty breathing, seek medical attention, but call by telephone in advance if possible and follow the directions of your local health authority. Why? National and local authorities will have the most up to date information on the situation in your area. Calling in advance will allow your health care provider to quickly direct you to the right health facility. This will also protect you and help prevent spread of viruses and other infections.
- Keep up to date on the latest information from trusted sources, such as WHO or your local and national health authorities. Why? Local and national authorities are best placed to advise on what people in your area should be Doing to protect themselves.

Center for Disease Control (CDC)

Protecting Yourself and Others Against COVID-19 and Related Informations [10]

Knowing How It Spreads

- There is currently no vaccine to prevent coronavirus disease 2019 (COVID-19).

- The best way to prevent illness is to avoid being exposed to this virus.
- The virus is thought to spread mainly from person-to-person.
  - Between people who are in close contact with one another (within about 6 feet).
  - Through respiratory droplets produced when an infected person coughs, sneezes or talks.
  - These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs.
  - Some recent studies have suggested that COVID-19 may be spread by people who are not showing symptoms.

Wash Your Hands Often

- Wash your hands often with soap and water for at least 20 seconds especially after you have been in a public place, or after blowing your nose, coughing, or sneezing.
- If soap and water are not readily available, use a hand sanitizer that contains at least 60% alcohol. Cover all surfaces of your hands and rub them together until they feel dry.
- Avoid touching your eyes, nose, and mouth with unwashed hands.

Avoid Close Contact

- Avoid close contact with people who are sick, even inside your home. If possible, maintain 6 feet (1.5 meters) between the person who is sick and other household members.
- Put distance between yourself and other people outside of your home.
  - Remember that some people without symptoms may be able to spread virus.
  - Stay at least 6 feet (about 2 arms' length) from other people.
  - Do not gather in groups.
  - Stay out of crowded places and avoid mass gatherings.
  - Keeping distance from others is especially important for people who are at higher risk of getting very sick.
  - Cover your mouth and nose with a cloth face cover when around others.
- You could spread COVID-19 to others even if you do not feel sick.
- Everyone should wear a cloth face cover when they have to go out in public, for example to the grocery store or to pick up other necessities.
  - Cloth face coverings should not be placed on young children under age 2, anyone who has trouble breathing, or is unconscious, incapacitated or otherwise unable to remove the mask without assistance.
- The cloth face cover is meant to protect other people in case you are infected.
- Do NOT use a facemask meant for a healthcare worker.
- Continue to keep about 6 feet between yourself and others. The cloth face cover is not a substitute for social distancing.

Cover Coughs and Sneezes

- If you are in a private setting and do not have on your cloth face covering, remember to always cover your mouth and nose with a tissue when you cough or sneeze or use the inside of your elbow.
- Throw used tissues in the trash.
- Immediately wash your hands with soap and water for at least 20 seconds. If soap and water are not readily available, clean your hands with a hand sanitizer that contains at least 60% alcohol.

Clean and Disinfect

- Clean AND disinfect frequently touched surfaces daily. This includes tables, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, and sinks.
- If surfaces are dirty, clean them. Use detergent or soap and water prior to disinfection.
- Then, use a household disinfectant. Most common EPA-registered household disinfectants external icon will work.

Monitor Your Health

- Be alert for symptoms. Watch for fever, cough,

shortness of breath, or other symptoms of COVID-19.
  - o Especially important if you are running essential errands, going into the office or workplace, and in settings where it may be difficult to keep a physical distance of 6 feet.
- Take your temperature if symptoms develop.
  - o Don't take your temperature within 30 minutes of exercising or after taking medications that could lower your temperature, like acetaminophen.
- Follow CDC guidance if symptoms develop.

Steps to Help Prevent the Spread of COVID-19 If You Are Sick

If you are sick with COVID-19 or think you might have COVID-19, follow the steps below to care for yourself and to help protect other people in your home and community.

Stay Home Except to Get Medical Care
- Stay home. Most people with COVID-19 have mild illness and can recover at home without medical care. Do not leave your home, except to get medical care. Do not visit public areas.
- Take care of yourself. Get rest and stay hydrated. Take over-the-counter medicines, such as acetaminophen, to help you feel better.
- Stay in touch with your doctor. Call before you get medical care. Be sure to get care if you have trouble breathing, or have any other emergency warning signs, or if you think it is an emergency.
- Avoid public transportation, ride-sharing, or taxis.
- Separate yourself from other people. As much as possible, stay in a specific room and away from other people and pets in your home. If possible, you should use a separate bathroom. If you need to be around other people or animals in or outside of the home, wear a cloth face covering.

