E-ISSN: 2791-8823

CSMJ

THE JOURNAL OF BAŞAKŞEHİR ÇAM AND SAKURA CITY HOSPITAL

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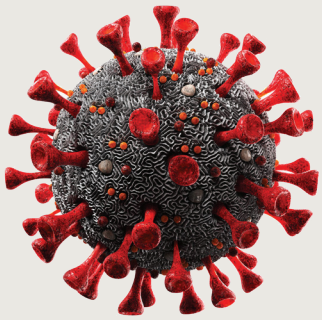

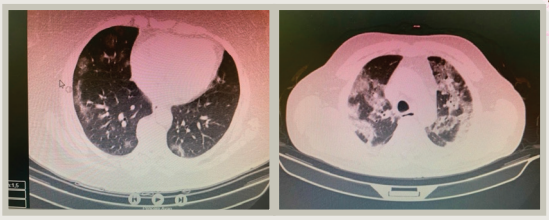

Figure 2. Ground-glass opacification with or without consolidative abnormalities

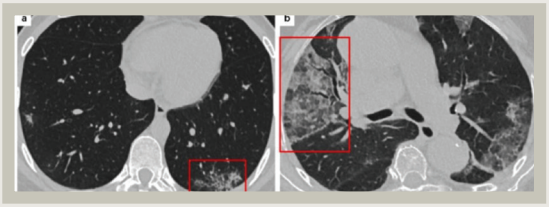

Figure 3. a) Reticular pattern in the left lower lobe and subpleural area (red frame). b) Reticular pattern superimposed on the background of GGO, resembling the sign of crazy paving stones (red frame) (9)
GGO: Ground-glass opacity

ÇAM & SAKURA MEDICAL JOURNAL

December
2022 Volume: 2 Issue: Suppl-1

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Volume: 2 • **Issue:** Suppl 1 • December **2022**

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Printing at: Son Sürat Daktilo Dijital Baskı Merkezi Sanayi ve Ticaret Ltd. Şti.
Gayrettepe Mahallesi, Yıldızposta Caddesi, Evren Sitesi A Blok No: 32
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Printing Date: December 2022

E-ISSN: 2791-8823
International scientific journal published quarterly.

CSMJ

Volume: 2 • Issue: Suppl 1 • December 2022

Editorial Board

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Journal History

Cam ve Sakura Medical Journal (CSMJ) is an international, scientific, open access periodical published journal. It has independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Basaksehir Cam & Sakura City Hospital. It is published three times per year (April, August, December). A special supplement including interesting, novel and attractive theme has also been published every year. The publication language of the journal is English.

Title: Cam ve Sakura Medical Journal

Official abbreviation: CSMJ, Csmedj

E-ISSN: 2791-8823

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Aims and Scope

Cam ve Sakura Medical Journal (CSMJ) is an international, scientific, open access periodical published journal. It has independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Basaksehir Cam & Sakura City Hospital. It is published three times per year (April, August, December). A special supplement including interesting, novel and attractive theme has also been published every year. The publication language of the journal is English.

Cam & Sakura Medical Journal publishes original experimental or clinical research, review articles, case reports, technical reports, diagnostic puzzle, clinical images, video article, novel insight, and letters to the editor in the field of general medicine. Review articles will be only prepared by expert academicians upon invitation. The journal's target audience includes academics and expert physicians working in all fields of general medicine.

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Title: Cam ve Sakura Medical Journal

Official abbreviation: CSMJ, Csmedj

E-ISSN: 2791-8823

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Peer Review, Publication Ethics and Malpractice Statement

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Editorial policies of the journal are conducted as stated in the rules recommended by the Council of Science Editors and reflected in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. Accordingly, authors, reviewers, and editors are expected to adhere to the best practice guidelines on ethical behavior contained in this statement.

Submitted manuscripts are subjected to double-blinded peer-review. The scientific board guiding the selection of the papers to be published in the journal consists of elected specialists of the journal and, if necessary, selected from national and international experts in the relevant field of research. All manuscripts are reviewed by the editor, section associate editors and at least three internal and external expert reviewers. All research articles are interpreted by a statistical editor as well.

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For the experimental, clinical and drug human studies, approval by ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the Cam ve Sakura Medical Journal (CSMJ) together with the manuscript.

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Peer Review, Publication Ethics and Malpractice Statement

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Peer Review, Publication Ethics and Malpractice Statement

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The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

Manuscripts are accepted only online and can be submitted electronically through web site (http://csmedj.org) after creating an account. This system allows online submission and review. The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org. The manuscripts gathered with this system are archived according to ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules. Rejected manuscripts, except artworks, are not returned.

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b. Abstract

The abstract should summarize the manuscript and should not exceed 300 words. The abstract of the original articles consists of subheadings including "Objective, Methods, Results, and Conclusion". Separate abstract sections are not used in the submission of the review articles, case reports, technical reports, diagnostic puzzles, clinical images, and novel articles. The use of abbreviations should be avoided. Any abbreviations used must be taken into consideration independently of the abbreviations used in the text.

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Instructions to Authors

c. Keywords

A list of minimum 4, but no more than 6 keywords must follow the abstract. Keywords in English should be consistent with "Medical Subject Headings (MESH)".

d. Original Article

The instructions in general guidelines should be followed. The main headings of the text should include "Introduction, Material and Methods, Results, Discussion, Study Limitations and Conclusion". The introduction should include the rationale and the background of the study. The results of the study should not be discussed in this part. "Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated. Results should also be given in detail to allow the reproduction of the study. The Discussion section should provide a correct and thorough interpretation of the results with the relevant literature. The results should not be repeated in the Discussion Part. The references should be directly related to the findings of the authors. Study Limitation should be detailed in the section. The conclusion section should be highlighted and interpreted with the study's new and important findings.

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

Original Articles should be no longer than 3500 words and include no more than 6 tables and 7 or a total of 15 figures and 40 references. The abstract word limit must be 250.

Introduction

The article should begin with a brief introduction stating why the study was undertaken within the context of previous reports.

Materials and Methods

These should be described and referenced in sufficient detail for other investigators to repeat the work. Ethical consent should be included, as stated above.
The name of the ethical committee, approval number should be stated. At the same time, the Ethics Committee Approval Form should be uploaded with the article.

Results

The Results section should briefly present the experimental data in text, tables, and/or figures. Do not compare your observations with that of others in the results section.

Discussion

The Discussion should focus on the interpretation and significance of the findings with concise and objective comments that describe their relation to other work in that area and contain study limitations.

Study Limitations

Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion

The conclusion of the study should be highlighted.

e. References

The reference list should be typed on a separate page at the end of the manuscript. Both in-text citations and references must be prepared according to the Vancouver style. Accuracy of reference data is the author's responsibility. While citing publications, preference should be given to the latest, most up-to-date references. The DOI number should be provided for citation of ahead-of-print publication, Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. All authors should be listed in the presence of six or fewer authors. If there are seven or more authors, the first three authors should be listed, followed by "et al." References should be cited in text, tables, and figures should be cited as open source („„4) in parenthesis numbers in parentheses. References should be numbered consecutively according to the order in which they first appear in the text. The reference styles for different types of publications are presented as follows:

i) Standard Journal Article

Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 2015;313:2340-2348.8.

ii) Book

Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

iii) Chapter of a Book

Volpe JJ: Intracranial hemorrhage; in Volpe JJ (ed): Neurology of the Newborn, ed 5. Philadelphia, Saunders, 2008, pp 481-588.

Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-380.

If more than one editor: editors.

iv) Conference Papers: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10;Geneva, Switzerland: North-Holland; 1992. p. 1561-1565.

v) Journal on the Internet: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

vi) Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

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f. Tables, Graphics, Figures, Pictures, Video:

All tables, graphics or figures should be numbered consecutively according to their place in the text and a brief descriptive caption should be given. Abbreviations used should be explained further in the figure's legend. The text of tables especially should be easily understandable and should not repeat the data of the main text. Illustrations already published are acceptable if supplied by permission of the authors for publication. Figures should be done professionally, and no grey colors should be used. Authors are responsible for obtaining permission to publish any figures or illustrations that are protected by copyright, including figures published elsewhere and pictures taken by professional photographers. The journal cannot publish images downloaded from the Internet without appropriate permission.
Figures or illustrations should be uploaded separately.

Special Sections

Reviews

Reviews will be prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors and subjects will be invited by the journal. All reviews within the scope of the journal will be taken into consideration by the editors; also, the editors may solicit a review related to the scope of the journal from any specialist and experienced authority in the field.

The entire text should not exceed 25 pages (A4, formatted as specified above).

Reviews should be no longer than 5000 words and include no more than 6 tables and 10 or a total of 20 figures and 80 references. The abstract word limit must be 250.

Case Reports

Case reports should present important and rare clinical experiences. It must provide novel and/or rare clinical data or new insights to the literature. Case reports should consist of an unstructured abstract (maximum 150 words) that summarizes the case. They should consist of the following parts: introduction, case report, discussion. Informed consent or signed releases from the patient or legal representative should be obtained and stated in the manuscript.
Reviews should be no longer than 1000 words and include no more than 200 tables and 10 or a total of 20 figures and 15 references. The abstract word limit must be 150.

Clinical Images

The journal publishes original, interesting, and high quality clinical images having a brief explanation (maximum 500 words excluding references but including figure legends) and of educational significance. It can be signed by no more than 5 authors and can have no more than 5 references and 1 figure or table. Any information that might identify the patient or hospital, including the date, should be removed from the image. An abstract is not required with this type of manuscripts. The main text of clinical images should be structured with the following subheadings: Case, and References.

Video Article

Video articles should include a brief introduction on case, surgery technique or a content of the video material. The main text should not exceed 500 words. References are welcomed and should not be more than 5. Along with the main document, video material and 3 images should be uploaded during submission. Video format must be mp4 and its size should not exceed 100 MB and be up to 10 minutes. Author should select 3 images, as highlights of the video, and provide them with appropriate explanations. Video and images must be cited within main text.

Technical reports

Technical reports are formal reports designed to convey technical information in a clear and easily accessible format. A technical report should describe the process, progress, or results of technical or scientific research or the state of a technical or scientific research problem. It might also include recommendations and conclusions of the research. Technical reports must include the following sections: abstract, introduction, technical report, discussion, conclusions, references. Technical reports should contain less than 20 references.

Diagnostic puzzle

Diagnostic puzzles report unusual cases that make an educational point. Since the aim of these articles is to stimulate the reader to think about the case, the title should be ambiguous and not give away the final diagnosis immediately. Diagnostic puzzles should include an introduction and answer part. The introduction part should include a brief clinical introduction to a case (maximum 250 words) followed by an image and a question designed to stimulate the reader to think about what the image shows. The legend should not indicate the diagnosis but should simply describe the nature of the image. Then, the answer part should appear later (maximum 250 words) outlines a brief description of the key diagnostic features of the image, the outcome, and a teaching point.
Diagnostic puzzles will not include more than 5 references. The quality of the image must be at least 300dpi and in TIFF, JPEG, GIF or EPS format. Videos are also welcome and should be in .mov, .avi, or .mpeg format.

Novel insight

This section will offer an opportunity for articles instead of the traditional category of Case Reports. Submissions to this section should contribute significant new insights into syndromological problems, molecular approach and real novelties on recognized or entirely new genetic syndromes or a new technique. The novel aspect(s) can be in the phenotype and/or genotype, the presentation, and the investigation. Submissions can be based around a single case or serial cases. Manuscripts for this section will go through the usual peer reviewing process. The manuscripts should contain abstract (maximum 150 words), a brief introduction, case report(s) and discussion.

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Instructions to Authors

Letters to the Editor

This section welcomes manuscripts that discuss important parts, overlooked aspects, or lacking parts of a previously published article in this journal. In addition, articles on subjects within the scope of the journal that might have an attraction including educative cases, may also be submitted in the form of a "Letter to the Editor." The manuscripts for this section should be written in an unstructured text including references. The editor may request responses to the letters. There are no separate sections in the text.

Letter to the editors should be no longer than 500 words.

Revision Process

During the submission of the revised version of a manuscript, the authors should submit a detailed "Response to the reviewers and editors" that states point by point how each issue raised by the reviewers and/or editors has been replied to and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts should be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue.

LIMITATION TABLE

Type of Manuscript	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review	5000	250	60	6	10 or total of 20 images
Case Report	1000	150	20	200	10 or total of 20 images
Letter to the Editor	500	No Abstract		No tables	No media
Video Article	500		5		
Diagnostic Puzzle	250 (as a brief clinical introduction		5		
Clinical Images	500 (as a brief explanation)		5	1	1
Technical Reports			20		

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Letter From The Chief Physcian

Dear Colleagues,

It is my great pleasure to be with you on the special issue of CSMJ of 2022 that has just been published. It has passed approximately 3 years as we met with the first cases and then pandemics of COVID-19. After the pandemics, there were lots of publications about COVID-19, especially in alla ge groups. However, as the time passed and vaccines were developed, although COVID-19 infections continued, we all had enough knowledge and data for both prevention and treatment of this coronavirus infection. Therefore, we aimed to establish the most updated data about COVID-19 infection and to discuss this topic from all aspects. As you will see in this issue, the authors of the reviews mentioned about epidemiology, pathophysiology, risk factors, clinical and radiological findings, diagnostic and therapeutic approaches and vaccination about Covid-19 infection. In this issue, you will also read about the COVID-19 infection in different specific populations. I think thses articles will provide several important and updated insights for all readers.

For this issue, I want to thank Merih Çetinkaya, Chief Editor of CSMJ, Özlem Altuntaş Aydın, Special Issue Editor, and all authors who contributed to this special issue with their articles. We will continue to discuss different important and up to date topics in special issues of CSMJ in future. I also want to thank all readers and authors for their support of CSMJ as we have been in four indexes and we believe to be indexed in more in the next months with all your kind help.

I wish you all a happy new year and want to meet you in the other issues of CSMJ in 2023.

Nurettin Yiyit

Chief Coordinator Physcian
Cam & Sakura City Hospital

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Special Issue Editor

Dear Colleagues,

The first cases of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) were reported from China on the last day of December 2019, and the disease it caused was named coronavirus disease-2019 (COVID-19). The epidemic all over the world was declared as a pandemic by the World Health Organization in March 2020 and spread rapidly, causing a high rate of morbidity and mortality. Subsequently, many agents for treatment and prevention were tried and their use was quickly approved by the health authorities. Much research has been done in the fields of basic and clinical medicine. There has been a constant and intense flow of information into the medical literature in a way that has never been seen before.

As we leave behind three years of pandemic, we have prepared the CSMJ special issue, which includes the current information we have learned about COVID-19. In this special issue, you can find up-to-date information on the structure of the causative agent of COVID-19, epidemiology, pathogenesis, diagnostic methods and clinical pictures of COVID-19 prepared by our professors, each of whom is an expert on their subject. In the emergence of CSMJ special issue, I would like to thank Prof. Dr. Merih Çankaya, the chief editor of CSMJ and Prof. Dr. Nurettin Yiyit, the head physician for their kind invitation, to all our esteemed professors and experts for their time and support for each department, and also to the valuable team of CSMJ for their contributions.

We are pleased to present this issue to you, our esteemed readers, hoping that it will contribute to your clinical practice. Wishing you a happy new year, we are waiting your articles for the future issues.

Kind regards,

Prof. Dr. Özlem Altuntaş Aydın

Special Issue Editor

DOI: 10.4274/csmedj.galenos.2022.2022-11-1

Cam and Sakura Med J 2022;2(Suppl 1):1-5

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COVID-19: Epidemiology, Virology, Transmission, and Prevention

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ABSTRACT

Coronavirus disease-2019 (COVID-19) is a major global human threat caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Following the first pneumonia case in China in December 2019, humanity faced a dreadful infection in a short period when the World Health Organization declared a pandemic on March 11, 2020. This review aims to look at the epidemiology of COVID-19, the virological characteristics of SARS-CoV-2, and the methods of transmission and prevention.

Keywords: COVID-19, SARS-CoV-2, pandemic, infectious disease and microbiology

Introduction

Epidemiology

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is a coronavirus strain that causes severe and potentially fatal respiratory symptoms (1). In March 2020, the World Health Organization (WHO) declared coronavirus disease-2019 (COVID-19) as the first coronavirus-initiated pandemic. Since then, Turkey has reported approximately 16 million total cases and 101.000 deaths. The WHO has received reports of nearly 620 million confirmed cases of COVID-19, including 6 million deaths (2).

SARS-CoV-2 infection can result in five outcomes (3):

· Asymptomatic infection

· Mild-to-moderate cases

· Severe cases

· Critical cases

· Death

The typical symptoms, such as fever, dry cough, myalgia, fatigue, dyspnea, normal/decreased leukocyte/lymphocyte counts, and radiographic evidence, can vary depending on the severity of the disease (4). The global case fatality rate has been reported to be around 1.2% late. Individuals with underlying medical conditions have a higher mortality rate. Hypertension, obesity, diabetes, cardiovascular disease, and kidney disease are all considered to be risk factors for death. Mortality rises from 0.9% in healthy people to 6% in hypertensive patients, 7.3% in diabetics, and 10.5% in people with cardiovascular diseases (5,6).

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Received: 01.11.2022 **Accepted:** 12.11.2022

CAM & SAKURA MEDICAL JOURNAL

Virology

SARS-CoV-2 is a member of the family *Coronaviridae*, subfamily *Orthocoronavirinae*.

