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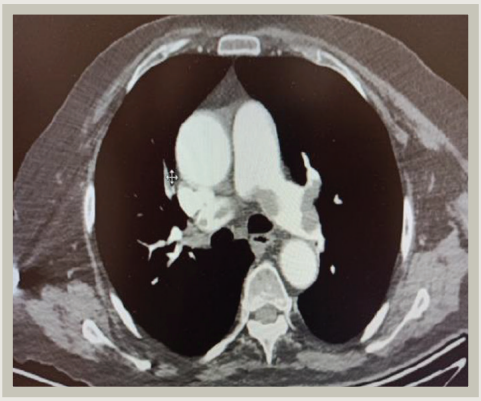

Figure 1. CT pulmonary angiogram
CT: Computed tomography

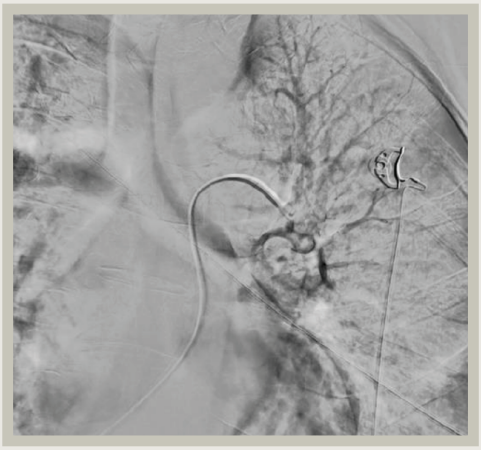

Figure 2. Pig tail catheter was placed in the left main pulmonary artery

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About Us

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

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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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The editorial and publication process of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

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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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Peer Review, Publication Ethics and Malpractice Statement

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The conflict of interest form that each author has to sign must be uploaded during the manuscript submission.

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Cover letter: The cover letter should include statements about the manuscript type, single-journal submission affirmation, conflict of interest statement, sources of outside funding, equipment (if applicable), approval of language for articles in English and approval of statistical analysis for original research articles.

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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prevention of pain and suffering should be declared in the manuscript. For manuscripts concerning experimental research on humans, a statement should be included that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. The authors have the responsibility to protect the patients' anonymity carefully. For photographs that may reveal the identity of the patients, signed releases of the patient or their legal representative should be obtained, and publication approval must be provided in the manuscript. Authors must provide disclosure/acknowledgement of financial or material support, if any was received, for the submitted study. If the article includes any direct or indirect commercial links or if any institution provided material support to the study, authors must state in the cover letter that they have no relationship with the commercial product, drug, a pharmaceutical company. Concerned; or specify the type of relationship. Authors must provide a conflict of interest statement and an authorship contribution form.

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All manuscripts selected for full peer review will be assessed by a statistical editor, and their comments must be addressed in full.

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The title page should include the full title of the manuscript; information about the author(s) including names, affiliations, highest academic degree and ORCID numbers; contact information (address, phone, mail) of the corresponding author. If the content of the paper has been presented before, and if the summary has been published, the time and place of the conference should be denoted on this page. If any grants or other financial support has been given by any institutions or firms for the study, information must be provided by the authors.

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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

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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 (1,2,3,4) 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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Editorial

Dear Colleagues,

We are glad to publish the first issue of Cam and Sakura Medical Journal (CSMJ) in 2022. It is important for us to be published regularly with your valuable contributions. We believe that CSMJ will be admitted to important indexes in near future. As in previous year, you can read an invited review, 4 original articles and 2 case reports in this issue.

You can read the review about COVID-19 vaccination during pregnancy in this issue. As some variants of SARS-CoV-2 showed more severe pattern in pregnant women, vaccination has been recommended by several societies and guidelines for pregnant women to decrease both maternal and neonatal mortality and morbidities associated with COVID-19 infection. This review will provide important recent data about this subject. You can also find an original article that evaluated the effects of adjuvant chemotherapy on insulin resistance in patients with breast cancer. The role of biomarkers for intubation of COVID-19 patients in intensive care unit has also been evaluated in another study. The route of clinical transmission and clinical course of COVID-19 infection in health professionals were established in a original study. Last study in this issue focused on the extended intensive care process and cost analysis of COVID-19 infection. You can read two different case reports. One case report was associated with patient management with pulmonary embolism response team in the emergency department. The other case report defined the treatment of isolated penile Fournier's gangrene and also reviewed the current literature about this topic.

We are waiting your articles and case reports for the future issues.

On behalf of Deputy Editors, Associate Editors and Editorial Secretary

Merih Cetinkaya

Editor in Chief

Cam & Sakura Medical Journal

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REVIEW

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COVID-19 Vaccination During Pregnancy

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ABSTRACT

A global health crisis named coronavirus disease-2019 (COVID-19) pandemic was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 pandemic created an immediate occasion to establish strategies for vaccination. Increasing evidence suggests the pregnancy-related COVID-19 risks substantially above the risk of non-pregnant woman. Women with pregnancy and lactation were not included in COVID-19 vaccination studies. To date, subsequent data from pregnant COVID-19 vaccinated women showed safety and efficacy during pregnancy. There is no evidence of harmful effects on pregnancy, fetal development, parturition and postnatal development both directly and indirectly for the COVID-19 vaccines. Vaccination for pregnant women is a healthy and safe way to prevent infection of SARS-CoV-2 and should be considered. From the knowledge of similar prior non-COVID-19 vaccine trials' experience, reproductive and developmental toxicology trials from animals, datas from trials of humans and different advisory committees of healthcare have published guidelines supporting vaccination for COVID-19 during pregnancy and breastfeeding.