Monitor Your Symptoms
- Symptoms of COVID-19 fever, cough, or other symptoms.
- Follow care instructions from your healthcare provider and local health department. Your local health authorities may give instructions on checking your symptoms and reporting information.

When to Seek Emergency Medical Attention

Look for emergency warning signs* for COVID-19. If someone is showing any of these signs, seek emergency medical care immediately:
- Trouble breathing.
- Persistent pain or pressure in the chest.
- New confusion.
- Inability to wake or stay awake.
- Bluish lips or face.

Call the Emergence Number or Your Doctor

Notify that you are seeking care for someone who has or may have COVID-19.

Call Ahead Before Visiting Your Doctor
- Call ahead. Many medical visits for routine care are being postponed or done by phone or telemedicine.
- If you have a medical appointment that cannot be postponed, call your doctor's office, and tell them you have or may have COVID-19. This will help the office protect themselves and other patients.

We also presented here the new section of the CDC about the Guidelines for pharmacological adjuvant treatment for COVID-19 (reviewed by CDC in May 12, 2020) [11].

Management of Persons with COVID-19
(Last updated June 11, 2020)

In general, adults with COVID-19 can be grouped into the following severity of illness categories, although the criteria in each category may overlap or vary across guidelines and clinical trials:

*This list is not all possible symptoms. Please call your medical provider for any other symptoms that are severe or concerning to you.

- Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.
- Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
- Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥94% on room air at sea level.
- Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO_2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, or lung infiltrates >50%.
- Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be used as the sole criteria to define COVID-19 illness category. Normal values for respiratory rate also vary with age in children, thus hypoxia should be the primary criteria to define severe illness, especially in younger children.

CDC Guidelines for Pharmacological Treatment of Patients

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can experience a range of clinical manifestations, from no symptoms to critical illness.

Currently, the Food and Drug Administration has not approved any drugs for the treatment of COVID-19. However, an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in several hundred clinical trials around the globe. Some drugs can be accessed through Emergency Use Authorization, expanded access programs, or compassionate use mechanisms.

Antithrombotic Therapy in Patients with COVID-19

COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers. Although the true incidence of thrombosis is unknown, there have been reports of increased incidence of thromboembolic disease associated with COVID-19 in patients in the intensive care unit.

A new section titled Antithrombotic Therapy in Patients with COVID-19 has been added to the guidelines to address many questions related to the role of coagulation markers and thrombolytic, anticoagulant, and antiplatelet agents in those with COVID-19. The COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations on the use of antithrombotic agents for the prevention of venous thromboembolic events in hospitalized patients with COVID-19. In addition, the Panel recommends carefully monitoring, evaluating, and treating hospitalized patients with COVID-19 for incident thrombotic events when indicated.

Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19

Study descriptions were updated to clearly indicate a study's publication status and to provide an assessment of a study's limitations and results. Data were also updated as needed based on changes to preprints or post-publication changes.

The following recommendations were added or revised in this section:

Remdesivir

The COVID-19 Treatment Guidelines Panel recommends the investigational antiviral

agent remdesivir for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen, as well as who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO), or not intubated receive 5 days of remdesivir. If the patients have not shown adequate improvement after 5 days of therapy, besides there are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, or patients who have not shown adequate improvement after 5 days of therapy, in these groups, some experts extend the total remdesivir treatment duration to up to 10 days.

There are insufficient data for the Panel to recommend for or against remdesivir for the treatment of patients with mild or moderate COVID-19.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors (Last updated May 12, 2020)

Rationale for Recommendation

The pharmacodynamics of HIV protease inhibitors raise concern regarding whether drug levels adequate to inhibit the SARS-CoV-2 protease can be achieved with oral dosing. Also, lopinavir/ritonavir was studied in a small randomized controlled trial in patients with COVID-19 with results that did not show efficacy.

Chloroquine or Hydroxychloroquine

The Panel recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial.

Hydroxychloroquine plus Azithromycin
(Last updated May 12, 2020)

The Panel recommends against the use of hydroxychloroquine plus azithromycin for the treatment of COVID-19, except in the context of a clinical trial.