Coronaviruses are positive-stranded RNA viruses with an envelope that primarily infect the respiratory system (7). SARS-CoV-2 is a beta-coronavirus in the same subgenus, according to full-genome sequencing and phylogenic analysis. SARS-CoV-2 has a zoonotic origin, beginning in bats and spreading to other species before reaching humans (8).

Structure proteins include spike, membrane, envelope and nucleocapsid proteins. The virion's nucleocapsid is composed of genomic RNA and phosphorylated nucleocapsid (N) protein, which is buried within phospholipid bilayers and protected by the spike glycoprotein trimmer (S). Among the S proteins, the membrane (M) protein hemaglutinin-esterase (HE) and the envelope (E) protein are located. (9). These proteins, which are required for the assembly of new viral particles, are encoded by one-third of the viral genome (10,11,12).

SARS-CoV-2 interacts with the angiotensin-converting enzyme-2 (ACE-2) binding site on host cells, which is abundant in the heart, lungs, kidney, and gastrointestinal tract. When the SARS-CoV-2 "S protein" binds to ACE-2 receptors, the infection is activated and clinical symptoms develop based on the location of the entry receptor in organs (1,13,14,15,16). The high affinity of SARS-CoV-2 for ACE-2 receptors explains its efficient spread and transmission from person to person that has been reported thus far. Men and individuals with diabetes mellitus or cardiovascular disease who may have higher levels of circulating ACE-2 had higher hospitalization and mortality rates (15,17).

The rapid spread of the SARS-CoV-2 (D614G variant), suggested that virus adaptation could occur between March and May 2020 (18). SARS-CoV-2 variants currently include (19,20):

· Alpha (B.1.1.7) variant

· Beta (B.1.351) variant

· Gamma (P.1) variant

· Delta (B.1.617.2) variant

· Omicron (B.1.1.529) variant

A new strain of the virus, VUI 202012/01 or B.1.1.7 (WHO Alpha variant), was discovered in the United Kingdom (UK) in September 2020. It is distinguished by multiple S-protein mutations as well as mutations in other regions of the genome. A mutation (N501Y) affects the cell receptor's binding site. The Alpha variant differs from the Wuhan strain by 29 nucleotides (21). Soon after the Alpha lineage emerged, different viral lineage, B.1.617.2 (Delta variant), swept through India and became dominant globally (22). The Delta variant was 40%-60% more transmissible than the B.1.1.7 Alpha variant, and the risk of hospitalization was higher in unvaccinated individuals (23).

A rise in the number of COVID-19 cases with *S* gene target failure (SGTF) was observed in South Africa in November 2021. The WHO identified this variant as one of concerns, naming it the B.1.1.529 Omicron variant, based on its mutational profile and extremely rapid spread. In December 2021, this variety spread quickly over the globe, leading to a record-high number of confirmed illnesses (24). Dominant sublineages of the Omicron variant were defined as BA.1, BA.2, BA.3, BA,4, and BA.5. These sublineages have been linked to local increases in SARS-CoV-2 infections.

BA.4 and BA.5 were found in South Africa and were predicted to have a replication advantage over BA.2, equivalent to BA.2's advantage over BA.1, based on an examination of the shifting predominance of Omicron sublineages (25). In the UK, where both sublineages are becoming more prevalent, the research found that BA.5 has a bigger projected replication advantage than BA.4 does (26).

Transmission

SARS-CoV-2 is primarily spread through airborne infectious particles and droplets from infected individuals to close contacts (27,28,29,30). The potential for SARS-CoV-2 transmission begins before symptoms and is highest early during COVID-19. Evidence suggests that each primary infected person causes two to three secondary infectious cases on average (6).

SARS-CoV-2 has three distinct transmission routes (31):

1. Directly from one infected individual to another, or indirectly via an intermediate contaminated object,

2. Droplet sprays transmission from person to person,

3. Transmission of aerosolized particles from person to person via the air.

SARS-CoV-2 in aerosols is viable for 3 h (32) and could land in other people's mucus membranes or on surfaces, causing cross-contamination. Potential transmission routes include also environmental cross-contamination and fecal shedding (33,34). The virus appears less stable on copper and cardboard surfaces than on plastic and stainless-steel surfaces, where it was detectable up to 72 h later (33,35,36).

Three to six days following the onset of symptoms is when viral RNA reaches its peak and there is the greatest chance that an infectious virus will be released (37). The median duration

of infectious Omicron virus detection in nasal specimens ranged from three to five days after diagnosis. Transmission after ten days following the onset of symptoms is considered unlikely with it (38,39).

In Taiwan, a study of over 2500 close contacts of 100 patients with COVID-19 found that all 22 secondary cases had their first exposure to the index case within six days of symptom onset. After this period, no infections were diagnosed in the 850 contacts who were exposed (40).

Prevention

The Centers for Disease Control and Prevention took the lead in developing infection prevention and control guidelines for both US and non-US healthcare settings as soon as SARS-CoV-2 had spread and the pandemic had been declared (31). The herd immunity theory and the presumption that virus exposure produced long-term immunity had been the basis of both pandemic control and national measures (41).

Lockdown, social distancing measures, and eventually, the use of face masks were among the non-pharmaceutical interventions (NPIs). The adoption of NPIs during the first wave of the pandemic flattened the curve, extending the period during which cases occurred (42). As a personal preventive measure, the following general measures are recommended to prevent infection:

1. Hand washing and respiratory hygiene: If the hands are not visibly dirty, using a hand sanitizer containing at least 60% alcohol is suggested as an alternative to hand washing (43).

2. Adequate ventilation of indoor spaces: By opening windows/doors, continuously running air conditioning fans, and using portable high-efficiency particulate air filtration systems (44,45).

3. Avoiding close contact with COVID-19 infected individuals: If community transmission levels are high, avoiding crowds and close contact with other people outside the household is also recommended to reduce the risk of exposure (46).

4. Wearing a mask: As part of a comprehensive strategy to reduce SARS-CoV-2 transmission in either outdoor or indoor settings with poor ventilation (47).

Although NPIs reduced viral spread at the population level, infection risk was not reduced equally across populations. In April and May 2020, healthcare and frontline workers were at a particularly high risk of infection (48). During a pandemic, a population's immunity to natural infection improved over time. Initial expectations for SARS-CoV-2 were that population immunity in regions with significant first waves would significantly lower future transmission (49).

Many countries around the world considered the administration of COVID-19 vaccines a top priority (50). mRNA vaccines are associated with a lower viral load and a shorter duration of illness before Delta transmission (51,52). mRNA vaccines from Pfizer/BioNTech (BNT162b2) and Moderna (CX-024414) have been critical in launching mass vaccination campaigns in the USA and around the world. Both vaccines generated higher titers of anti-SARS-CoV-2 spike (protein-specific) antibodies capable of neutralizing the original circulating SARS-CoV-2 strains as well as subsequent vaccine design variations. Antibodies produced by mRNA vaccines in animal models and humans appear effective in protection from COVID-19. Laboratory tests on PfizerBioNTech vaccines showed that three doses provide a high level of protection against the Omicron variant. Only the booster dose can increase neutralizing antibody titers by a factor of 25 compared with the other two doses (53,54).

A study from Singapore showed that BNT162b2 vaccination was associated with a faster decrease in viral loads among those vaccinated (55). Ad26.COV2.S (Janssen Vaccine) and BNT162b2 were associated with a lower probability of viral culture positivity; this suggests that vaccinated people are shedding less contagious Delta virus (56). Before the spread of Delta, a study in England found that BNT162b2 or AZD1222 (The Oxford-AstraZeneca Vaccine) reduced transmission in a household setting (57).

In conclusion, the most successful strategies for decreasing transmission remain to be the vaccine programs and tests, as well as tracking and isolating the system (58).

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.İ., S.T., Concept: P.İ., S.T., Design: P.İ., S.T., Data Collection or Processing: P.İ., S.T., Analysis or Interpretation: S.T., Literature Search: P.İ., S.T., Writing: P.İ., S.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/csmedj.galenos.2022.2022-11-7
Cam and Sakura Med J 2022;2(Suppl 1):6-13

CSMJ

COVID-19 Pathogenesis and Diagnosis

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ABSTRACT

The end of 2019 marked the beginning of a pandemic that shook of the whole world. This newly emerged viral agent was quickly identified with the help of molecular techniques and classified as a novel coronavirus severe acute respiratory syndrome-coronavirus-2. In the first part of this article, the general virological features and pathogenesis of this viral agent, which caused many deaths at the beginning and changed in the pathogenesis with different variants over time, were discussed. In the second part of the article, information is given about the diagnostic tests applied in pandemic conditions.

Keywords: COVID-19, SARS-CoV-2, pathogenesis, molecular tests, serological tests

CAM & SAKURA MEDICAL JOURNAL

Introduction

A new coronavirus emerged in late 2019 in China and spread throughout the world. This virus is identified as the third member of the coronaviruses causing severe acute respiratory syndrome (SARS) and still continues its pandemic. The disease caused by this new coronavirus was named as coronavirus disease-19 (COVID-19) by the World Health Organization (WHO) on February 11, 2020. At similar dates, the International Committee on Taxonomy of Viruses named this new coronavirus as SARS-coronavirus-2 (CoV-2). The first case of COVID-19 in our country was detected on March 11, when the WHO declared the disease as a pandemic (1,2,3,4,5). In this article, the basic virology pathogenesis and new approaches and diagnostic methods of SARS-CoV-2, which causes COVID-19, are reviewed.

Basic Virology

Coronaviruses belong to the order Nidovirales in the family coronaviridae and includes four genera, alpha, beta, gamma, and delta coronavirus. Alpha-coronaviruses include HCoV-229E, NL63, beta-coronaviruses include Middle East respiratory syndrome (MERS)-CoV, SARS-CoV, HCoV-OC43, HCoV-HKU1. SARS-CoV-2 is closely related to the beta-coronaviruses according to phylogenetic analysis. Comparing the DNA viruses RNA viruses have a higher mutation rate and shorter replication times so the SARS-CoV-2 has high mutation rate and variants (5,6).

The virus particle is 60-100 nm in diameter and has a round or oval appearance with an envelope. Similar to other betacoronaviruses, the SARS-CoV-2 genome is a positive-sense single-stranded RNA and lenth is about 29.9 kb. SARS-CoV-2 genome, has 5' and 3' terminal sequences (265 nt at 5' end and 229 nt at 3' end) with open reading frame (ORF) 1ab-spike (S)- envelope (E) - arranged in membrane (M) -nucleocapsid (N) regions. The predicted *S* (3822 bp), *ORF3a* (828 bp),

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Received: 15.11.2022 **Accepted:** 18.11.2022

E (228 bp) *M* (669 bp) and *N* genes (1260 bp) of SARS-CoV-2 are, nucleotides long, respectively. Similar to SARS-CoV-1, the SARS-CoV-2 genome carries a predicted *ORF8* gene (366 nt long) located between the *M* and *N ORF* genes (5,6,7,8). ORF1a/b covers about 65% of viral genome encodes two polyproteins pp1a and orpp1ab. pp1a clavage products are nsp1-11, orpp1ab products are nsp1-16. S protein is critical protein for viral attachment to cell receptor, which is angiotensin-converting enzyme-2 (ACE-2). S protein includes two unit, S1 is responsible for receptor binding and S2 is mainly responsible for cell membrane fusion (5,6). Six amino acids are critical for receptor binding that are L455, F486, Q493, S494, N501, and Y505 (6). Many mammalian body tissue cells (lung cells, kidney cells, gastrointestinal tract cells, heart, liver, and blood vessels epithelial cells) express ACE-2 receptors on their surface (9).

The N protein mainly attaches and covers the viral genome. It also involves an RNA replication process, formation of virion structure and immune evasion. The M protein mainly responsible assembly and budding of viral particles interacts with N protein. This protein is conserved part of genomes. The E protein responsible for production, maturation and releasing of viron. This is the smallest part of virion structure (10,11).

Viral Life Cycle and Pathogenesis

In SARS-CoV-2 infections, clinical findings including fever, dry cough, shortness of breath, myalgia, fatigue, normal or decreased leukocyte counts and radiological pneumonia are also seen in individuals with infection or clinical disease due to COVID-19 or other factors. While most COVID-19 patients (>80%) are asymptomatic or have a mild course, up to 5% of them may develop acute respiratory distress syndrome (ARDS), shock, and single or multiple organ failure, as in some other severe coronavirus infections (5,12). Our knowledge of the physicochemical properties of SARS-CoV-2 has also increased, since it is an enveloped virus, it is sensitive to external environments and SARS-CoV-2 can be inactivated by UV or heating at 56°C for 30 min, also diethyl ether, 75% ethanol and chlorine. It is inactivated by most disinfectants such as peracetic acid and chloroform. SARS-CoV-2 can remain stable on plastic and steel surfaces for longer periods than copper and cardboard surfaces, and live virus can be detected up to 72 h after virus application on these surfaces (7).

The S protein plays the main role in entry into the host cell. The process of entry into the cell begins with the binding of the S glycoprotein, which consists of trimeric S1 and S2 subunits, to its receptor on the cell. After SARS-CoV-2 binds to ACE-2 on the host cell with the S1 subunit, various proteases of the host cell such as cathepsin L, trypsin, elastase, serine transmembrane proteases (TMPRSSs) cleave the S1 and S2 units from the junction site and the S2 subunit becomes active, initiating membrane fusion. SARS-CoV-2 has a higher affinity for ACE-2 than SARS-COV-1. There is an insertion of 4 amino acids between the S1 and S2 subunits of SARS-CoV-2 that functions as the cleavage site of proteases and furins; these 4 amino acid regions are not found in any other coronavirus and are thought to have important contributions to the transmission ability of SARS-CoV-2 (5,13,14). ACE-2 is expressed in the oral mucosa, gastrointestinal tract, cardiovascular system, and kidneys, and these tissues can be infected by SARS-CoV. Clinical trials have been conducted after some studies have shown that TMPRSS2 has a key role in cutting S and S2 subunits at entry into the host cell and that blocking this enzyme may be a treatment option (14).

After the virus enters the cells, the viral RNA genome is released in the cytoplasm and ORF1ab polyproteins are first synthesized; synthesized polyproteins are formed by autocatalytic mechanisms, especially functional non-structural proteins required for replication. Then, the negative-sense complement of the viral genome is synthesized, and this newly synthesized RNA and positive-sense genomic RNA is replicated and m-RNAs of structural proteins are synthesized. The synthesized envelope glycoproteins pass through the endoplasmic reticulum or Golgi apparatus and are formed by the combination of nucleocapsid, genomic RNA, and nucleocapsid protein. Next, the viral particles bud into the endoplasmic reticulum-Golgi intermediate compartment. Finally, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus (4,5,7).

The antigenic structures of the intracellular virus are presented to the antigen presenting cells, which play a key role in the antiviral immune system, via the major tissue compatibility complex [(MHC); or human leukocyte antigen (HLA) in humans]. These structures are then recognized by virus-specific cytotoxic and helper T-lymphocytes. Therefore, understanding the antigen presentation of SARS-CoV-2 is important for understanding the pathogenesis of COVID-19. Antigen presentation of SARS-CoV is mainly dependent on MHC I molecules, but MHC II also contributes to its presentation. Again, based on previous data, individuals with allerines HLA-B * 4601, HLA-B * 0703, HLA-DR B1*1202 and HLA-Cw*0801 are more susceptible to infections caused by SARS-CoV, HLA-DR0301, HLA. There are publications reporting that -Cw1502 and HLA-A * 0201 alleles are associated with resistance to infection. In silico studies, HLA-B*46:01 binds weakly to SARS-2 peptides; it has been reported that HLA-B*15:03 has the highest capacity to present peptides from SARS-2, so people

with this tissue group may be more resistant. Additionally, mannose-binding lectin gene polymorphisms associated with antigen presentation have been associated with the risk of SARS-CoV infection. These studies and future studies will provide valuable clues for the treatment and understanding of the pathogenesis of COVID-19 (4,5,11,15,16).

After antigen presentation, humoral and cellular immunity in the body is mediated by virus-specific B and T-cells. As with other viral infections, antibody production against SARS-CoV virus classically takes the form of immunoglobulin M (IgM) and IgG production. IgM antibodies specific for SARS disappear at the end of the 12th week of the disease, while the IgG antibody can remain detectable in the body for a long time. Although antibodies develop against many proteins of the virus, they are specific antibodies to the protective neutralizing antibodies, especially S and N antigens (6,11). There is more research on the cellular immune response to coronaviruses compared to the humoral immune response, and current data show that the number of CD4 and CD8 T-cells in the peripheral blood of SARS-CoV-2 infected patients is significantly reduced, while the acute phase response in SARS-CoV patients is significantly reduced by CD4+. It has been reported to be associated with severe reduction in T and CD8+ T-cells. Although SARS-CoV-2 infects monocytes, macrophages and T-lymphocytes, the mechanism by which they enter these cells is unknown due to the low expression of ACE-2 in these cells. Even in the absence of antigenic stimulation, CD4+ and CD8+ memory T-cells can remain active for up to four years in individuals with SARS-CoV infection, so these clones are capable of T-cell proliferation, delayed-type hypersensitivity response and interferon (IFN-γ) production (2,7,17). Six years after SARS-CoV infection, 14 of 23 recovered SARS patients had T-cell memory responses specific to the SARS-CoV S peptide library. The specific CD8+ T-cells also exert a similar effect on the clearance of MERS-CoV in mice. When the data are examined, it shows that ARDS is the underlying cause of deaths due to COVID-19. ARDS is the common immunopathological event in SARS-CoV-2, SARS-CoV, and MERS-CoV infections. One of the main mechanisms in the development of ARDS is the uncontrolled release of large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, and the release of chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells (cytokine storm). When patients with SARS-CoV and MERS-CoV infections are classified according to their severity, individuals with severe symptoms have higher serum levels of IL-6, IFN-α and CCL5, CXCL8, CXCL-10 compared to those with mild-to-moderate symptoms. It is thought that cytokine storm can cause a severe immune response in the body by the immune system, causing ARDS and multi-organ failure and may lead to death in severe cases of SARS-CoV-2 infection, as in SARS-CoV and MERS-CoV infection (4,18,19).