Rationale for Recommendation

Chloroquine and hydroxychloroquine for COVID-19 have been used in small randomized trials and in some case series with conflicting study reports. The combination of hydroxychloroquine and azithromycin is associated with QTc prolongation in patients with COVID-19. Given the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the two drugs are used sequentially instead of concomitantly.

New Sections of the Guidelines

Acute Kidney Injury and Renal Replacement Therapy

The Panel recommends continuous renal replacement therapy (CRRT) in critically ill patients with COVID-19 who have acute kidney injury and who develop indications for renal replacement therapy. If CRRT is not available or not possible due to limited resources, the Panel recommends prolonged intermittent renal replacement therapy rather than intermittent hemodialysis. The primary rationale for these recommendations is to reduce the risk of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to health care workers, since there is no evidence that one modality is more beneficial than another.

Immune-Based Therapy

- There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARSCoV-2 immune globulins for the treatment of COVID-19.
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of non-SARS-CoV-2-specific intravenous immune globulin (IVIG) for the treatment of COVID-19, except in the context of a clinical trial. This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
- There are insufficient data to recommend either for or against the use of the following agents for the treatment of COVID-19:
  - Interleukin-1 inhibitors (e.g., anakinra)

  - Interleukin-6 inhibitors (e.g., sarilumab, siltuximab, tocilizumab)
- Except in the context of a clinical trial, the Panel recommends against the use of other immunomodulators, such as:
  - Interferons, because of the lack of efficacy in treatment of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) and toxicity.
  - Janus kinase inhibitors (e.g., baricitinib), because of their broad immunosuppressive effect.

Interleukin-1 Inhibitors

New clinical data from a single-center case series and a single-center retrospective cohort study that evaluated the use of anakinra to treat of COVID-19 have been added. There is no change to the Panel's recommendation for interleukin-1 inhibitors.

There are no Food and Drug Administration-approved drugs for the treatment of COVID-19. Although reports have appeared in the medical literature and the lay press have claimed that patients with COVID-19 have been successfully treated with a variety of agents, definitive clinical trial data are needed to identify safe and effective treatments for this disease. Recommended clinical management of patients with COVID-19 includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.

Interleukin-6 Inhibitors

(Last updated June 11, 2020)

Recommendation

- There are insufficient data to recommend either for or against the use of interleukin-6 (IL-6) inhibitors (e.g., sarilumab, siltuximab, tocilizumab) for the treatment of COVID-19.

IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells. Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.

Sarilumab

Sarilumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is approved by the Food and Drug Administration (FDA) for use in patients with rheumatoid arthritis. It is available as a subcutaneous (SQ) formulation and is not approved for cytokine release syndrome (CRS). A placebo-controlled clinical trial is evaluating the use of an intravenous (IV) formulation administered as a single dose for COVID-19.

The SQ formulation of sarilumab is not approved for CRS. The IV formulation is not approved by the FDA, but it is being studied in a clinical trial of hospitalized patients with COVID-19.

Siltuximab

Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and that is approved by the FDA for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6R, inhibiting IL-6 signaling. Siltuximab is dosed as an IV infusion. There are limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19. There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome.

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and CRS induced by chimeric antigen receptor T cell (CAR-T) therapy. Tocilizumab can be dosed for IV or SQ injection. For CRS, the IV formulation should be used.

Immune-Based Therapy Under Evaluation for Treatment of COVID-19

Convalescent Plasma and Immune Globulins

New information has been added to the section on convalescent plasma and SARS-CoV-2-specific immune globulins. A new section for non-SARS-CoV-2 intravenous immune globulin (IVIG) was created, in which the Panel recommends against the use of non-SARS-CoV-2-specific IVIG for the treatment of COVID-19, except in the context of a clinical trial (AIII). This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Corticosteroids

Preliminary clinical trial data from a large, randomized, open-label trial suggest that dexamethasone reduces mortality in hospitalized patients with COVID-19 who require mechanical ventilation or supplemental oxygen.

The recommendations for using corticosteroids in patients with COVID-19 depend on the severity of illness. Before initiating dexamethasone, clinicians should review the patient's medical history and assess the potential risks and benefits of administering corticosteroids to the patient.

Recommendations

- The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated.
- The Panel recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen.

It has been proposed that the anti-inflammatory effects of corticosteroids have a potential therapeutic role in suppressing cytokine-related lung injury in patients with COVID-19. Data from other respiratory infections have shown that systemic corticosteroids can affect the pathogenesis of these infections in various ways. In outbreaks of other novel coronavirus infections5 (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, corticosteroid therapy may worsen clinical outcomes, including secondary bacterial infection and mortality.

For Management of COVID-19

- The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated.
- The Panel recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen.

Usefull Links

In the section below we presented the links for interventions, protocols, guidelines and guidance for COVID-19 followed by the majority of countries – International and government guidelines for general care – as well as other usefull links.

General

World Health Organization. Coronavirus disease (COVID-19) pandemic
https://www.who.int/emergencies/diseases/novel-coronavirus-2019.

Centers for Disease Control and Prevention. United States Department of Health and Human Services. Coronavirus (COVID-19)
https://www.cdc.gov/coronavirus/2019-ncov/index.html.

Food and Drug Administration. United States Department of Health and Human Services. Coronavirus Disease 2019 (COVID-19)
https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-COVID-19.

European Centre for Disease Prevention and Control. An agency of the European Union. COVID-19
https://www.ecdc.europa.eu/en/COVID-19-pandemic.

Pandemic Preparedness
https://www.ecdc.europa.eu/en/seasonal-influenza/preparedness/why-pandemic-preparedness.
https://www.who.int/docs/default-source/coronaviruse/COVID-19-sprp-unct-guidelines.pdf.
https://www.who.int/influenza/preparedness/pandemic/WHO_Guidance_for_surveillance_during_an_influenza_pandemic_082017.pdf.

Diagnostic
https://www.finddx.org/COVID-19.
https:/ourworldindata.org/coronavirus-testing-source-data.
Epidemiological surveillance (https://wwwnc.cdc.gov/eid/article/25/1/17-1901_article)

Cochrane Database of Systematic Reviews
https://www.cochranelibrary.com.

Internacional

World Health Organization (WHO): Country and technical guidance – Coronavirus disease (COVID-19)
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications

- Surveillance protocol for SARS-CoV-2 infection among health workers
  https://www.who.int/publications-detail/WHO-2019-nCoV-HCW_Surveillance_Protocol-2020.1
- Interim guidance on clinical management of COVID-19
  https://www.who.int/publications-detail/clinical-management-of-COVID-19
- Cleaning and disinfection of environmental surfaces in the context of COVID-19
  https://www.who.int/publications-detail/cleaning-and-disinfection-of-environmental-surfaces-inthe-context-of-COVID-19
- Immunization in the context of COVID-19 pandemic
  https://www.who.int/publications/i/item/immunization-in-the-context-of-COVID-19-pandemic
- Laboratory biosafety guidance related to coronavirus disease 2019 (COVID-19)
  https://www.who.int/publications/i/item/laboratory-biosafety-guidance-related-to-coronavirus-disease-2019-(COVID-19)
- Contact tracing in the context of COVID-19
  https://www.who.int/publications/i/item/contact-tracing-in-the-context-of-COVID-19
- Community-based health care, including outreach and campaigns, in the context of the COVID-19 pandemic
  - https://www.who.int/publications/i/item/community-based-health-care-including-outreach-and-campaigns-in-the-context-of-the-COVID-19-pandemic
- Clinical care of severe acute respiratory infections – Tool kit
  https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit
- Interim guidance on the rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages
  https://www.who.int/publications/i/item/rational-use-of-personal-protective-equipment-for-coronavirus-disease-(COVID-19)-and-considerations-during-severe-shortages
- Interim guidance on advice on the use of masks in the context of COVID-19
  https://www.who.int/publications/i/item/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak
- Interim guidance on global surveillance (with case definitions) for human infection with coronavirus disease (COVID-19)
  https://www.who.int/publications/i/item/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)