Breathlessness, fatigue, and decreased exercise tolerance are persistent symptoms after acute SARS-CoV-2 infection. These findings called “long COVID” and biological mechanisms underlying “long COVID” syndrome remain unknown. Pulmonary endotheliopathy and microvascular immunothrombosis in may play key role acute COVID-19 and long COVID. Autopsy studies also support these hypothesis (20).

A lesson learned from SARS-CoV-2 is that this agent uses multiple strategies to better survive and inhibit the immune response in host cells. Evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) can be recognized by pattern recognition receptors (PRRs). Because of prevention detection of RNA genomes by the host cell.

SARS-CoV-2 can induce the production of double-membrane vesicles that lack PRRs and then replicate in these vesicles. IFN-I (IFN-α and IFN-β) has a protective effect on SARS-CoV and MERS-CoV infection, but inhibition of the IFN-I pathway has been shown in infected mice. The accessory protein 4a of MERS-CoV is thought to block IFN induction at the level of MDA5 activation through direct interaction with double-stranded RNA. Additionally, MERSCoV’s ORF4a, ORF4b, ORF5, and membrane proteins inhibit nuclear transport of IFN regulatory factor 3 and activation of the IFN β promoter. Again, gene expression due to the antigen presentation decreases after MERS-CoV infection. These factors may be the basic mechanisms that SARSCoV-2 uses to escape in the immune system (4,6,11,18).

In Table 1, main proteins and their properties, mutation rates during pandemics and roles presented for SARS-CoV-2 (21,22).

COVID-19 Diagnosis

Clinical signs and respiratory symptoms of patients infected with SARS-CoV-2 are generally the same with the other upper respiratory infections. Therefore, patient anamnesis is the starting point for the diagnosis of COVID-19, and the epidemiological history, clinical signs, computed tomography (CT) scan, blood count, and biochemistry test results needs confirmation for diagnosis. Nucleic acid testing strategies, which includes real-time polymerase chain reaction (RT-PCR) assays and serological tests [mainly, lateral flow tests, point-of-care tests (POCT)] that detects IgM/IgG antibodies or antigen tests are used. CT is highly instructive for rapid pre-diagnosis and prognosis estimation, especially during periods of high

Table 1. Main proteins and functions of SARS-CoV-2 (21,22)

Gene	Amino acid length in SARS-CoV-2	Number of amino acid residues with mutation rate greater than 0.01 during the pandemic (n)	Functional name	Function
Nsp1	180	0	Virulent factor	Inhibits host translation Invasion from immune response efficient viral gene expression
Nsp2	628	5	Endosome-associated protein	It is entirely unknown Mitochondrial biogenesis ???
Nsp3	1922	10	Cutting and untagging protein	Interacts with other viral nsps and RNA Removes tags from old proteins set for destruction
Nsp4	500	1	Double-membrane vesicle maker	Probably nucleate and anchor viral replication complexes on double-membrane vesicles in the cytoplasm.
Nsp5	306	5	Protease (3CLpro)	3CL protease
Nsp6	390	6	Double-membrane vesicle factory	Probably nucleate and anchor viral replication complexes on double-membrane vesicles in the cytoplasm.
Nsp7	83	1	Copy assistant	Dimerizes and interacts with other proteins
Nsp8	198	0	Primase	*De novo* initiation of replication and has been proposed to operate as primase
Nsp9	113	1	RNA-binding protein	Single-stranded RNA-binding protein.
Nsp10	139	0	Methyltransferase stimulator	Stimulates nsp16 to execute S-adenosyl-L-methionine-dependent methyltransferase activity
Nsp11	13	0		Unclear
Nsp12	932	7	RNA-dependent RNA polymerase	Core of RNA dependet RNA polymerase
Nsp13	601	5	Helicase	Unwinds dsRNA or DNA with 5′→3′ polarity
Nsp14	527	2	Proofreading exonuclease	N-terminal exoribonuclease domain, which has a proofreading role Prevents lethal mutagenesis
Nsp15	346	4	Endonuclease	Cleaves 3′ of uridines in a manganese dependent manner. Antiviral defance
Nsp16	298	1	Methyltransferase	Methyltransferase
S	1273	21	Spike protein	Attachment of virus
ORF3a	275	9	Accessory protein	Interactions S, M, and E proteins Inducing apoptosis (*in vitro*)
ORF3b	151	-	Accessory protein	Induces apoptosis, necrosis and hinders the antiviral innate immune response
E	75	0	Envelope protein	Production, maturation and releasing of viron
M	222	0	Matrix protein	M protein mainly responsible assembly and budding of viral particles interacts with N protein
ORF6	61	0	Accessory protein	Suppress IFN induction and IFN signaling pathway
ORF7a	121	1	-	May play a pivotal function in the recruitment of monocytes to the lung During COVID-19
ORF7b	43	1	-	Interfere with some cellular processes Involving leucine zipper formation and epithelial cell-cell adhesion
ORF8	121	2	-	Apoptosis and antagonizing the IFN signaling pathway Supporting replication

Table 1 continued

N	419	16	Nucleocapsid protein	Assembly and budding of viral particles interacts with N protein
ORF9a	97	-	-	Modulate the host immune response by compromising type I IFN synthesis
ORF9b	73	4	-	Impaired interferon signaling, antigen processing and presentation, complement signaling and induced IL-6 signaling
ORF10	38	-	Hypothetical protein	Biological functions have not been described yet, Immun modulation ???

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, IFN: Interferon, COVID-19: Coronavirus disease

prevalence, in suspected SARS-CoV-2 infection. Typical thorax CT images classically show a ground glass image with bilateral pulmonary parenchymal involvement and consolidations. However, it should be kept in mind that these findings cannot be distinguished from other viral pneumonia and similar images can be obtained in some different clinical situations (4,6,18,23).

The virus begins to spread in the upper respiratory tract 1-3 days before the onset of symptoms and is especially high in the first week of the disease. However, starting from the second week, the virus load in the upper respiratory tract decreases and it is found in greater amounts in the lower respiratory tract samples. In the diagnosis of COVID-19, upper respiratory samples are generally recommended, but sputum or lower respiratory tract samples such as bronco-alveolar lavage fluid (BALF), endotracheal aspirate can also be taken in patients who cannot produce sputum. Lower respiratory tract samples should be preferred, especially if they can be taken in the second week of the disease. Upper respiratory tract samples include nasopharyngeal and oropharyngeal swab samples, either alone or preferably in combination, nasopharyngeal washes and nasal aspiration fluids. These can be taken by health personnel or the patients can give an example themselves. Similar results to nasopharyngeal swabs can be obtained with nasal swabs obtained by the patient their self. Apart from this, more reproducible results can be obtained, especially with saliva samples originating from the posterior wall of the pharynx. Caution should be exercised during the collection of lower respiratory tract specimens such as induced sputum, BALF, or endotracheal aspirates, as there is a high risk of aerosol generation. In the first 14 days after disease onset, the most reliable specimen for detecting SARS-CoV-2 has been reported to be a nasopharyngeal swab followed by sputum, followed by a throat swab. Additionally, the virus begins to be excreted with faces, especially from the second week and continues to be excreted with faces for a long time. Especially in the advanced stages of the disease, stool samples can also be used for diagnosis, since viral excretion in upper respiratory tract samples may be low or irregular. However, since the viral load varies according to the samples and severity/stage of the disease, a negative test result obtained especially with the samples taken from the upper respiratory tract does not exclude the disease, and in case of clinical suspicion, the test should be repeated a second time or with a different sample with higher sensitivity (4,6,18). In the diagnosis of COVID-19, factors such as sample collection technique (experience of the sample taker), timing, amount, where the sample was taken, sample transport and storage, performance of the molecular test used and the severity of the disease can seriously affect the test results. Sample collection at the right time and with the right technique greatly affects the sensitivity of molecular tests. Single nasopharyngeal swab samples are also becoming the more preferred sampling because they are better tolerated by the patient and safer for the sampler. In a real life experience, 3 different samples (taken by the healthcare worker, by the patient and saliva) performance compared and the sensitivity of the three samples in the diagnosis of the COVID-19 was 100%, 98.7%, and 96.1%, respectively. The authors conclude these results are accepted to be accurate (24).

The widely used technology for SARS-CoV-2 is test RT-PCR technology. RT-PCR is currently used in many microbiology laboratories in the form of syndromic panels for the diagnosis of different infectious agents, pathogen identification and quantitation in single form, and disease diagnosis and follow-up. Following the emergence and rapid spread of SARS-CoV-2 in China, many organizations published diagnostic protocols, and then different commercial companies released RT-PCR test kits for diagnosis, some of them such as Food and Drug Administration (FDA), WHO. It has been pre-approved or approved by different institutions/organisations (18,25).

The first step in RT-PCR is the synthesis of complementary DNA (cDNA) from the RNA genome. The cDNA is then amplified and detected using unique primer probe systems. The development process for these tests generally includes two main steps: i. selection of appropriate gene regions, conserved region in known sequences, and primer/probe design ii. optimization

and validation of the developed test. In a study by Corman et al. (25), viral genomes associated with SARS include the *RdRP* gene (RNA-linked RNA polymerase gene), ORF1ab region, *E* gene (envelope protein gene), and *N* gene (nucleocapsid protein gene) conserved regions. These regions are still frequently used target regions for RT-PCR. Studies on these gene regions have reported that both RdRP and E genes have high analytical sensitivity (3.6 and 3.9 copies per reaction), and the *N* gene has weaker analytical sensitivity (8.3 copies per reaction). Reaction buffers, realtime PCR instruments extraction devices used for nucleic acid extraction may also effect performance of test (18,25,26).

The pooling can be a good strategy spatially limited testing resources and reagents. Testing by pooling samples requires very well established RNA extraction step for increasing sensitivity. Also careful monitoring of RT-PCR test sensitivity can avoid false negative results due to low-viral load. Therefore, laboratories should arrange their own validation of pooling

Studies based on the prevalence of COVID-19 (27).

In the initial period in the United States, the CDC recommended two nucleocapsid protein targets (N1 and N2), while WHO recommended initial screening with the *E* gene, followed by a confirmatory test using the *RdRp* gene. Because viral genes are present in equal copy numbers, the assay needs to be well optimized, as assay performance is usually determined by the reagent design and not the target itself. At least two molecular targets should be included in the analysis to avoid false positive or negative results from potential genetic alterations of SARS-CoV-2, as well as potential cross-reactivity with other endemic coronaviruses. However, WHO states that single-target test formats with high specificity can also be used alone, especially during the epidemic period. Molecular methods are being developed and evaluated worldwide, unlike RT-PCR. These include loop-mediated isothermal amplification (LAMP), multiplex isothermal amplification methods, followed by microarray detection and CRISPR/Cas systems. The Cas13-based specific high-sensitivity enzymatic reporter unlocking (SHERLOCK) platform is used in patient samples at concentrations as low as 1 copy per microliter. It has been used to detect Zika and dengue viruses. Currently, Tang et al. (28) they used a CRISPR/Cas13-based SHERLOCK technology to detect SARS-CoV-2, and the test has received FDA pre-approval (5,6,23,29).

Droplet digital PCR (ddPCR) is an sensitive alternative of realtime PCR technique. It enables us to detect a few copies and can do absolute quantification. ddPCR allows quantitative data that more insightful than regular RT-PCR. Because of specific instrument needs and cost, the ddPCR assays are still very rarely studied in COVID-19 (30,31). Recently, FDA approved SARS-CoV-2 ddPCR kit developed assay detected as low as 0.260 to 0.351 copies/µL.

LAMP is a new isothermal nucleic acid amplification method. This method can give rapid results and no need complicated equipments. So these properties allows to decreasing cost of SARS-CoV-2 RNA detection. It can detecte a few copies (3.4 copies) of RNA. Penn RAMP technology is a modification of LAMP technology and mainly an updated two-step LAMP protocol. For amplification of target this system combines recombinase polymerase amplification with LAMP so sensitivity increased approximately 10-100 times (32). A meta-analysis result showed that the overall pooled sensitivity of RT-PCR was 0.96 [95% confidence interval (CI), 0.93-0.98] and RT-LAMP was 0.92 (95% CI, 0.85-0.96). RT-PCR had 0.06 (95% CI, 0.04-0.08) and RT-LAMP had 0.12 (95% CI, 0.06-0.16) false-negative rates. Mixed sampling and multiple target selection for diagnostic methods had better value than single site sampling and single target (33).

According to WHO, the immediate priority for COVID-19 diagnostic research is the development of nucleic acid and protein testing and the provision of POCT. The longer-term priority is to integrate these tests into multiple panels, as leading multi-parametric respiratory pathogens panel manufacturers have added SARS-2 to their panels. Serological tests using proteins in addition to nucleic acid tests are needed to improve surveillance efforts. These tests have the advantages of post-recovery detection, unlike nucleic acid tests. This enables clinicians to monitor both sick and recovered patients, providing a better estimate of total SARS-CoV-2 infections. POC tests are cost-effective devices used to diagnose patients outside central facilities. These can be run in areas such as community centres to reduce the burden on clinical (6,18).

Pandemic conditions also had a catastrophic effect laboratories and the same time on the world economy and human civilization. So there is an urgent need to develop robust fast technologies and nanotechnology based approaches as nanobiosensors used for detection of SARS-CoV-2 with high sensitivity, specificity, and fast analysis (34).

Serological tests are being developed for the rapid detection of SARS-CoV-2 antigens or antibodies, and some of them have been approved by many institutions. Different commercial companies are developing serological tests for detecting SARS-CoV-2 infection in lateral flow tests, automated chemiluminescence immunoassay systems, ELISA, and other formats. Although antibodies begin to be detected from the seventh day of the disease during COVID-19, IgM responses generally increase to more reliably detectable levels from the second week and IgG responses from the third week. Antibody responses can also be affected by factors such as disease severity and host immune

status. Although IgM responses remain positive for a shorter time, IgG positivity may persist for a long time. The level of protection and duration of antibody responses that develop after SARS-2 virus infections are not yet known precisely. It is estimated that its protection will not be very long (more than 6 months). It is attractive that rapid antigen tests would theoretically allow for low cost and rapid detection of SARS-CoV-2, but as with influenza viruses, their sensitivity would be lower than molecular tests. As a matter of fact, the sensitivity of an antigen test approved by the FDA is 80%. Especially with the development of monoclonal antibodies, more and more sensitive antigen tests are being developed (6,35).

Considering the variability of viral loads and sample diversity in COVID-19 patients, the sensitivity problem of antigen tests will be better understood. Antibody tests, which examine the host's response to the agent, may be more useful in demonstrating the past infection. They can also be used as additional testing to confirm COVID-19 infection; however, in a low prevalence situation, although the specificity of these tests is high, false positivity rates will be very high (for example, if the seroprevalence in the population is 1%), the probability of an antibody positivity obtained with a test with a specificity of 99% will be around 50%. Therefore, the following: For the moment, it is recommended that they be used with caution, considering the limitations mentioned in auxiliary testing and seroepidemiological studies. The use of antibody tests for purposes such as investigating the presence of protective antibodies in people should be avoided. Previously, this type of serological testing has was central to the epidemiology of SARS and other coronavirus outbreaks. Rapid lateral flow tests that can detect both IgM and IgG antibodies will undoubtedly $1 are central to COVID-19.

However, IgM responses have specificity problems and specific IgG response development takes time. It seems unlikely that biology tests will play a role in active case management, apart from tasks such as diagnosing/confirming late cases of COVID-19 or determining a person's immunity (18,28,35,36).

Next-generation DNA sequencing analysis, although its use is limited in the diagnosis of SARS-CoV-2 due to its high cost, is especially used for understanding and monitoring viral evolution and for genoepidemiological studies. US-FDA has approved the Illumina COVIDSeq that is an amplicon-based NGS platform. This was the qualitative detection method that uses different sets primers and probes leveraged from ARTIC multiplex PCR protocol. Similarly, Thermo Fischer Scientific has launched Ion AmpliSeq SARS-CoV-2, but this is a research panel for NGS. For new generation and long read protocol introduced by Oxford nanotechnology. This protocol has substantial benefits for analytical innovations due to long reads (37).

Ethics

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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DOI: 10.4274/csmedj.galenos.2022.2022-11-9
Cam and Sakura Med J 2022;2(Suppl 1):14-20

CSMJ

Radiological and Biochemical Findings of COVID-19

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ABSTRACT

Coronavirus disease-2019 (COVID-19) is a new COVID-19 that causes various health and safety concerns and socioeconomic difficulties worldwide. Early and accurate diagnosis, isolation, and management are critical public health concerns. Real-time reverse transcription polymerase chain reaction (RT-PCR) of viral nucleic acids was the reference in diagnosing COVID-19. In addition to RT-PCR, serological tests based on antibodies tested against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) have been used for diagnosis and epidemiological research. In cases where the reference tests are negative, radiological imaging guides the diagnosis. Chest radiography and thoracic computed tomography (CT) are the most commonly used radiological methods in imaging for COVID-19. Chest radiography and CT play a critical role in diagnosing, following, and staging pneumonia. However, it can also evaluate the progression of the disease, prognosis prediction, and treatment follow-up. The clinical forms of COVID-19 can range from asymptomatic infection to severe pneumonia. Biochemical findings vary in patients with different clinical forms. Therefore, biochemical parameters help diagnose the disease, determine disease severity, and predict clinical outcomes. SARS-CoV-2 is present in many tissues, including the endothelium, liver, and kidney. It can also progress with multiorgan involvement. Among the biochemical parameters, those showing organ damage play a significant role.