- Interim guidance on infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected
  https://www.who.int/publications/i/item/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125
- Technical documentation on considerations for quarantine of individuals in the context of containment for coronavirus disease (COVID-19)
  https://www.who.int/publications/i/item/considerations-for-quarantine-of-individuals-in-the-context-of-containment-for-coronavirus-disease-(COVID-19)
- Interim guidance on laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases
  https://www.who.int/publications/i/item/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117
- Interim guidance on risk assessment and management of exposure of health care workers in the context of COVID-19
  https://www.who.int/publications/i/item/risk-assessment-and-management-of-exposure-of-health-care-workers-in-the-context-of-COVID-19-interim-guidance
- Interim guidance on home care for patients with COVID-19 presenting with mild symptoms and management of their contacts
  https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts
- Protocol for assessment of potential risk factors for 2019-novel coronavirus (2019-nCoV) infection among health care workers in a health care setting
  https://www.who.int/publications/i/item/protocol-for-assessment-of-potential-risk-factors-for-2019-novel-coronavirus-(2019-ncov)-infection-among-health-care-workers-in-a-health-care-setting
- Coronavirus disease (COVID-19) travel advice
  https://www.who.int/emergencies/diseases/novel-coronavirus-2019/travel-advice

United States

Centers for Disease Control and Prevention (CDC): Coronavirus (COVID-19)
https://www.cdc.gov/coronavirus/2019-ncov/index.html

- Information for healthcare professionals about coronavirus (COVID-19)
  https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html
  - o Evaluating and testing persons for coronavirus disease 2019 (COVID-19)
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fclinical-criteria.html
  - o Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19)
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
  - o Information for clinicians on investigational therapeutics for patients with COVID-19
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html
  - o Discontinuation of isolation for persons with COVID-19 not in healthcare settings (interim guidance)
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html
  - o Interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home care.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fguidance-home-care.html
  - o Discontinuation of transmission-based precautions and disposition of patients with COVID-19 in healthcare settings (interim guidance)
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html
  - o Interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html
  - o Using personal protective equipment (PPE)
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/using-ppe.html

- Hand hygiene recommendations – Guidance for healthcare providers about hand hygiene and COVID-19
  https://www.cdc.gov/coronavirus/2019-ncov/hcp/hand-hygiene.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Finfection-control%2Fhcp-hand-sanitizer.html
- Outpatient and ambulatory care settings – Responding to community transmission of COVID-19 in the United States
  https://www.cdc.gov/coronavirus/2019-ncov/hcp/ambulatory-care-settings.html
- Preparing for COVID-19 – Long-term care facilities, nursing homes
  https://www.cdc.gov/coronavirus/2019-ncov/hcp/long-term-care.html
- Strategies to optimize the supply of PPE and equipment
  https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html
- Interim US guidance for risk assessment and public health management of healthcare personnel with potential exposure in a healthcare setting to patients with coronavirus disease 2019 (COVID-19)
  https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html
- Criteria for return to work for healthcare personnel with confirmed or suspected COVID-19 (interim guidance)
  https://www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work.html
- Preparedness tools for healthcare professionals and facilities responding to coronavirus (COVID-19)
  https://www.cdc.gov/coronavirus/2019-ncov/hcp/preparedness-checklists.html

- Healthcare facilities – Preparing for community transmission
  https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-hcf.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhealthcare-facilities%2Fguidance-hcf.html
  - Prepare your practice for COVID-19
    https://www.cdc.gov/coronavirus/2019-ncov/hcp/preparedness-resources.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhealthcare-facilities%2Fpractice-preparedness.html

- Health departments
  https://www.cdc.gov/coronavirus/2019-ncov/php/index.html
  - Contact tracing
    https://www.cdc.gov/coronavirus/2019-ncov/php/open-america/contact-tracing-resources.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fphp%2Fopen-america%2Fcontact-tracing.html
  - Public health guidance for potential COVID-19 exposure associated with international travel or cruise travel
    https://www.cdc.gov/coronavirus/2019-ncov/php/risk-assessment.html
  - Public health recommendations for community-related exposure
    https://www.cdc.gov/coronavirus/2019-ncov/php/public-health-recommendations.html
  - Interim guidance for public health professionals managing people with COVID-19 in home care and isolation who have pets or other animals
    https://www.cdc.gov/coronavirus/2019-ncov/animals/interim-guidance-managing-people-in-home-care-and-isolation-who-have-pets.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fphp%2Finterim-guidance-managing-people-in-home-care-and-isolation-who-have-pets.html

- Information for laboratories about coronavirus (COVID-19)
  https://www.cdc.gov/coronavirus/2019-nCoV/lab/index.html
  - Interim guidelines for COVID-19 antibody testing
    https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
  - Interim guidelines for collecting, handling, and testing clinical specimens from persons for COVID-19
    https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html

  - o Interim laboratory biosafety guidelines for handling and processing specimens associated with coronavirus disease 2019 (COVID-19)
    https://www.cdc.gov/coronavirus/2019-nCoV/lab/lab-biosafety-guidelines.html