Keywords: COVID-19, biochemical parameters, CT, radiologically features

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Introduction

Radiological Findings of COVID-19

In December 2019, the disease caused by the virus called severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which emerged in Wuhan, Hubei Province of the People's Republic of China, was officially named coronavirus disease-2019 (COVID-19) by the World Health Organization. Later, it was declared on March 11, 2020, that this disease was developed into a pandemic (1).

Clinical forms of COVID-19 have spread across a wide spectrum, ranging from asymptomatic infection, mild upper respiratory tract disease, severe viral pneumonia-causing respiratory failure, sepsis, multiple organ failure, and death (2). The most common symptoms are fever, cough, sore throat, headache, fatigue, muscle pain, and dyspnea. Real-time reverse transcription polymerase chain reaction (RT-PCR) of viral nucleic acids is the reference standard in diagnosing COVID-19. While the sensitivity of RT-PCR is 60-70% in the early period, it reaches 95% in the later period

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Received: 18.11.2022 **Accepted:** 23.11.2022

(3). In the early period of the pandemic, false-negative results appeared due to technical problems during inappropriate viral sample material or nucleic acid extraction. Computed tomography (CT) was the diagnostic test because of the RT-PCR study and access difficulties, long duration of the outcome, or exceedance of test usability with the accumulation of suspicious cases, and early RT-PCR false negativity, particularly at the beginning of the epidemic. The COVID-19 pandemic has caused a unique situation in this respect.

Chest radiography and thoracic CT are the most commonly used radiological methods for COVID-19. Thoracic ultrasonography was used in some centers for diagnosis and follow-up. Chest radiography and CT play a significant role in diagnosing, following up, and staging pneumonia. However, it can also predict disease severity and prognosis. CT is also extensively used to evaluate the progression of the disease and response to treatment. Therefore, recognizing CT findings, frequently present in COVID-19 patients, is critical in their complementary role in the early diagnosis and follow-up of disease progression.

Lung radiography and CT are frequently used radiological methods in COVID-19 and are described in the following section.

Chest Radiography

Chest radiography is the first preferred radiological method. Its sensitivity in showing lung involvement varies between 30 and 60%. The fact that the radiograph is normal because to its low sensitivity does not exclude COVID-19 pneumonia. The multifocal opacity with bilateral middle and lower zone involvement may be diagnostic. However, the foci of low-density pneumonia can also be present in other viral pneumonia. It is insufficient to show the appearance of ground glass opacities in the early period compared to CT (Figure 1).

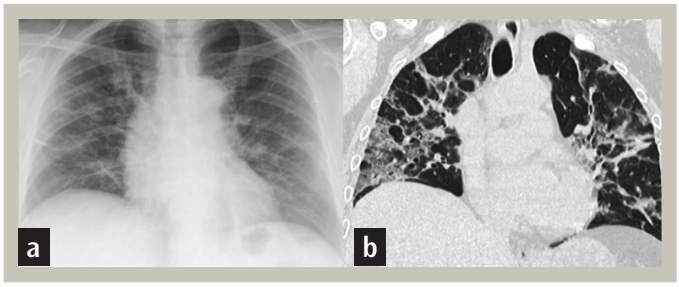

Figure 1. (a) CXR image. (b) CCT imaging, coronal reconstruction. COVID-19-positive patient. GGO are more easily identified on CCT imaging compared to CXR

CXR: Chest X-ray, CCT: Cardiac computed tomography, COVID-19: Coronavirus disease-2019, GGO: Ground-glass opacity

Lung radiography is preferred because it is practical, easily accessible and contains a low-dose radiation. It is crucial for monitoring the course of lesions in patients with severe progression (4,5).

Computed Tomography

SARS-CoV-2 uses the angiotensin-converting enzyme-2 (ACE-2) receptor in humans and first causes pulmonary interstitial damage and then parenchymal changes (6). Although bilateral ground glass opacities and consolidation have been reported as dominant imaging features in COVID-19, chest CT findings may vary in different patients and stages (7). In addition to the diagnosis of COVID-19, CT is also critical in monitoring the progression of the disease and evaluating its therapeutic effectiveness.

The studies reported various values for the sensitivity of CT. This may be related to the day of the symptoms of CT scanning and the variability of the disease according to the stage of the disease. In a meta-analysis, the sensitivity and specificity of the first chest CT scan were 87% and 43%, and the positive predictive and negative predictive values were 67% and 84%, respectively. This means that 67% of individuals with CT findings have positive RT-PCR, and 84% of individuals with negative CT scans have negative RT-PCR. Therefore, CT scanning is a complementary diagnostic tool compared to RT-PCR. CT is involved in staging the disease rather than being a screening test (8).

Ground Glass Opacities

The most critical and most common CT feature of COVID-19 is the bilateral distribution of consolidated or unconsolidated ground-glass opacities, mainly in the periphery and posterior of the lungs. Increases in lung parenchyma density due to alveolar partial filling of ground-glass opacity (GGO), partial collapse, and increased capillary blood flow, which tend to retain multiple segments. In a meta-analysis, the incidence of ground-glass opacities was 14-91% (9). In another study, ground-glass opacities were present with consolidation in 41% of 1099 cases (10). Studies have revealed that ground-glass opacities are the most common imaging feature and the earliest CT finding. Reticular and/or interseptal thickening, consolidation, and subsegmental vasodilation frequently accompany ground-glass opacities. This appearance may be due to hyaline membranes and pulmonary edema (11).

Various CT imaging features, such as “crazy paving”, air bronchograms, inverted halo signs, bronchiectasis, bronchial and pleural thickening, vascular enlargements, nodules, and pleural effusion, which are associated with the possible lung injury mechanism, have also been present. Typical and

atypical CT features are in Table 1 (5). Typical imaging features are not specific to COVID-19 and can also be present in other viral pneumonia. They are influenza pneumonia, acute lung injury, drug toxicity, lung involvement of connective tissue diseases, and organized pneumonia. In the presence of ground-glass opacities with no specific distribution, acute hypersensitivity pneumonia, pneumocystis infection and alveolar bleeding should be considered in the differential diagnosis. The differential diagnosis of atypical findings includes lobar and aspiration pneumonia and necrotizing pneumonia. Therefore, if atypical findings are present, it would be appropriate to confirm with PCR. If it cannot be confirmed, it would be appropriate to reach the diagnosis with the epidemiological factors of the case (7).

Consolidation

The lung parenchyma condensation occurs by erasing the veins and airways with pus, pathological fluid, blood, or cell filling into the alveoli (12). COVID-19 is accused of filling fibromyxoid exudate into the alveoli. In COVID-19, segmental, peripheral, and irregular limited consolidations appear. It is the most common finding after GGO, and the most accompanying finding of GGO (13). While ground glass is an early finding, consolidation is an advanced finding. It can also be present as a unilateral lesion in the early period. The newly emerging consolidations in the follow-ups predict that the disease may be progressive (14).

Consolidations may also be accompanied by airway changes, such as air bronchograms, bronchial wall thickening, and bronchiectasis. Air bronchograms can manifest frequently. While air-filled low attenuated alveoli between liquid-filled alveoli are as bronchograms in CT, fibrosis resulting from bronchial wall damage is as bronchial wall thickening (12). Studies associate bronchial thickening with poor prognosis.

The sidewalk stone pattern is interlobular septa accompanying the ground glass, which results from edema and inflammation by lung damage (15). Although it is not as common as ground glass, it can be defined as poor progression of the disease when present.

Pulmonary vascular enlargement is the enlargement of the subsegmental vessels with a diameter greater than 3 mm. Studies reported a rate of 50%, although not as often as ground glass or consolidation. Vascular enlargement accompanying the lesions is of diagnostic significance for COVID-19 (Figures 2, 3) (9).

Table 1. COVID-19 CT imagine features

Typical features	Atypical features
Ground glass opacities	Pleural effusion
Consolidation	Lymphadenopathy
Crazy paving	Pericardial effusion
Air bronchograms	Cavitation
Airway cysts	
Reticular pattern	
Nodules (with halo/revers halo sign)	

CT: Computed tomography, COVID-19: Coronavirus disease-2019

Other Findings

Nodules are common in viral pneumonia, but are rare in COVID-19. Halo and reverse halo marking may also accompany. Invasive fungal infections can be confused with lung metastases.

Air bubble signs, subpleural lines, pleural effusion, and thickening are rare atypical findings. While subpleural streaking occurs during the recovery period, pleural effusion and thickening manifest in the advanced stages of the disease (Figure 4).

Lymphadenopathy and pericardial effusion are rare atypical findings (16).

According to the abovementioned findings, the COVID-19 Reporting and Data System (CO-RADS) created a categorical

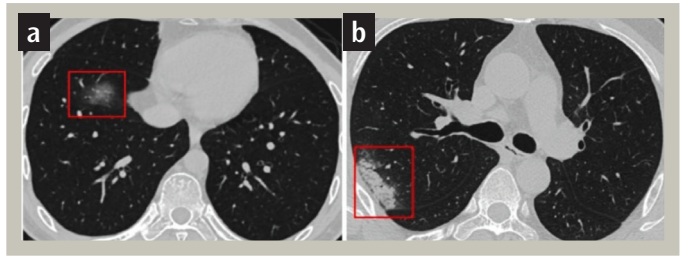

Figure 2. a) CT scan shows pure ground glass opacity in the right lower lobe (red frame). b) CT scan shows consolidation in the right lobe subpleural area (red frame) (9)

CT: Computed tomography

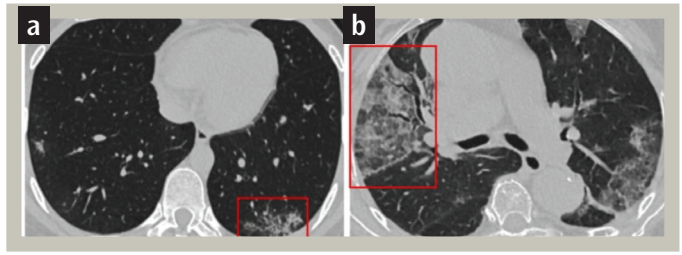

Figure 3. a) Reticular pattern in the left lower lobe and subpleural area (red frame). b) Reticular pattern superimposed on the background of GGO, resembling the sign of crazy paving stones (red frame) (9)

GGO: Ground-glass opacity

evaluation scheme for pulmonary involvement of COVID-19 in non-contrast chest CT, which performed well in predicting COVID-19 CO-RADS definitions are in Table 2 (17). Although it created a common language in the reporting system of radiologists, it has been the scale that clinicians frequently use in practical life.

Although CT findings occur over an average of four days, they may also occur before symptoms begin. According to the change in thoracic CT images, the disease can progress in four stages (18).

Early period: It covers the first four days from the first symptoms of the disease. Ground-glass opacities are in the lower lobes. Uni/bilateral subpleural areas are the main radiological findings.

Progressive period: This period covers the 5th-8th days from the onset of symptoms. The progression of the disease is rapid during this period. Radiological findings in this period are as follows: Bilateral, common, multilobar ground glass opacities, paving stone appearance, and consolidations.

Peak period: It covers the 9th-13th days from the onset of symptoms. During this period, infiltration areas in the lungs reach the highest level. Intensive consolidation areas are more prominent, and parenchymal bands can appear.

Regression period: It covers the 14th day and after the onset of symptoms. The infection is now under control, and consolidations are gradually regress. Sidewalk stone views are lost. Sequelae fibrotic bands may occur.

There is no need to provide a contrast agent in imaging for diagnosing COVID-19. However, if pulmonary embolism is considered a complication, contrast-enhanced CT angiography is recommended.

Table 2. CO-RADS definitions

		CT findings
CO-RADS 1	No	Normal or non-infectious abnormalities
CO-RADS 2	Low	Abnormalities consistent with infections other than COVID-19
CO-RADS 3	Indetermine	Unclear whether COVID-19 is present
CO-RADS 4	High	Abnormalities suspicious for COVID-19
CO-RADS 5	Very high	Typical COVID-19
CO-RADS 6	PCR+	

CO-RADS: COVID-19 Reporting and Data System, CT: Computed tomography, PCR: Polymerase chain reaction, COVID-19: Coronavirus disease-2019

Biochemical Findings of COVID-19

The clinical forms of COVID-19 can range from asymptomatic infection to severe pneumonia (1,2). Biochemical findings vary in patients different clinical forms (19). Therefore, biochemical parameters help diagnose the disease, determine the severity of the disease and predict clinical outcomes (20). SARS-CoV-2 can be present in many tissues, including the endothelium, liver, and kidney (21). It can also progress with multiorgan involvement. Among the biochemical parameters, those showing organ damage play a critical role (20). Biomarkers, according to the systems and situations in which they are used, are reviewed in the following section.

Inflammatory biomarkers: SARS-CoV-2 replicates at the site of infection after host cell invasion. Thus, the response

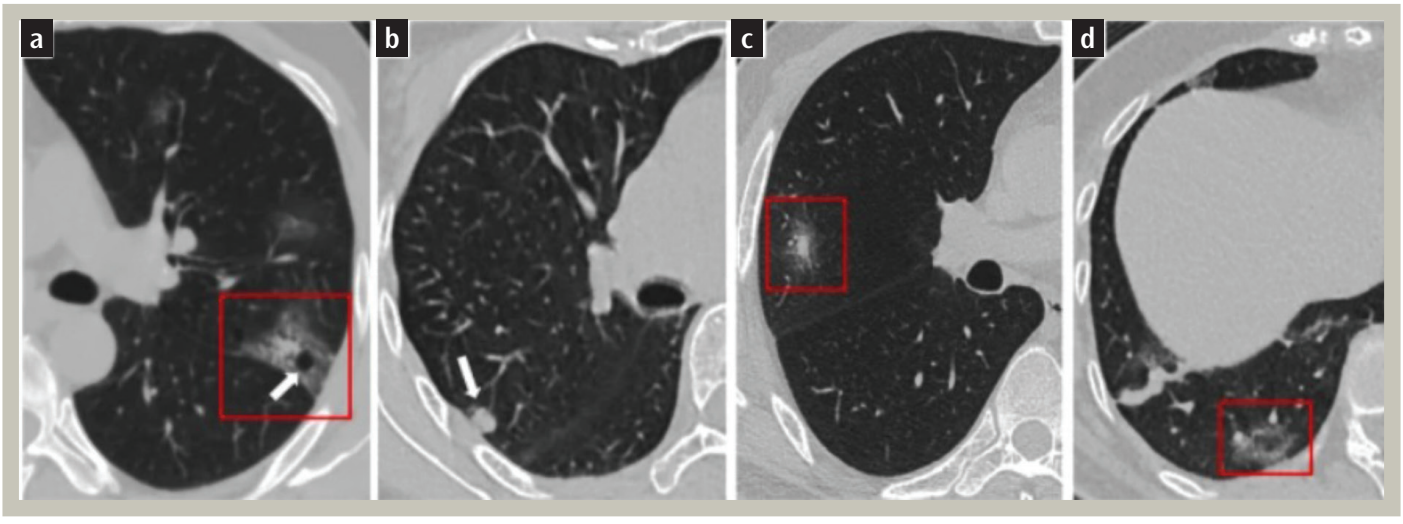

Figure 4. a) CT scan showing a patchy GGO (red frame) with an air bubble sign (white arrow) in the apicoposterior segment of the upper left lobe. b) An irregular nodule (white arrow). c) A solid nodule surrounded by a ground glass halo (red frame). d) A reversed halo sign (red frame) (9)

CT: Computed tomography, GGO: Ground-glass opacity

to innate and adaptive immunity is triggered (22). The inflammatory response to systemic immunity is activated. If this response cannot be controlled, it evolves into an inflammatory response called a cytokine storm (23). This response causes damage to different tissues, worsens the patient (20). In severe cases, it may result in multiple organ failure. Proinflammatory cytokines, particularly interleukin (IL)-6 and tumor necrosis factor (TNF)-α, have been associated with death in severe COVID-19 patients. Other examples are as follows: IL-1b, IL-2, IL-8, interferon-g-induced protein 10, granulocyte colony-stimulating factor, monocyte chemoattractant protein 1, and macrophage inflammatory protein-1. Additionally, cluster differentiation (CD) 3+, CD4+, CD8+, CD25+, CD127- T-cells, and natural killer cells were depressed in severe COVID-19 (24). Cytokine testing is not routine in laboratories. CRP and ESR, routine biomarkers, can evaluate the severity of the disease (25). Procalcitonin levels are an indicator that they are accompanied by bacterial infection. Among the hematological parameters, a high platelet-to-lymphocyte ratio, high neutrophil-to-lymphocyte ratio (NLR), and lymphopenia are strongly associated with the severity of the disease (26,27,28).