- Communities, schools, workplaces, and events
  https://www.cdc.gov/coronavirus/2019-ncov/community/index.html
  - o Interim guidance for general population disaster shelters during the COVID-19 pandemic
    https://www.cdc.gov/coronavirus/2019-ncov/downloads/Guidance-for-Gen-Pop-Disaster-Shelters-a-Pandemic_cleared_JIC_ADS_final.pdf
  - o Interim guidance on implementing safety practices for critical infrastructure workers who may have had exposure to a person with suspected or confirmed COVID-19 – Interim guidance
    https://www.cdc.gov/coronavirus/2019-ncov/community/critical-workers/implementing-safety-practices.html
  - o Cleaning and disinfecting your facility
    https://www.cdc.gov/coronavirus/2019-ncov/community/disinfecting-building-facility.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019ncov%2Fprepare%2Fdisinfecting-building-facility.
  - o Resources to support people experiencing homelessness
    https://www.cdc.gov/coronavirus/2019-ncov/community/homeless-shelters/index.html
  - o Interim guidance on management of coronavirus disease 2019 (COVID-19) in correctional and detention facilities
    https://www.cdc.gov/coronavirus/2019-ncov/community/correction-detention/guidance-correctional-detention.html

- Travel
  https://www.cdc.gov/coronavirus/2019-ncov/travelers/index.html

Centers for Medicare and Medicaid Services (CMS): Coronavirus – Clinical and technical guidance
https://www.cms.gov/About-CMS/Agency-Information/Emergency/EPRO/Current-Emergencies/Current

National Institutes of Health (NIH): Coronavirus disease 2019 (COVID-19) treatment guidelines
https://www.covid19treatmentguidelines.nih.gov/

- Overview and spectrum of COVID-19
  https://www.covid19treatmentguidelines.nih.gov/overview/
- Care of critically ill patients with COVID-19
  https://www.covid19treatmentguidelines.nih.gov/critical-care/
- Potential antiviral drugs under evaluation for the treatment of COVID-19
  https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/
- Immune-based therapy under evaluation for treatment of COVID-19
  https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/
- Antithrombotic therapy in patients with COVID-19
  https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/
- Considerations for certain concomitant medications in patients with COVID-19
  https://www.covid19treatmentguidelines.nih.gov/concomitant-medications/

US Food and Drug Administration (FDA): Coronavirus disease 2019 (COVID-19)
https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-COVID-19.

Europe

European Centre for Disease Prevention and Control (ECDC): COVID-19
https://www.ecdc.europa.eu/en/COVID-19-pandemic

- Risk assessment on COVID-19
  https://www.ecdc.europa.eu/en/current-risk-assessment-novel-coronavirus-situation
- Preparedness for COVID-19
  https://www.ecdc.europa.eu/en/COVID-19/preparedness-and-response
  - o Infection prevention and control for COVID-19 in healthcare settings
    https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-COVID-19-healthcare-settings

- o Guidance for health system contingency planning during widespread transmission of SARS-CoV-2 with high impact on healthcare services
  https://www.ecdc.europa.eu/en/publications-data/guidance-health-system-contingency-planning-during-widespread-transmission-sars
- o Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19
  https://www.ecdc.europa.eu/en/publications-data/COVID-19-guidance-discharge-and-ending-isolation
- o Guidelines for the use of non-pharmaceutical measures to delay and mitigate the impact of 2019-nCoV
  https://www.ecdc.europa.eu/en/publications-data/guidelines-use-non-pharmaceutical-measures-delay-and-mitigate-impact-2019-ncov
- o Personal protective equipment (PPE) needs in healthcare settings for the care of patients with suspected or confirmed novel coronavirus (2019-nCoV)
  https://www.ecdc.europa.eu/en/publications-data/personal-protective-equipment-ppe-needs-healthcare-settings-care-patients