Pulmonary involvement: Although not specific to lung disease, various biomarkers have been identified in different stages of lung involvement in COVID-19 and have been associated with pulmonary, systemic hyperinflammation, and fibrotic damage (23,29). In the early period of the disease, neuron-specific enolase (NSE) can distinguish patients who will develop dyspnea. At baseline, the following conditions are associated with a lower risk of death: Higher lymphocyte and platelet counts, lower ferritin, D-dimer, lactate dehydrogenase (LDH), and aspartate transaminase (AST) (22,28). Surfactant protein-D, angiopoietin 2, triggers receptor expressed on myeloid cell (TREM)-1, and TREM-2 levels were higher in mild/moderate and severe COVID-19 pneumonia than in asymptomatic patients. Thiol, ferritin, and LDH are prognostic biomarkers for Acute respiratory distress syndrome (ARDS) in severe COVID-19 cases. After extubation, survivors of COVID-19 have higher platelet counts and NLRs but low levels of C-reactive protein (CRP), D-dimer, ferritin, LDH, and AST (27,30).

Cardiac biomarkers: It causes coagulopathy because SARS-CoV-2 triggers endothelial dysfunction. Endothelial damage and the generalized inflammatory response conduct the process of thrombosis, which constitutes cardiovascular findings (21). Clinical evidence has shown that severe COVID-19 patients have a significant cardiovascular impairment (31). The increase in the D-dimer coagulation margin indicates an increased likelihood of various thrombosis; it has the following conditions: worsening disease and pulmonary microthrombosis, pulmonary embolism, deep vein thrombosis, and diffuse intravenous coagulation (26). Similarly, plasma fibrinogen is associated with hyperinflammation and disease severity. The following are coagulopathy-associated indicators: Elevated levels of soluble vascular cell adhesion molecule (sVCAM)-1, von Willebrand factor (vWF), thrombomodulin, soluble TNF receptor I (sTNFRI), heparan sulfate, C5b9 complement, plasminogen activator inhibitor-1, and alpha-2 antiplasmin. Some of these markers are also associated with the severity of the disease: sVCAM-1, vWF, sTNFRI, heparan sulfate, and ADAMTS13 activity (21,23).

Recent evidence has shown that cardiac biomarkers and troponin levels, including natriuretic peptides (NPs), may reflect the cardiovascular involvement and are strongly associated with poor prognosis and mortality. Troponin elevation in COVID-19 has been associated with changes in ECG, intensive care unit admission, and in-hospital death. However, routine testing is still controversial despite the confirmed prognostic effect of troponin levels (32).

These cardiac and non-cardiac biomarkers have been findings of cardiovascular diseases associated with COVID-19: Creatine kinase-MB, myoglobin, brain NP (BNP) and its N-terminal prohormone (NT-proBNP), mid-regional pro-adrenomedullin (MR-proADM) (22).

Metabolic Functions

Lipid metabolism plays a role in the regulation of inflammation and immunity. Fat-soluble vitamins such as vitamin D also suppress the cytokine storm and strengthen the immune response. Therefore, investigating lipid metabolism and biomarkers may have diagnostic and prognostic value in COVID-19 (23).

Metabolic comorbidities such as obesity, diabetes, cardiovascular diseases, and hypertension have been associated with poor prognosis in COVID-19 (22,23).

COVID-19 patients with low levels of high-density lipoprotein levels are more prone to hospitalization. However, higher low-density lipoprotein resulted in more hospitalization. Critical patients with COVID-19 showed significantly lower vitamin A levels than non-critical patients. This has been associated with high inflammation. Vitamin A levels below 0.2 mg/L were significantly associated with the development of ARDS and higher mortality. Vitamin D does not appear to affect mortality or length of hospital stay despite known immunomodulatory function.

Thyroid hormones showed a significant relationship with disease severity. It is recommended to evaluate thyroid

function early in hospitalized COVID-19 patients and to initiate thyroid therapy when necessary (22).

Neurological involvement: Although COVID-19 primarily rarely affects the brain, neurological complications are common. Because of neurological involvement, various biological markers can detect neuroinflammation and damage. In addition to the inflammatory and coagulopathy markers mentioned in other sections, these indicators can be beneficial: antiphospholipid antibodies, fibrillary acidic protein (GFAP), neurofilament light polypeptide, tau, S100B calcium-binding protein, and NSE (33).

Hepatic biomarkers: Several studies have shown abnormal liver function in severe COVID-19 patients. High aminotransferase levels were present in 14-58% of hospitalized patients. AST and ALT elevations are usually mild (<5 times the upper limit of normal). However, higher aminotransferase levels and severe acute hepatitis are also present (25).

Increased GGT, increased bilirubin, and decreased serum albumin levels were associated with severe COVID-19.

Possible mechanisms of liver dysfunction during COVID-19 include the following:

1. Immune-mediated damage due to a severe inflammatory response because of infection.

2. Direct cytotoxicity by active viral replication in biliary epithelial cells expressing ACE-2.

3. Hypoxic hepatitis by anoxia.

4. Drug-induced liver injury (20).

Renal biomarkers: COVID-19 is associated with acute kidney injury (AKI), although the mechanism is not fully known. The prevalence of AKI was between 0.5-19.1% in various studies. Blood urea nitrogen and creatinine levels are the general indicators of kidney damage. According to Cheng et al. (34), 102 patients with higher basal blood creatinine levels were more likely to be admitted to intensive care.

COVID-19 care, early diagnosis and management of kidney injury, adequate physiological balance, and restriction of toxic drugs can be critical. Therefore, monitoring creatinine and other renal markers is crucial. In addition to serum and urine albumin, total protein may be beneficial as a prognostic marker in COVID-19 (20).

Additionally, it should be considered that biochemical markers may vary with the development of SARS-CoV-2 variants (35,36).

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Y.S., C.A.T., Design: D.Y.S., C.A.T., Data Collection or Processing: D.Y.S., C.A.T., Analysis or Interpretation: D.Y.S., C.A.T., Literature Search: D.Y.S., C.A.T., Writing: D.Y.S., C.A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/csmedj.galenos.2022.2022-11-6
Cam and Sakura Med J 2022;2(Suppl 1):21-26

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COVID-19: Clinical Manifestations and Management in Outpatient/Hospitalized Adults

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ABSTRACT

A new coronavirus, emerging toward the end of 2019, rapidly disseminated around the world and resulted in a pandemic. The virus was named as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the disease caused by the virus as coronavirus disease-2019 (COVID-19). The clinical spectrum of COVID-19 in adults varies from asymptomatic infection to acute respiratory distress syndrome and multi-organ dysfunction. Information on the disease and its management has been continuously updated, especially with the development of SARS-CoV-2 variants and vaccines against the virus. The disease is generally mild in most patients with COVID-19 and requires no medical intervention or hospitalization; follow-up and treatment in an outpatient setting are adequate. Patients with a risk of severe disease or unvaccinated patients, and elderly patients with comorbidities with dyspnea and deteriorated oxygenation should be admitted, treated and followed up at hospital. Current local sources and the individual evaluation of the patients is important in the management of the disease.

Keywords: Clinical findings, COVID-19, management, SARS-CoV-2

Introduction

Clinical Findings and Patient Management

Coronavirus disease-2019 (COVID-19), a newly emerging disease, originally emerged with symptoms of respiratory tract infection alone. In time, we learned that it is a disease with possible clinical findings in a spectrum from asymptomatic infection and mild respiratory tract symptoms to acute respiratory distress syndrome (ARDS), severe pneumonia and cardiovascular complications. Experience with the diagnosis, clinical properties and treatment of COVID-19 has gradually increase. Our understanding of the disease spectrum and optimal management strategies, particularly in the presence of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) variants and the vaccines, has been developing continuously. The clinical severity of the disease might be variable according to the viral load received and the immune response of the individual. Asymptomatic disease is quite common with a reported rate of 20%-40% varying on the population analyzed (1,2,3,4).

Individuals, asymptomatic at the time of the polymerase chain reaction (PCR) test might later develop symptoms, hence be presymptomatic. The start of the symptoms was an average of four days (3-7 days) after the first positive RT-PCR test in a study (5).

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Received: 08.11.2022 **Accepted:** 18.11.2022

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The incubation period was 2-14 days in 98% of the patients, with a mean of 4-5 days (6,7,8). The median incubation period in SARS-CoV-2 Omicron variant (B.1.1.159) seems to be a little shorter and the first symptoms emerged in about three days (8,9).

Clinical Presentation

The most commonly reported symptoms in patients with COVID-19 are cough, muscle pain and headache. The fatigue, weakness, diarrhea, sore throat and abnormalities in taste and smell can also be seen. Mild upper respiratory tract symptoms (i.e. nasal congestion and sneeze) are seen more commonly in Delta and Omicron variants (10). Pneumonia is the most serious clinical picture (6,11). Some complaints such as loss of taste and smell are seen more frequently in COVID-19 compared with other viral respiratory tract infections; however, there are no specific and reliable symptoms to differentiate COVID-19. Nevertheless, the development of dyspnea approximately a week after the start of the first symptoms may suggest COVID-19. Clinical findings of Delta and Omicron variants were compared in an observational study evaluating the clinical symptoms of 63.000 confirmed COVID-19 cases. The most common symptoms in both variants were nasal congestion, headache, sore throat and sneezing, while sore throat was seen more frequently and abnormalities in the sensation of taste and smell were seen less commonly in the Omicron variant (10,12).

Symptoms are variable according to the severity of the disease. For example; fever, cough and dyspnea have been reported more widely in hospitalized individuals compared to outpatients. Atypical signs might be seen in the elderly and individuals with comorbidities, and manifestation of fever and respiratory symptoms might be delayed (13,14). However, the presence of fever and cough is inadequate to differentiate mild and severe cases and to reflect the prognosis (15). Dyspnea, on the other hand, is a powerful marker of severe disease. Dyspnea, in general, may develop in the second week of the disease course and might advance into hypoxemia (6). A clinical picture of viral pneumonia, possibly with fever, cough and hypoxia is dominant. Bilateral ground glass images and infiltration are seen in chest imaging (16).

Clinical Course of the Disease

The severity of COVID-19 infection is generally mild but can be variable from mild to a critical course (11,17). There is no definite and accepted clinical classification; although some authors have used the following grading (18):

· Mild cases: Symptomatic cases with no pneumonia in imaging studies,

· Ordinary cases: Fever and pneumonia in imaging studies,

· Severe cases: Dyspnea, hypoxia (SpO_2 ≤93%), abnormal blood gas analysis (PaO_2 <60 mmHg, $PaCO_2$ >50 mmHg),

· Critical cases: Dyspnea requiring mechanical ventilation, shock and other organ failure requiring admission to intensive care unit (ICU).

The risk of severe disease varies according to the age, underlying comorbidity and status of vaccination. Also, different variants of SARS-CoV-2 have been associated with varying severity of disease risks. For example, the Omicron variant seems to be associated with a less severe disease (10,19).

The case fatality rate reflects the death rate only among the confirmed cases. The infection fatality ratio (namely, expected death rate among all individuals with infection) is quite low since asymptomatic infection is common and many mild infections get undiagnosed, and should be around 0.15%-1% among unvaccinated individuals, though quite variable depending on the localization and risk groups (20,21,22). The rate of critical illness and mortality is higher among hospitalized and unvaccinated patients (15,23).

Advanced age is a significant risk factor for severe disease, the development of complications and death (6,11). The rates of severe disease and mortality may be higher in populations with a low socioeconomic level due to the scarcity of the sources. Cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer (especially hematologic malignancies, lung cancer, and metastatic disease), chronic kidney disease and obesity are significant comorbidities increasing the risk of severe disease (13,23,24,25). Vaccination decreases the risk of severe disease substantially and is associated with decreased mortality.

Complications

The most common complications are ARDS, arrhythmia, myocardial damage, heart failure, shock, thromboembolic complications, encephalopathy, stroke, motility disorders, ataxia, seizures and inflammatory complications.

Laboratory Findings

The most commonly seen laboratory findings in patients diagnosed with COVID-19 are lymphopenia, high levels of aminotransferase, lactate dehydrogenase (LDH) and inflammatory markers [i.e. ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate] and abnormalities in coagulation tests (6,11,18,25). Lymphopenia is the most frequent laboratory sign of COVID-19; is present in 83% of hospitalized patients (6,11) and with a high D-dimer level, has

been associated with mortality (25). Procalcitonin, although in normal ranges at admission, is probably elevated in patients admitted to the ICU (11,17).

Outpatient Management

The clinical course is mild in the great majority of patients with COVID-19 and no medical intervention or hospitalization is required (26,27).

The phone consultation is appropriate to decrease the risk of communal spread whenever an individual with a definitive diagnosis has no complaints. However, patients should be encouraged to apply to hospitals when they have complaints such as high fever and dyspnea.

The risk of severe disease should be evaluated to deciding to hospitalize a patient presenting at the hospital. Hypoxia (SpO_2 <93%), tachypnea and infiltration in more than 50% of the lungs using imaging techniques and requirement of respiratory support have been defined as criteria for admission to the hospital in many countries, though they are still controversial. Other indications for hospitalization are conditions such as immunosuppression and acute renal failure. Patients with severe and critical disease (18) should absolutely be hospitalized. Dyspnea is an indication of hospitalization in the clinical picture of intermediate disease (28). In this country, according to the guidelines of the Ministry of Health, uncomplicated patients and cases with pneumonia with a mild-intermediate course are recommended to be followed up as outpatients and receive their drugs from hospital pharmacies (29).

Patients with the following criteria were assessed as having severe disease:

· Over 50 years of age (higher risk if over 65 years)

· Unvaccinated or inadequately vaccinated (30)

· Have comorbidities (13,23,25)

Dyspnea and impairment in oxygenation with the risk factors for developing severe disease might be used to guide clinicians for a decision to hospitalization. Anamnesis related to dyspnea, even when talking, should be carefully obtained. The patient can be hospitalized when the SpO_2 is ≤93% at admission, regardless of the severity of the dyspnea. Note that dyspnea can be manifested 4-8 days, and in some cases, even 10 days after the start of the symptoms (11,31). Outpatients with no dyspnea should be educated about the possible development of dyspnea later. Increasing dyspnea, dyspnea particularly at rest and chest pain, suggest development or advancement of pulmonary involvement.

Patients followed up at home, though not every patient, was asked to check their oxygen level by a pulse oximeter, if possible, twice daily and to inform their physicians if case the value was less than 95%.

Other than the respiratory status, orthostasis, dizziness, fall, hypotension, changes in consciousness (i.e. lethargy, confusion, behavioral changes, difficulty in weakening), cyanosis, and decreased urinary output are conditions that the outpatients should inform their physicians when present and should apply to the hospital. In that case, the patient should absolutely be re-examined and re-evaluated for hospitalization.

We observed that the clinical condition of the patient was more important in deciding the type of treatment in most patients with COVID-19 whom we had evaluated, rather than the laboratory tests and imaging of the lungs since the latter provided a limited benefit.

Patients followed up at home should be told about the appropriate infection control and isolation precautions during the disease and recovery periods (including to use a separate bedroom, whenever possible). Patients should be told who to call when they need help and how and when they should reach the emergency medical services. The home environment and social factors should be considered when deciding to determine whether the outpatient follow-up and treatment is appropriate.

Management of Hospitalized Patients

A patient admitted to the hospital is asked to wear a medical mask and is placed in a separate area so that the distance between the patient and other patients would be 2 meters. The patient is admitted into a single bed room, if available, and droplet isolation and personal protective precautions are applied both for the patient and the attending persons. Regular ventilation and cleaning of the room is provided. The vital signs of the patient (heart rate, rhythm, respiratory rate, blood pressure, body temperature, and oxygen saturation) are observed (32).

Our experience in the management of patients hospitalized for COVID-19 has substantially accumulated compared with the early days of the disease. Updated national and international guidelines should be followed on this subject (28,32).

Levels of CRP, D-dimer, LDH, troponin, CPK, ferritin, absolute lymphocyte count, associated with serious disease but with unknown prognostic value, and the tests reflecting organ dysfunctions and various comorbidities (i.e. alanine aminotransferase, aspartate aminotransferase, urea,

creatinine) that might affect the potential treatment should be assessed. Some of those tests are repeated daily, every other day and some when there is clinical deterioration.

Chest X-ray can be used in the follow-up of hospitalized patients. Computed tomography is necessary when a chest X-ray is inadequate or in cases of clinical deterioration (33). A routine electrocardiogram is initially obtained; however, no echocardiogram (ECHO) is necessary. ECHO should be obtained in cases of hemodynamic deterioration, increased troponin, or in cases suggesting cardiomyopathy.

The risk of secondary bacterial infections is quite low in COVID-19. Nevertheless, two sets of blood cultures and a sputum culture should be obtained and procalcitonin level should be checked when suspected. Laboratory values must be carefully evaluated not to reach unnecessary conclusions. For example, high levels of troponin do not necessarily show acute coronary syndrome in a patient with COVID-19 (34).

Clinical deterioration and ARDS might develop immediately after the emergence of dyspnea. Advancement into ARDS was seen to occur in a mean of 2.5 days after the start of dyspnea in patients with COVID-19 and development of ARDS in the initial studies (13). Supportive oxygen treatment is applied in most of the patients with dyspnea and SpO_2 ≤93%. Antiviral, anticytokine, anti-inflammatory and other current treatment modalities should be applied based on the oxygen requirement, presence of macrophage activation syndrome, level of chest involvement in imaging studies and the laboratory findings. No empirical antibiotic treatment should be administered to the patients diagnosed with COVID-19 for bacterial pneumonia. Secondary infection is not a prominent specification of this disease. However, when the diagnosis is uncertain, empirical bacterial pneumonia treatment can be started after obtaining samples such as sputum culture and urinary antigen test.

Anticoagulation should be started in all patients for venous thromboembolism prophylaxis in all hospitalized patients. However, recommendations for the intensity of the dosage are dynamic and the new evidence obtained from the clinical studies during the pandemics has changed to reflect the changes in the disease severity, such as in the milder disease with omicron variant and in vaccinated individuals. Additionally, the decision of prophylactic or therapeutic dose is based on a risk-benefit evaluation.

No negative effects of the non-steroidal anti-inflammatory drug have been proven in recent studies, in spite of concerns about their potential negative effects of them during the early days of COVID-19 (35,36).

The respired drugs should be applied through a measuring inhaler instead of a nebulizer, if possible to prevent the risk of aerosolization of SARS-CoV-2 by nebulization. Patients receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blockers should continue to receive those medications, unless there is otherwise a need to stop the treatment (i.e. hypotension, acute renal damage) (37). No supportive evidence was found for associating use of renin-angiotensin system inhibitors and severe disease, in spite of the speculation about the possible high risk of COVID-19 patients taking these agents. Statin or aspirin should not be started in COVID-19 patients who had no indications for these drugs before the disease. No benefit of these medications was demonstrated in randomized studies. However, patients already on aspirin or statin should continue to receive their drugs.

Severe disease can be characterized as severe respiratory tract infection, ARDS, sepsis, septic shock, myocarditis, arrhythmia and cardiogenic shock, metabolic acidosis and coagulation dysfunction, acute renal damage, exacerbations of chronic lung disease and clinical pictures of multi-organ failure. ICU admission is required in such critical diseases.

Patients are evaluated for discharge with decreased oxygen requirement, regression of fever and improvement in the laboratory values. Patients should be followed up for a while by outpatient appointments or by phone calls after the discharge.

Ethics

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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DOI: 10.4274/csmedj.galenos.2022.2022-11-4
Cam and Sakura Med J 2022;2(Suppl 1):27-36

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Management of Patients with COVID-19 in the Intensive Care Unit

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ABSTRACT

Coronavirus disease-19 (COVID-19), which was first seen in Wuhan, China in December 2019, caused a pandemic. According to the data of the World Health Organization, it has been reported to caused 6,566,610 deaths since the day it was defined. COVID-19 causes a wide variety of clinical conditions in adults, ranging from asymptomatic infection, mild respiratory symptoms, acute respiratory distress syndrome and multi-organ dysfunction to severe pneumonia. All these conditions require multidisciplinary patient care. Intensive care units (ICU) play a critical role for treating the most severe cases. In this process, it has been difficult for clinicians to meet the increasing need for hospitalization and intensive care, to provide clinical management of patients by following the current case approach. In our country, according to the constantly renewed COVID-19 guidelines of the Ministry of Health, the clinical follow-up of the patients was carried out. In this review, our aim is to present the management of patients with a diagnosis of COVID-19 who were followed up in ICUs.

Keywords: Coronavirus disease-19 (COVID-19), Intensive care unit, ARDS, ventilation

Introduction

Coronavirus disease-19 (COVID-19), first identified in China's Wuhan province in December 2019, has since become a serious health problem and caused a pandemic (1). The entire world has been affected economically, socially and psychologically.

It was declared a "public health emergency of international concern" by the World Health Organization in January 2020, and as of July of the same year, approximately more than 10 million cases recorded in 6 months, and more than 6,500,000 deaths have been reported to date (2). COVID-19 causes a wide variety of clinical conditions in adults, ranging from asymptomatic infection, mild respiratory symptoms, acute respiratory distress syndrome and multi-organ dysfunction to severe pneumonia (3). In this process, healthcare practitioners are making a high level of effort to respond to the increasing demand; on the other hand, they are following the scientific literature with new clinical and experimental studies and benefiting from the experiences of clinicians from worldwide about the pandemic. In this article, our aim is to present the management of patients with a diagnosis of COVID-19 who were followed up in the intensive care units (ICU).

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Received: 03.11.2022 **Accepted:** 08.11.2022

CAM & SAKURA MEDICAL JOURNAL

Risk Factors for Severe COVID-19

Many risk factors and comorbidities, such as old age, male gender, obesity, hypertension, diabetes, chronic lung diseases, heart, liver and kidney diseases and tumors have been identified in the progression of COVID-19 to a severe and critical stage (Table 1). Additionally, clinically significant immunodeficiencies and pregnancy are also considered important risk factors (4).

Table 1. Definitions of critical and severe COVID-19

Category	Definiton
Severe	Clinical manifestations of pneumonia (fever, cough, shortness of breath, rapid breathing) and any of the following: • Respiratory rate >30 breaths/min; • Severe respiratory distress; or • Oxygen saturation in room air <90%
Critical	ARDS*, sepsis or septic shock or presence of respiratory failure requiring ventilation

**ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus disease-2019*

Indications for the Admission to the ICU

Patients with severe pneumonia and COVID-19 should be followed up in the ICU (1).

- Severe pneumonia,
- Acute respiratory distress syndrome,
- Sepsis, septic shock,
- Myocarditis, arrhythmia, cardiogenic shock or
- Multiple organ failure can be observed in severe clinical conditions.

According to the intensity of the required treatment and ideally where it should occur (out of hospital, emergency room, service, ICU and after discharge), COVID-19 patients are followed and treated; admissions to the ICU depend on the severity of the disease and the ICU capacity of the health system. According to the COVID-19 guideline of the Ministry of Health dated April 12, 2022, ICU admission should be considered in the following cases (5):

Patients Who Need to be Treated in the ICU:

- Dyspnea and respiratory distress
- Respiratory rate >30 breaths/min
- PaO_2/FiO_2 <300
- Increased oxygen requirement during follow-up
- SpO_2 <90% and PaO_2 <70 mmHg despite 5 L/min oxygen therapy
- Hypotension (SBP <90 mmHg and more than 40 mmHg decrease from normal SBP and MAP <65 mmHg, tachycardia >100/min)
- Patients with acute kidney and liver injury, confusion, other acute organ dysfunction (acute bleeding diathesis and immunosuppression)
- Cardiac biomarkers elevation and arrhythmia
- Lactate >2 mmol/L
- Skin disorders (prolonged capillary refill time and cutis marmaratus.

Patient Follow-up in the ICU

Monitoring

Standard monitoring parameters; non-invasive or invasive arterial pressure, oxygen saturation, electrocardiogram, body temperature, urine output monitoring. Additionally, end-tidal CO_2 monitoring should be applied to patients on mechanical ventilator support with severe respiratory failure (1).

In patients with critical illness with hemodynamic unstability (Table 1), it is important to monitor dynamic parameters that can evaluate cardiac output, at least with central venous catheterization and even invasive and non-invasive methods. In this group of patients, the results obtained from these parameters are critical both in the decision of vasopressor and inotropic treatment and in fluid management. The National Institutes of Health (NIH) states that dynamic parameters (body temperature, capillary refill time, and/or lactate level) should be preferred over static parameters in fluid response (6). Other tools that guide treatment are echocardiography and lung ultrasonography (1).

Laboratory

In laboratory monitoring; with daily hemogram; white blood cell, lymphocyte, neutrophil lymphocyte ratio, thrombocyte and erythrocyte amount are important in clinical follow-up (1). Laboratory findings in critically ill patients with COVID-19 include leukopenia or leukocytosis, lymphopenia, and elevated D-dimer, aminotransferases, lactate dehydrogenase, and ferritin levels. Abnormalities are typically more pronounced in critically ill patients, although these can also be seen with less severe COVID-19 (7).

Arterial blood gas measurement; they are also precious parameters in terms of oxygenation, ventilation, acid-base status, blood lactate level, and thus the appropriate management of respiratory support in the patient, and tissue perfusion, fluid, sepsis, septic shock management (1).

Critically ill patients diagnosed with COVID-19 may also have an elevated procalcitonin (PCT) level. PCT indicates that there is a secondary bacterial infection focus, which is important for antibiotic selection. Coagulation parameters are important for the follow-up of processes such as coagulopathy and vasculitis that may develop in these patients. Monitoring of prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer and ferritin is recommended (1).

In some patients with severe COVID-19, there is laboratory evidence of a severe inflammatory response similar to cytokine release syndrome, with persistent fever, elevated inflammatory markers (e.g., D-dimer, ferritin, interleukin-6). Abnormalities in laboratory results indicate a poor prognosis.

Clinic

Deterioration in the respiratory system is associated with mechanical ventilation, which we can consider as the beginning of the ICU period.

Frequently, lung gas volume and respiratory system compliance are decreased, oxygenation impaired, and $PaCO_2$ may rise.

Applied sedation and neuromuscular blocking causes loss of skeletal and diaphragmatic muscle mass, resulting in insufficient understanding of the actual driving pressure applied during spontaneous breathing, resulting in hypoventilation at lower tidal volumes and protective driving pressures (8). These changes trigger atelectasis formation and resulting loss of lung gas volume. It is possible that the additional fluid load during this phase is at least one factor that contributes to the increase in pulmonary edema and impaired lung function. This condition, defined as type H lung by Gattinoni et al. (8), is characterized by high elastance, high lung weight, high right-to-left shunt, and a high rate of recovery.

Radiological Imaging

Bedside lung imaging should be performed daily or every other day order to monitor the underlying viral pneumonia and acute respiratory distress syndrome (ARDS) course, as well as to monitor complications such as atelectasis and pneumothorax. Reports of a few patients showing computed tomography (CT) scan image properties consistent with fibrosis but showing near-normal improvement in chest radiography, caution should be exercised against the early prognosis of irreversibility and established fibrosis (8).

Chest radiography: Chest radiography may be normal in early or mild disease. In a retrospective study of 64 patients diagnosed with COVID-19, Wong et al. (9) reported that 20% of the patients did not have any abnormality in the chest radiography throughout the disease. Common abnormal radiographic findings increased throughout the disease course with a peak in severity 10 to 12 days after symptom onset; it is a lung involvement with bilateral, peripheral and lung bases consolidation and ground glass opacities (Figure 1) (9).

Lung CT: Although more sensitive than chest radiography and some CT findings are characteristic of COVID-19, no findings can completely rule out the possibility of COVID-19.

Ground-glass opacification with or without consolidative abnormalities is most commonly seen on lung CT in patients with a diagnosis of COVID-19, which is consistent with viral pneumonia (Figure 2). As an example, in a systematic review of studies evaluating lung CT findings in more than 2.700 COVID-19 patients, the following abnormalities were noted (10).

- Ground glass opacification-83%
- Mixed consolidation ground glass opacities-58%
- Pleural thickening-52%
- Interlobular septal thickening-48%
- Air bronchograms-46%

Lung ultrasound (LUS): COVID-19 has bilateral, asymmetric and patchy involvement in the periphery of the lungs is involved, which can increase the effectiveness of LUS. Some findings detected with LUS are as follows: B lines (It is the most important ultrasonographic finding of the disease. Although these lines are the typical finding of the disease, they can also be seen in different interstitial diseases, therefore, their specificity is low). Irregular pleural line (may be regular or

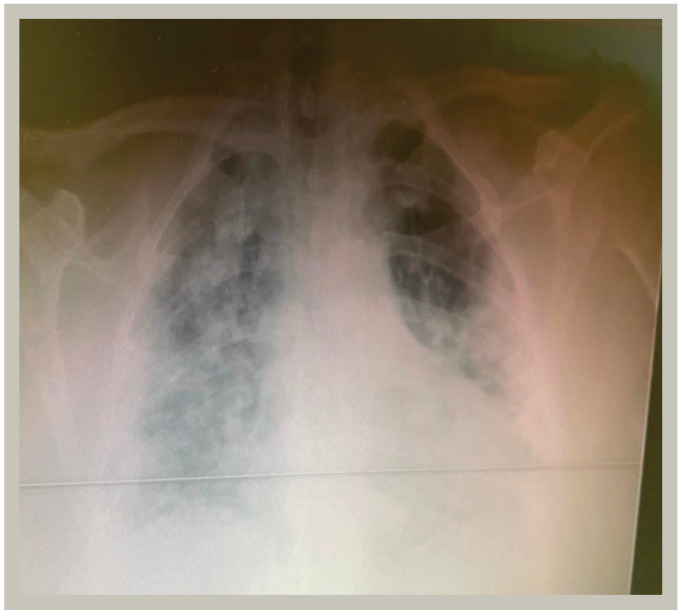

Figure 1. Bilateral, peripheral and lung bases consolidation and ground glass opacities

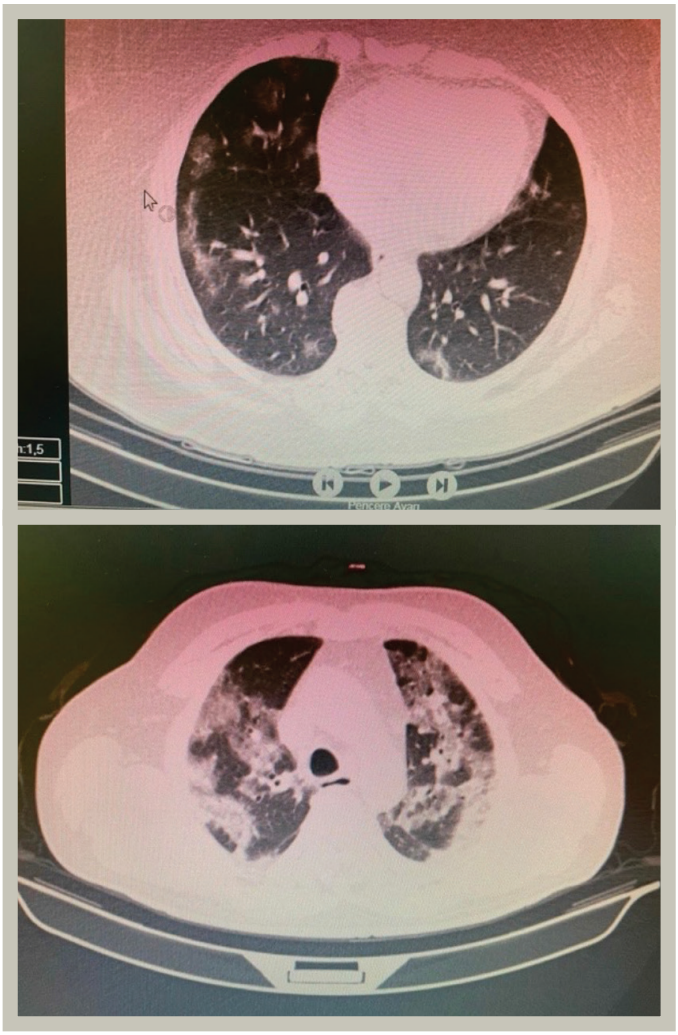

Figure 2. Ground-glass opacification with or without consolidative abnormalities

fragmented), punctate defect, subpleural consolidation, air bronchogram, and in severe cases, pleural sliding movement ("sliding") deterioration can be observed (11).

Management of Acute Respiratory Failure and Acute Respiratory Distress Syndrome

ARDS: The diagnosis of ARDS, which can occur in patients with severe pneumonia and has a high mortality rate, is defined according to the Berlin criteria (Table 2) (3).

As patients' clinic worsens, increased respiratory support is required, often requiring the level of ICU care, depending on hospital and patient characteristics.

Respiratory support includes oxygenation with low-flow and high-flow systems, non-invasive ventilation (NIV), and the use of other adjunctive therapies (e.g., nebulized medications) and rescue therapies (e.g., prone positioning).

Table 2. The Berlin definition of the ARDS

Timing	Respiratory distress that has occurred or worsened in the past week
Chest imaging	Bilateral opacities not explained radiologically by volume overload, lobar or lung collapse, or nodules
Origin of edema	Respiratory failure cannot be explained by heart failure or fluid overload alone
Hypoxemia	
• Mild ARDS	200 mmHg $<PaO_2/FiO_2$ ≤300 mmHg (PEEP ≥5 cm H_20)
• Moderate ARDS	100 mmHg $<PaO_2/FiO_2$ ≤200 mmHg (PEEP ≥5 cm H_20)
• Severe ARDS	PaO_2/FiO_2 ≤100 mmHg (PEEP ≥5 cm H_20)

ARDS: Acute respiratory distress syndrome, PEEP: Positive end-expiratory pressure

While some patients recover and the need for respiratory support can be reduced; in some, oxygenation continues to deteriorate; a decision needs to be made regarding intubation and mechanical ventilation. In the ICU, treatment principles should not differ significantly from those recommended for treating ARDS. However, close attention should be paid to the PEEP setting, as prerequisites for PEEP efficacy (i.e., pulmonary edema or atelectasis) exist only in the intermediate stages of COVID-19 and are less common too early or too early stages. Optimally, the hemodynamics and respiratory system mechanics should be carefully monitored and the patient should be given the most appropriate ventilator therapy.

Respiratory Support in Patients Diagnosed with COVID-19 Pneumonia

Awake prone position

For hospitalized patients with hypoxemic respiratory failure due to COVID-19, an awake/sedated prone position receiving oxygen or non-invasive support methods [including low-flow oxygen, high-flow oxygen delivered via nasal cannula (HFNC), or NIV] is recommended. Titration of oxygen therapy is highly recommended to prevent hypoxemia in acute hypoxemic respiratory failure. A range of 90-96% oxygen saturation confirmed by pulse oximetry is a reasonable target (12).

While an optimally beneficial time has not been established, the prone position should be encouraged in the eligible patient for at least 6 to 8 hours, typically within a 24-hour period. However, it has been experienced in clinics that some patients have difficulty in the prone position due to personal ailments (e.g., face, neck or arm pain, inability to sleep prone) or discomfort from external equipment (e.g., mask and tube).