- EU level surveillance of COVID19
  https://www.ecdc.europa.eu/en/COVID-19/surveillance
  - o Case definition and European surveillance for COVID-19
    https://www.ecdc.europa.eu/en/COVID-19/surveillance/case-definition
- Laboratory support for COVID-19 in the EU/EEA
  https://www.ecdc.europa.eu/en/novel-coronavirus/laboratory-support
  - o Contact tracing – Public health management of persons, including healthcare workers, having had contact with COVID-19 cases in the European Union
    https://www.ecdc.europa.eu/en/COVID-19-contact-tracing-public-health-management
  - o Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19
    https://www.ecdc.europa.eu/en/publications-data/guidance-wearing-and-removing-personal-protective-equipment-healthcare-settings
  - o Disinfection of environments in healthcare and non-healthcare settings potentially contaminated with SARS-CoV-2
    https://www.ecdc.europa.eu/en/publications-data/disinfection-environments-COVID-19
  - o Using face masks in the community – Reducing COVID-19 transmission from potentially asymptomatic or pre-symptomatic people through the use of face masks
    https://www.ecdc.europa.eu/en/publications-data/using-face-masks-community-reducing-COVID-19-transmission

World Health Organization (WHO) Europe: Interim guidance on preparedness, prevention and control of COVID-19 in prisons and other places of detention
http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-COVID-19/technical-guidance/2020/preparedness,-prevention-and-control-of-COVID-19-in-prisons-and-other-places-of-detention,-15-march-2020

Brasil

Ministério da Saúde do Brasil. Protocolo de Manejo Clínico do Corona Vírus (COVID-19) na Atenção Primária à Saúde (8ª versão)
http://189.28.128.100/dab/docs/portaldab/documentos/20200422_ProtocoloManejo_ver08.pdf.

Ministério da Saúde. Diretrizespara Diagnóstico e Tratamento da COVID-19 (4ª versão)
https://portalarquivos.saude.gov.br/images/pdf/2020/May/08/Diretriz-Covid19-v4-07-05.20h05m.pdf.

Anvisa
https://www20.anvisa.gov.br/segurancadopaciente/index.php/alertas/category/COVID-19

Discussion

Despite the presentation of the main international protocols and guidelines of referred Centers and

Organizations, concerning the adjuvante treatment of mild and severe patients, Xu and colleagues [12] presented seven clinical guidelines on the management of COVID-19 pneumonia (mild, severe and crtical) by international or national professional:

1. WHO: Interim guidance on clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. World Health Organization. Clinical management of severe acute respiratory infection when COVID-19 is suspected 2020 [13];
2. Infectious Diseases Society of America (IDSA): Guidelines on the treatment and management of patients with COVID-19 [14];
3. Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with COVID-19 [15];
4. People's Republic of China's National Health Commission (NHC): Guidelines on the treatment of COVID-19 (7th edition) [16];
5. The Lombardy Section of the Italian Society of Infectious and Tropical Diseases (Società Italiana di Malattie Infettive e Tropicali) (SIMIT Lombardy Section): Vademecum for the treatment of people with COVID-19. Edition 2.0, 13 March 2020 [17];
6. The Netherlands' Working Party on Antibiotic Policy (Stichting Werkgroep Antibiotica Beleid) (SWAB): Drug treatment options in patients with COVID-19 [18];
7. Belgium's Sciensano (scientific institute of public health): Interim clinical guidance for adults with suspected or confirmed COVID-19 in Belgium [19].

As there is no general consensus on the clinical classification of COVID-19 and each guideline tends to use its own defined clinical categories of COVID-19, the authors [12] compared each other and classified the categories across the several guidelines into "mild", "pneumonia", "severe" and "critical" groups according to case definitions put forth by the WHO [20], which led the classification "moderately severe" group to re-categorized to "severe" category to match WHO's case definition, as we defined. So, the guidelines from the countries on the use of adjunctive treatments could then be compared based on fairly similar descriptions of clinical severity [12].

Conclusion

The COVID-19 pandemic is spreading fast and new informations about the disease comes up everyday so that the guidelines and protocols change all the time. However, all these guidelines or guidance as well as protocols can be easily find in the links we pointed in this paper pretending to facilitate the search of these importante informations. So, it doesn't matter if what we wrote here tomorrow will be outdated, because the links will address the reader to the novel status of the guidelines. And the rapid and effective enforcement of existing international and national action plans, as well as parallel review and improvisation, is facilitating the affected countries to contain transmission and possibly delay the peak of outbreak and mortality. Also, all guidelines and protocols tend to use WHO as a reference with particular differences between countries. However, the more the COVID-19 is known, the more the protocols and guidelines change. Although the global economy is suffering with the pandemic, it is important to review the current action plans and suitably improvise the future action plans to mitigate the disease and avoid potential recurrences.

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