Although oxygenation can be partially restored, a progressive rise in $PaCO_2$ and dead space, as commonly described, becomes evident in connection with structural changes in the lung parenchyma. Responses to recruitment, higher PEEP, and the prone position gradually fades. Indeed, in nearly 50% of patients, oxygenation may decrease rather than increase. This phenomenon is consistent with a progressive shift from edema to a fibrotic state (8). The NIH does not recommend the awake prone position as a salvage therapy to avoid intubation in patients with refractory hypoxemia with indications for intubation and mechanical ventilation (6).

Low flow oxygen

For patients with hypoxemic respiratory failure due to COVID-19, supplemental oxygenation via a nasal cannula with a low-flow system (i.e., up to 6 L/min) is appropriate as an initial strategy. The degree of viral aerosolization at low flow rates is unknown but probably minimal (13).

High Flow Nasal Cannula Oxygen Therapy

If SpO_2 continues to be low despite O_2 treatment with a nasal cannula and mask with sufficient flow, HFNC can be given up to 20-80 L/min, FiO_2 up to 21-100% O_2 can be given. HFNC devices are systems that provide clearing of the anatomical dead space from CO_2, positive nasopharyngeal pressure, a more stable FiO_2 and improvement in mucociliary function. It can give about 30-40 L/min O_2 and 4-7 cmH_2O positive end-expiratory pressure (PEEP) (14). This helps open collapsed alveoli by reducing physiological dead space and maintaining a modest PEEP, resulting in better comfort by reducing the work of breathing (12).

At the onset of the COVID-19 pandemic, fear of disease transmission by exhaled aerosol led to avoidance of HFNC use and preference for early intubation in patients. However, observations of aerosol concentrations in the environment of COVID-19 patients in clinical studies show that aerosol masses are not significantly different before and after HFNC use and are further reduced when a surgical mask is worn on the patient's face (15). For this reason, experts recommend that clinicians use HFNC therapy for COVID-19 patients, with attention to the correct use of personal protective equipment, no different from those without infection (16).

Despite the lack of controlled studies in COVID-19, large case series have reported positive outcomes for patients treated with HFNC. A recent computer simulation study concluded that strategies involving HFNC may result in greater mechanical ventilator availability and fewer deaths for patients who do not need emergency intubation (17).

Non-invasive Mechanical Ventilation (NIMV)

NIMV is defined as positive pressure respiratory support administered through a mask instead of an endotracheal tube as the interface. Positive airway pressure can be applied either continuously (continuous positive airway pressure, CPAP) or bilevel (bilevel positive airway pressure, BiPAP; different pressures in inspiration and expiration). CPAP maintains a constant level of pressure throughout the respiratory cycle. BiPAP, on the other hand, provides different levels of positive airway pressure during inspiration (IPAP) and expiration (EPAP). The difference between IPAP and EPAP is called pressure support and it increases ventilation. With NIMV application, functional residual capacity increases, collapsed or non-ventilated alveoli open, oxygenation improves, respiratory work load, respiratory muscle fatigue and upper airway resistance decrease.

NIMV indications:

- Dyspnea (moderate-severe),
- Tachypnea (>24/minute obstructive pulmonary diseases, >30/minute restrictive lung diseases)
- Increased respiratory workload (use of accessory respiratory muscles, abdominal paradoxal breathing),
- Impaired gas exchange (acute respiratory failure of acute or chronic background);
- $PaCO_2$ >45 mmHg, pH <7.35)
- Hypoxemia (PaO_2/FiO_2 <200)

Respiratory arrest and the presence of an obstacle to applying the mask to the face (such as burns, trauma) are absolute contraindications for NIMV application. There are also relative contraindications; hemodynamic instability, uncontrolled myocardial ischemia or arrhythmia, uncontrolled upper gastrointestinal bleeding, agitation, lack of cooperation, inability to protect the airway, difficulty swallowing, excessive secretion, multiple organ failure, recent upper airway or upper gastrointestinal tract surgery.

In a multicenter randomized study (the RECOVERY-RS randomized clinical trial) conducted in the UK, tracheal intubation and 30-day mortality were found to be statistically significantly lower in the CPAP-applied group when CPAP was compared with conventional oxygen therapy in acute respiratory failure due to COVID-19 infection. NIMV can be applied within a protocol in intermediate intensive care or ward conditions outside the ICU but intubation should not be delayed in case of failure criteria (18).

Invasive mechanical ventilation (IMV)

In patients who will undergo IMV, endotracheal intubation should be performed by trained and experienced practitioners with a rapid sequential intubation protocol. To provide balanced anesthesia in these patients who will undergo elective endotracheal intubation, induction should be performed using anesthetic agents to be selected according to patient characteristics. If possible, the use of bag-mask should be avoided during preoxygenation. Intubation should be performed with a video laryngoscope, if possible. Unless necessary, the mechanical ventilator circuit should not be disconnected, and if disconnection is necessary, personal protective equipment must be used. If possible, the closed system aspiration method should be used (5).

In COVID-19 patients who require endotracheal intubation, lung protective mechanical ventilation should be applied in patients who undergo IMV for ARDS. Tidal volume should be set at 4-8 mL/ideal body weight. The plateau pressure should be <30 cmH_2O and the driver pressure (plateau pressure-PEEP) <15 cmH_2O.

The ventilation frequency can be adjusted 16-24/min. In cases with pH <7.15 and hypercapnia, the respiratory rate may increase up to 30/min. Permissive hypercapnia can be applied unless the pH is <7.15. If the tidal volume, plateau pressure and driving pressure are too high and patient ventilator dyssynchrony occurs sedation, analgesia or neuromuscular blocking agents can be administered. Excessive sedation should be avoided (5).

Table 3. Treatment options for severe acute respiratory distress syndrome due to COVID-19 (19)

Treatment	Implementation
HFNC	This may have prevented or delayed the need for intubation
Tidal volume	Use 6 mL/kg of predicted body weight (may decrease to 4 mL/kg of predicted body weight)
Plateau airway pressure	<30 cm H_2O
Positive end-expiratory pressure	Consider moderate to high levels if needed
Recruitment maneuvers	At low pressures
Use of neuromuscular blockers	For ventilator non-compliance, increased airway pressure, hypoxemia
Prone position	For worsening hypoxemia, PaO_2:FiO_2 <100-150 mmHg
Inhaled NO	Use 5-20 ppm*
Fluid management	Aim for a negative fluid balance of 0.5-1.0 L per day
Renal replacement therapy	For oliguric renal failure, acid-base management, negative fluid balance
ECMO	Use the EOLIA criteria (23)

**ppm: Parts per million, HFNC: High-flow oxygen delivered via nasal, ECMO: Extracorporeal membrane oxygenation, COVID-19: Coronavirus disease-2019*

If hypoxemia progresses to a ratio below PaO_2:FiO_2 <100-150 mmHg, there are several treatment options. The PEEP level can be increased by 2-3 cm H_2O every 15-30 minutes to keep the plateau airway pressure below 30 cm H_2O to increase oxygen saturation to 88-90%. The use of high PEEP versus a low PEEP strategy is recommended by the NIH (6). Recruitment maneuvers may have little effect, but moderate pressures of about 30 cm H_2O for 20-30 seconds following hemodynamics can be applied (19). If static compliance is >40 mL/cm H_2O, recruitment and high PEEP values may not be required. However, patients with low compliance should be treated like classical ARDS, especially in moderate-severe ARDS, PEEP should be applied, which will prevent atelecto-trauma and provide alveolar patency, but at pressures that will not cause excessive stretching and will not disrupt hemodynamics, which will provide the best compliance and oxygenation. Additionally, the prone position should be applied if there are no specific contraindications and in conjunction with the previously described interventions (19). A prone position of 12-16 hours per day is recommended for mechanically ventilated patients. Although the use of neuromuscular blocking agents is not routinely recommended, use of neuromuscular blockers as bolus or infusion (up to 48 h if persistent patient ventilator dyssynchrony) is recommended during lung protective ventilation (6).

The prone position may improve oxygenation of 5-20 ppm inhaled as an alternative if persistent refractory hypoxemia persists despite efforts to optimize neuromuscular blockade and PEEP therapy (Table 3) (19). However, routine use of inhaled nitric oxide is not recommended (6).

Extracorporeal membrane oxygenation (ECMO)

Although ECMO is often life-saving, it represents a form of support that sometimes takes several weeks to allow for recovery and recovery, or time to determine the potential reversibility of lung injury (Table 3). No NIH recommendation due to insufficient evidence on the benefits of using ECMO in patients with refractory hypoxemia (6).

Weaning

Preparation for extubation should be performed after standard spontaneous breathing trials (SBT) applications. Weaning and extubation should be performed when clinical (neurological well-being, good hemodynamics, improved

respiratory distress) and laboratory parameters (pH >7.35 in arterial blood gas, $PaCO_2$ <45 mmHg, PaO_2 >60 mmHg) are appropriate.

However, attention should be paid to infection control measures changes for COVID-19. Equipment; while we recommend using closed systems, and T-track testing is not recommended for SBTs. To reduce the risk of reintubation following extubation, patients with COVID-19 should have a higher degree of extubation readiness. The implementation may vary and may include higher criteria for passing an SBT. For example, some experts use lower pressure assisted ventilation parameters (e.g., 0-5 cm H_2O) instead of the typical high PEEP to overcome endotracheal tube resistance during extubation, while others use SBT for longer durations (e.g., typical two four hours instead of one hour) they deem appropriate (20). Newer procedures such as "mask-on-tube" extubation can reduce exposure to droplets and aerosols. We recommend that the steps for weaning from mechanical ventilation not be changed unless there is evidence to the contrary. Extubation can be performed safely by adhering to standard PPE (personal protective equipment) practices.

Extubation

Extubation in the isolation room should be preferred in patients with continued infection control measures for COVID-19. Close communication with a clinician experienced in intubation when extubating a patient with a diagnosis of COVID-19 is advocated, especially for patients with predetermined difficulty in airway when rapid reintubation is required (1).

Tracheostomy

Approximately 10% of patients followed in the ICU with a diagnosis of COVID-19 require tracheostomy (21).

• **Indications:** Similar to patients without COVID-19 (e.g., weaning failure, failed extubation, secretion management, airway edema, failure to protect the airway (e.g., poor mental state) (22).

• **Timing:** The optimal timing for tracheostomy in COVID-19 patients is uncertain, but it is usually delayed until after 10 days of intubation (14-21 days or longer) although the practice varies (22).

• Procedure; for patients who are contagious during the procedure, tracheostomy is considered a high-risk procedure for aerosolization (22).

Nutritional support

The same nutritional principles used in critically ill patients without COVID-19 should be applied to critically ill patients with COVID-19 (24).

Fluid and Electrolyte Management

Conservative fluid management with crystalloids is recommended for patients with acute respiratory distress syndrome unless patients have sepsis or hypovolemia due to high fever or gastrointestinal losses (1).

While the NIH recommends the use of balanced/buffered solutions for acute fluid resuscitation of patients in shock due to COVID-19, it does not recommend the use of albumin. Norepinephrine is recommended as a first-line vasopressor. It is recommended to keep the MAP around 60-65 mmHg. The use of hydroxyethyl starch solution is not recommended for intravascular volume support. If norepinephrine is available in shock patients with a diagnosis of COVID-19, the use of dopamine is not recommended. Vasopressin and epinephrine are recommended as second-choice vasopressors. The use of low-dose dopamine is not recommended for the preservation of kidney functions. The use of dobutamine is recommended in patients with cardiac dysfunction who show signs of hypoperfusion despite adequate fluid therapy and vasopressor support. Invasive blood pressure monitoring is recommended in patients on vasopressor support. Low-dose corticosteroid therapy is recommended in patients with refractory septic shock who have completed corticosteroid therapy (6).

If there is no shock picture in patients with pulmonary edema, it is recommended to stay negative for 500 mL in the acute period. Renal function should be carefully monitored (6).

Complications

In addition to the difficulties experienced in the clinical management of COVID-19, many complications caused by the disease itself have been reported (Table 4). Common complications of acute respiratory distress syndrome associated with COVID-19 include acute kidney injury (AKI), elevated liver enzymes, delirium/encephalopathy, heart damage (e.g., cardiomyopathy, arrhythmia, and sudden cardiac death), and thrombosis (25,26).

• **AKI:** It occurs in 15 to 30% of critically ill patients with COVID-19. Some of these patients require renal replacement therapy (27). In a cohort study of 40,000 critically ill patients, Cummings et al. (28) reported that one-third (31%) of patients required renal replacement therapy for AKI.

• **Gastrointestinal complications:** Gastrointestinal complications appear more common in patients with ARDS due to COVID-19 than in patients with ARDS for other reasons (74% vs. 37%) These rates include high aminotransferase levels (55%), severe ileus (48%) and mesenteric ischemia (4%) clinics (29).

• **Neurological complications:** Neurological complications are common in critically ill patients hospitalized in the ICU (30). Delirium or encephalopathy is the most common complications and present with marked agitation and confusion and corticospinal system findings (hyperreflexia). Consistent with this, ICUs have observed that sedation requirements are high in this population, particularly immediately after intubation. Other common complications include acute ischemic stroke, myositis, Guillain-Barré, and focal neuropathy. Encephalitis is rare (31).

• **Cardiovascular complications:** In critically ill patients, it may develop after heart damage, a complication that is concurrent with respiratory disease, or after respiratory disease has resolved. Cardiomyopathy, atrial arrhythmias, myocardial infarction, acute right heart failure and cardiac arrest are cardiac complications seen in patients with COVID-19 (32).

• **Thrombosis:** Hypercoagulable state resulting in arterial and venous thrombosis is common in critically ill patients with COVID-19. The actual incidence is unknown, although some studies report an incidence as high as 30% (33).

• **Sepsis, shock, multi-organ failure:** Sepsis, shock, and multi-organ failure may occur in critically ill patients with COVID-19, but appear less common compared with non-COVID-19-related ARDS. The need for vasoactive agents is variable (32,34). According to the literature, hypotension is unusual in the absence of a specific cause and the need for vasoactive agents is typically associated with sedative agents, cardiac dysfunction, or secondary bacterial infections.

• **Secondary infections:** Although our data is limited, critically ill patients with COVID-19 are at risk of secondary infections. Secondary infections include pneumonia (e.g., bacterial, fungal), vascular catheter infections, urinary tract infections, Epstein-Barr and cytomegalovirus reactivation, and rarely strongyloides reactivation (20). Empirical antibiotic therapy should be avoided unless there is a proven or suspected focus of bacterial infection. Patients receiving antibiotic therapy during hospitalization should be evaluated daily and unnecessary antibiotic use should be avoided (6).

• **Pneumothorax and barotrauma:** Pneumothorax may occur in critically ill patients with a diagnosis of COVID-19 who is spontaneously breathing or mechanically ventilated. Patients with COVID-19-related ARDS under mechanical ventilation therapy may have an increased risk of barotrauma compared with patients with other ARDS, but data are variable, ranging from 2 to 40%. Patients undergoing invasive ventilation have higher rates than NIV, and those undergoing invasive ventilation have a higher risk of death compared with non-COVID-19 patients with barotrauma (35).

Prognosis

• **Mortality:** Retrospective studies have reported variable mortality in ARDS associated with COVID-19 (27,34). The death rate from COVID-19 appears to be due to the presence of severe ARDS, and the rate ranges from 12 to 78%, with an average of 25 to 50%. However, death can occur from certain other conditions such as cardiac arrhythmia, cardiac arrest, and pulmonary embolism. Limited data show that there is no difference in mortality among people with ARDS between those with COVID-19-related ARDS and those with non-COVID-19-related ARDS (36).

• **Mortality risk factors:** Globally, the major mortality-related risk factor in critically ill patients with COVID-19 is advanced age. In a study by Gupta et al. (37) on 2.215 patients diagnosed with COVID-19, mortality was associated with ≥80 years of age, and it was stated that the risk of death increased 11 times. Other risk factors associated with death in critically ill patients are (37):

• ARDS, particularly severe ARDS development and the need for mechanical ventilation,

• Comorbidities (e.g.: Obesity, chronic heart and lung conditions, hypertension, diabetes, chronic kidney disease, renal replacement therapy, cancer),

• Markers of inflammation or coagulation (e.g.: Fever, D-dimer level >1 microg/mL, high fibrin degradation products, long-term activated partial thromboplastin, and prothrombin times),

• Laboratory parameters (e.g.: Worsening lymphopenia, neutrophilia, troponin elevation),

• Male gender,

• Severity of organ dysfunction at admission,

• Right ventricular dysfunction.

Table 4. Difficulties in clinical management (38)

Epidemiology and clinical features	Suggestions
• It is difficult to predict the course of the disease from the onset of symptoms.	• Support research to develop and validate prognostic tools and biomarkers.
Diagnosis	
• Clinical features are not specific; the risk of missing an early case in a local outbreak should not be ignored. The sensitivity of RT-PCR tests for critically ill patients unknown. • RT-PCR tests may not be available in many intensive care units; if any, the assays will take time to complete.	• Adopt a low threshold for diagnostic testing, if applicable. • Repeat sampling, preferably from the lower respiratory tract, if necessary. • Maintain a high index of suspicion for COVID-19.
Management of acute respiratory failure	
• The benefits of NIV and HFNC and the risks of viral transmission via aerosolization are unclear. • Intubation poses a risk of viral transmission to healthcare workers. • ECMOs are a limited number centralized in designated centers.	• Reserve for mild ARDS with airborne measures, preferably in single rooms and at low intubation threshold. • Perform intubation drills; the most experienced practitioner should intubate with full PPE and limited balloon-mask ventilation. • Balance the needs of more patients with less severe disease (unproven) against the few benefits.
Other intensive care management	
• These patients often develop myocardial dysfunction in addition to acute respiratory failure.	• Care should be taken in fluid management due to hypovolemia; myocardial involvement should be detected early by troponin and betanatriuretic peptide measurements and echocardiography.
• Bacterial and influenza pneumonia or co-infection is difficult to distinguish from COVID-19 alone.	• Consider empirical broad-spectrum antibiotics and neuraminidase inhibitors and then taper them off quickly.
• The benefits and risks of systemic corticosteroids are unclear.	• Routine use should be avoided until further evidence is available.
• Transfer from the intensive care unit for investigations such as CT scans carries a risk of viral transmission	• Minimize transfers by using alternative methods such as bedside ultrasound.
• In severe COVID-19, viral transmission in the upper respiratory tract continues 10 days after the onset of symptoms.	• The isolation of patients should be terminated after clinical recovery and after two negative RT-PCR tests 24 h apart.
• The use of purposeful and experimental treatments unsupported by strong evidence.	• Seek expert guidance from local or international communities and enroll patients in clinical trials if possible.

ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus disease-2019, ECMO: Extracorporeal membrane oxygenation, HFNC: High-flow nasal cannula, ICU: Intensive care unit, NIV: Non-invasive ventilation, PPE: Personal protective equipment, CT: Computed tomography, RT-PCR: Reverse transcription-polymerase chain reaction

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.B.Ş., H.C., Concept: E.B.Ş., Design: H.C., Data Collection or Processing: H.C., Analysis or Interpretation: E.B.Ş., Literature Search: E.B.Ş., H.C., Writing: E.B.Ş., H.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/csmedj.galenos.2022.2022-11-10
Cam and Sakura Med J 2022;2(Suppl 1):37-42

CSMJ

Update on COVID-19 in Children

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ABSTRACT

Since the start of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, it has been clear that most children who have been infected with the virus remain asymptomatic or very mildly ill. Since asymptomatic children are less often examined, the true prevalence of asymptomatic SARS-CoV-2 infection is probably underestimated. Children rarely get anosmia/ageusia, yet it is the best indicator of a positive SARS-CoV-2 test. Children with coronavirus disease-2019 (COVID-19) generally have a lower risk of hospitalization and potentially fatal consequences. Immunization with effective and safe vaccine in children and adolescents is likely to provide protection against severe COVID-19 infection. Recent results from COVID-19 vaccine studies indicate good efficacy and tolerability in children.

Keywords: COVID-19, COVID-19 in children, pandemic, SARS-CoV-2

Introduction

In December 2019 in Wuhan, China, the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) made its first appearance before fast spreading throughout the world. On March 11, 2020, the World Health Organization (WHO) declared coronavirus disease-2019 (COVID-19) a pandemic (1). As of November 10th, 2022, 14,950,786 pediatric COVID-19 cases had been reported in the USA, making up 18.3% of all cases and occurring at a rate of 19,864 instances per 100,000 children (2).

All ages, including children, are susceptible to SARS-CoV-2 infection. Numerous pediatric investigations have described the multiple unusual clinical manifestations of children with COVID-19 during the pandemic. Although pediatric age groups have also reported fatal cases, the illness appears to affect children less severely than it affects adults (3). Asymptomatic, mild, or moderate disease is present in approximately 90% of pediatric patients. The true incidence of COVID-19 pediatric infections may have been underestimated at the time because of the high percentage of asymptomatic children and low testing rate (2). Additionally, 6.7% of cases may be severe. Generally, the disease has a severe course in patients younger than 1 year and with underlying disease (3).

Five SARS-CoV-2 variants, including Alpha, Beta, Gamma, Delta, and Omicron, as reported by the WHO, have been identified as of September 11, 2020. All age groups experienced an increase in infectivity due to variations, particularly Delta and Omicron. Recent research has demonstrated that Omicron variations are less severe but more contagious than prior SARS-CoV-2 variants, and that they replicate more readily in the upper respiratory tract than in the lower respiratory tract (4).

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Received: 18.11.2022 **Accepted:** 23.11.2022

CAM & SAKURA MEDICAL JOURNAL

Several studies have been conducted on the diagnosis and treatment of COVID-19. However, there are not enough studies to study pediatric patients (5).

Clinical Manifestations

When compared to adult cases, pediatric COVID-19 cases typically present with milder symptoms and reduced risks of hospitalization and death. Furthermore, a substantial percentage of children with COVID-19 infections have no symptoms. Between 15% and 65% of pediatric COVID-19 cases have been observed to be asymptomatic (6).

According to the child's age, COVID-19 has a different clinical presentation. Fever (46%), cough (37%), headache (15%), diarrhea (14%) and sore throat (13%) were the most common symptoms in children under nine years of age. Children between the ages of 10 and 19 years are more likely to have symptoms similar to COVID-19 in adults, including headache (42%), cough (41%), fever (35%), myalgia (30%), sore throat (29%), and shortness of breath (16%) (6). Although fever and cough are the most commonly reported symptoms in children with COVID-19, other lower respiratory tract diseases, such as pneumonia and bronchiolitis, are also observed (3).

Since angiotensin-converting enzyme-2 (ACE-2), the SARS-CoV-2 receptor, is also present in other organs such the kidneys, adipocytes, heart, brain, enterocytes, and liver COVID-19 is a systemic illness that affects numerous organs. Extrapulmonary symptoms of COVID-19 may be brought on by ACE-2-linked signaling pathways (3).

Children with COVID-19 have rarely had cutaneous abnormalities documented (6). Cutaneous manifestations may include painful lesions of the fingers and feet as well as a rash (maculopapular, urticarial, or vesicular). Changes are typically seen on the feet (74%-100%) but have also been reported to occur on the hands (6).

The clinical spectrum of COVID-19 severe illness presentation in pediatrics is similar to that in adults. Children may show multi-system organ failure, encephalopathy, myocarditis, shock, acute renal failure, coagulopathy, and neurological involvement (including Guillain-Barré syndrome, cerebral edema, and stroke) (6).

Risk factors for serious diseases are categorized by age group. Children aged 2 to 17 years are at risk for chronic lung illness, neurological problems, cardiovascular disease, obesity, and diabetes. Additionally, infants under 1 year of age had the highest prevalence of hospitalization and severe COVID-19 compared to other age groups (7).

Post-infectious Complications

• Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C or multisystem inflammatory syndrome in children, is a rare but possibly fatal COVID-19 consequence (8). Significant cardiovascular, gastrointestinal, and mucocutaneous abnormalities characterize the presentation, which shares significant characteristics with Kawasaki illness, septic shock, and toxic shock syndrome (9). Clinical and laboratory characteristics are used in the case definition of MIS-C to identify suspected or confirmed cases. The case definitions used by the WHO and Centers for Disease Control and Prevention (CDC) differ slightly. Both categories share the same features, including a fever (duration varies), elevated inflammatory markers, at least two indications of multisystem organ involvement, proof of SARS-CoV-2 infection or exposure, and the exclusion of other possible sources of inflammation. Additionally, the child must have serious clinical signs necessitating hospitalization according to the CDC case criteria (8,9).

Supportive treatment should be a part of the regimen to maintain haemodynamic stability and guarantee appropriate systemic perfusion. For the quick identification and treatment of any arrhythmias, continuous cardiac monitoring is necessary. Typically, immediate empiric broad-spectrum antibiotic treatment should be initiated on patients who present with severe multisystem involvement and shock while awaiting culture findings (9). For most patients with MIS-C, intravenous immune globulin (IVIG) and/or glucocorticoids can be used in the treatment. Patients are considered refractory to initially therapy, if they do not show improvement within 24 h of treatment. For MIS-C patients who do not react to IVIG plus low- to moderate-dose steroids, pulse-dose steroid therapy, infliximab (a tumor necrosis factor inhibitor), or anakinra [an interleukin-1 (IL-1) inhibitor] may be administered (10).

Thrombosis is more likely in patients with MIS-C. Because of the risk of thrombosis, low-dose aspirin may be added to the treatment regimen. Additionally, patients with a current or past history of venous thromboembolism usually require therapeutic anticoagulation with low-molecular-weight heparin (9).

Despite the lack of long-term follow-up data, the prognosis for MIS-C is good because most children make complete clinical recovery. Generally, death rates range from 1 to 2 percent. Most kids with cardiac involvement recover function by the time they are released from the hospital. After discharge, cardiology should be performed on children with heart problems (10).

• Long COVID-19

A significant number of people who had an acute SARS-CoV-2 infection are now suffering from various persistent symptoms because of the COVID-19 pandemic. This group consists of patients whose symptoms began during or shortly after COVID-19, persisted for at least four weeks, and could not be accounted for by any other condition. Several terminology, including "post-COVID conditions", "long COVID", "postacute sequelae of SARS-CoV-2 infection", "post-acute COVID-19", "chronic COVID-19", and "post-COVID syndrome", have been used to describe prolonged symptoms following COVID-19 (11).

On "long COVID", there is not much information available in pediatrics. However, most children's symptoms appear to last no more than 12 weeks (12).

Physical symptoms that last after covid 19 are common and frequently involve weakness, breathlessness, chest pain, and coughing. Anosmia, joint discomfort, headache, rhinitis, dysgeusia, poor appetite, dizziness, myalgias, sleeplessness, alopecia, sweating, and diarrhea are less frequent chronic physical complaints. Additionally, patients may report psychological or cognitive issues such post-traumatic stress disorder, anxiety, depression, and difficulties concentrating. A COVID-19 follow-up visit is not routinely recommended in patients with mild-to-moderate disease who do not require hospitalization unless the patient requests it or has persistent, progressive, or new symptoms. The need for further investigation is determined by the severity of the disease, previous abnormal tests performed during the illness and current symptoms. Routine retesting of patients for active infection with SARS-CoV-2 for which hospitalization is not required, is not recommended. Instead, non-test-based approaches to eliminate infectious measures are preferred (11).

Vaccinations

A large portion of the world must develop virus immunity in order for this pandemic to be over. Also using vaccination to perform this is the safest option. Within the less than a year after the outbreak began, numerous research teams have developed vaccines to prevent SARS-CoV-2. The challenge now is to make these vaccines accessible to people worldwide. It is critical that all individuals receive the necessary protection, not just those in rich countries. Worldwide, 12.94 billion doses have been given; today, 1.93 million are given every day. 68.2% of people worldwide have received at least one dose of the COVID-19 vaccination, whereas only 23.6% of people in low-income countries have (13). The COVID-19 vaccination should be administered to all children to avoid the disorder. CDC recommends COVID-19 vaccines for everyone ages 6 months and older, and boosters for everyone ages 5 years and older if eligible. Table 1 lists the eleven vaccines that the WHO authorizes for use in emergencies. Four vaccines have been approved for use in Turkey and their characteristics are described in Table 2 according to current data (14,15). Although that is known that many countries in the world have inactivated COVID vaccine applications for the pediatric age group, Pfizer-BioNTech COVID-19 vaccines, Nonavax and Moderna COVID-19 vaccines are among the COVID-19 vaccines approved for use in children (16,17).

The bivalent vaccines, also referred to as "updated boosters" contain two mRNA components of SARS-CoV-2 which has been approved by the US Food and Drug Administration (FDA), according to a report published on August 31, 2022. Following this announcement, the FDA amended the emergency use authorizations (EUA) for Moderna COVID-19 Vaccine, Bivalent and Pfizer-BioNTech COVID-19 vaccine, Bivalent to allow their use as a single booster dose in younger age groups. Pfizer-BioNTech COVID-19 vaccine, Bivalent is approved for administration in children up to five years of age or at least two months following the completion of booster vaccination, while Moderna COVID-19 vaccine, Bivalent is approved for administration in children up to six years of age (18). Bivalent vaccines, which have been started to be used by many countries such as America and Canada, but are not yet available in our country, should be made available, especially for populations at risk (17).

Although the vaccines are well tolerated by children and adolescents, except injection site pain, fever and fatigue, some cases of myocarditis/pericarditis have occurred among adolescents and young adults, particularly males, following routine use of mRNA vaccines (18). However, most cases of myocarditis and pericarditis are mild, self-limiting and resolve without complications (16,18).

Diagnosis

• Laboratory Tests

Real-time reverse transcriptase polymerase chain reaction detection of SARS-CoV-2 nucleic acid is one of the most efficient methods for diagnosing COVID-19 (19).

Compared with other hospitalized patients, children who require admission to the Pediatric Intensive Care Unit experience greater rates of elevations in C-reactive protein (CRP), procalcitonin, pro-B-type natriuretic peptide, and platelet count. Organ dysfunction was linked to elevated CRP, a higher white blood cell count, and thrombocytopenia (20,21).

Table 1. Eleven vaccines granted emergency use listing by WHO (16)

Protein subunit	RNA-based	Non-replicating viral vector	Inactivated
- Serum Institute of India: Covovax (Novavax formulation)	- Moderna	- CanSino	- Bharat BioNTech: Covaxin
-Novavax	- Pfizer/BioNTech	- Janssen	- Sinopharm (Beijing): Covilo
-Serum Institute of India: Covishield (Oxford/ AstraZeneca formulation)		-Oxford/AstraZeneca	-Sinovac: CoronaVac

WHO: World Health Organization

Table 2. **Four vaccines approved for use in Turkey (17)**

RNA-based	Non-replicating viral vector	Inactivated
- Pfizer/BioNTech: Comirnaty	Gamaleya: Sputnik V	- Health Institutes of Turkey: Turkovac - Sinovac: CoronaVac

In adult patients with COVID-19, hyperinflammation was related to poor outcomes and was accompanied by elevated lactate dehydrogenase, D-dimer, IL-6, CRP, and ferritin and decreased lymphocyte count, platelet count, and albumin levels (22).

- **Radiographic Findings**

In children with mild or moderate disease, radiographic results (ground glass opacity and consolidation, respectively) may be normal or suggestive of viral/bacterial processes. The American College of Radiology currently advises against using a routine chest X-ray or computed tomography (CT) to diagnose COVID-19 (23).

Chest X-ray is recommended to establish an imaging baseline and assess for alternative diagnosis for clinical symptoms that range from moderate to severe and require hospitalization. Chest CT should only be used to answer specific clinical concerns or to explain worsening clinical deterioration. It is not recommended to use it as the initial diagnostic procedure for pediatric patients with known or suspected COVID-19 pneumonia because children are more radiation sensitive than adults (24).

Management of COVID-19

The cornerstone of therapy for COVID-19 patients is supportive care. The self-isolation should occur at home, at a COVID-19-approved health facility, or in a community facility. In addition to providing age-appropriate nutrition and hydration, antipyretics should be used to manage fever and pain. Patients with mild COVID-19 are not advised to receive antibiotic treatment or prophylaxis (25).

Most children with COVID-19, including those with severe disease, recover with supportive care. The children have been excluded from most clinical trials involving COVID-19 treatment protocols, so there is currently little data to support treatment recommendations in this age group. Decisions about the use of antiviral therapy should be made in consideration of the disease's severity, clinical course, current data of its efficacy, and any underlying diseases that might increase the risk for progression. Additionally, it can be necessary for children who have a mild-to-moderate illness and an underlying condition that increases the risk of contracting a severe illness (26).

Remdesivir, a nucleotide analog found to be effective against SARS-CoV-2 in vitro, has been approved by the FDA in patients over the age of 12 with severe disease necessitating hospitalization despite not been advised for use in children by the WHO (27).

The FDA has approved the drug baricitinib for emergency use in children patients older than two years old who are hospitalized with COVID-19 and need oxygen, ventilator support, or extracorporeal membrane oxygenation.

Bamlanivimab-etesevimab, a monoclonal antibody treatment, has been approved by the FDA for use in infants under the age of two who are hospitalized with mild-to-moderate COVID-19 and at risk of the condition progressing to severe disease. Hydroxychloroquine, which was used in the first months of the pandemic, is no longer recommended for COVID-19 treatment (25).

The use of glucocorticoids for immune-mediated COVID-19 problems is decided on a case-by-case basis based on the severity of the illness (25). The advantages and risks of glucocorticoids for pediatric patients are unknown, although they have been related to decreased mortality in adult patients (26). Low-dose glucocorticoids may be necessary for some children with severe or critical COVID-19 who need mechanical ventilation or additional oxygen and have risk factors for disease progression at the time of admission;

the therapy's duration is up to 10 days or until discharge, whichever is shorter (26).

Despite limited data on the advantages and risks of tocilizumab, which is a monoclonal antibody, in children with COVID-19, an EUA has been granted by the FDA for this drug, which reduces inflammation by blocking the IL-6 receptor, for use in hospitalized patients under two years of age who require extracorporeal membrane oxygenation, supplemental oxygenation, or mechanical ventilation (non-invasive or invasive) (25).

When compared with adult COVID-19 infections, pediatric infections are often milder and have reduced the risks of hospitalization and mortality. Fever and cough are still the most prevalent clinical signs, but other symptoms, including "COVID toes", anosmia, and croup, are also possible. Post-infectious problems in children, such as MIS-C and long COVID, are a possibility. It is strongly recommended to use vaccination as a kind of prevention. The mainstays of diagnosis and treatment continue to be symptomatic management and respiratory nucleic acid amplification tests.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.G., Concept: H.T., Design: H.T., Data Collection or Processing: E.G., Analysis or Interpretation: H.T., Literature Search: E.G., H.T., Writing: E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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