Keywords: Pregnancy, SARS-CoV-2, vaccination, COVID-19

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Introduction

The extraordinary years of 2020 to 2022 will never been forgotten due to the impacts of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). A global health crisis named coronavirus disease-2019 (COVID-19) pandemic was caused by SARS-CoV-2. Human lives, global economies and public healthcare systems have been devastated by COVID-19 (1). To date, more than 452 million confirmed illness and 6 million deaths have been globally attributed to COVID-19 (2). The most promising control patterns for this pandemic were personal hygiene, social distancing, face mask, isolation and vaccination (3). For this reason, pandemic of COVID-19 created an immediate occasion to establish strategies for vaccination.

Multiple vaccines were developed, manufactured and approved for global COVID-19 pandemic use. In this process, many vaccines have been researched for safety and efficacy. It has been shown that vaccination reduces SARS-CoV-2 infection risk and reduces the disorder severity (4). It is critical to mention that women with pregnancy and lactation were not included in COVID-19 vaccine trials. Since the start of the pandemic, millions of people have had pregnancy and labor. This has become an ethical and clinical situation to protect them with lacked empirical evidence. Therefore, the COVID-19 pandemic and rapid developed novel vaccines need to decode the vaccine-induced immunity and safety for pregnancy.

Pregnancy and Infection of SARS-CoV-2

A RNA virus named SARS-CoV-2 causes an infectious process. The host receptor for cell entry is a receptor named angiotensin-converting enzyme-2 (ACE-2). This receptor is found mostly in the alveolar stroma and epithelium. Variants have evolved in two years period (3). Person to person direct transmission is the primary way to SARS-CoV-2 transmission. The routes of transmission, infectious period, immune response and reinfection risk are the same for pregnant and non-pregnant women. Most related COVID-19 issues are the same for women with and without pregnancy, with a few exceptions (5).

Pregnancy includes complex immunological differences, involving immun system modulation to tolerate the fetus as semiallograft (6). The infections could be more complex because of this immune tolerance state. Pregnancies with the infection of SARS-CoV-2 may be asymptomatic or symptomatic. An increased risk factor for severe sequelae of COVID-19 and some pregnancy complications is common in symptomatic pregnancy infection. It is known that SARS-CoV-2 infected pregnant women are increased probability of hospitalization, severe illness, ventilation support, intensive care unit admission and preterm labor compared with uninfected women pregnancy. Miscarriage and congenital anomalies do not appear to be increased in infected pregnancy. In utero vertical transmission is rare, and the neonatal outcome is usually good. Pregnant women are potential candidates for COVID-19 prevention (3).

To date, all the available evidence supports the assurance of administering current vaccines of SARS-CoV-2 during pregnancy (7). The known limited data, World Health Organization (WHO), American College of Obstetricians and Gynecologists, Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices, American Academy of Pediatrics and the Republic of Turkey Ministery of Health have published guidelines indicating that current COVID-19 vaccines should not be retained from the women with pregnancy (8,9,10,11,12).

COVID-19 Vaccines

Multiple effective vaccines have been unprecedently developed by the scientists, goverments, and pharmaceutical companies. None of these vaccines contained replicative live viruses. They do not cause SARS-CoV-2 infection (7). The vaccines can be separated mainly into three various categories with their action mechanism. These main groups are mRNA, viral vector and inactivated COVID-19 virus vaccines.

i- mRNA Vaccines

These are vaccines of mRNA with lipid nanoparticle. The mRNA vaccine codes for SARS-CoV-2 spike protein, that holds this virus for ACE-2 receptor to start the infective process. At the site of vaccine injection, nanoparticles of lipid simplify to enter the cell of host. Then, the mRNA transcribed in this cell to produce the spike protein, that is presenting to T and B lymphocytes on the cell surface for the immune response (13,14,15). Food and Drug Administration and WHO approved mRNA vaccines (16,17). mRNA-based vaccines have presented strong immunity reaction and prevention against severe illness. Moderna and Pfizer-BioNTech vaccines use mRNA technology. In Turkey, Pfizer-BioNTech (Pfizer, Inc. Philedelphia, PA, USA) is the only available mRNA vaccine for COVID-19 protection to date. Pfizer-BioNTech vaccine's reported efficacy is 95% in phase III clinical trials for protecting COVID-19. Injection site reactions (most common), muscle pain, fatigue, chills, headache, fever, joint pain are common side effects. All of the side effects generally resolve within two days. Most of these side effects were observed after the second dose. mRNA-based vaccines may rarely cause Bell's palsy, anaphylaxis, pericarditis and myocarditis (18). Because of this reason, CDC recommended monitoring recipients for 15-30 minutes after the COVID-19 mRNA vaccine. Pfizer-BioNTech

confirmed for people 12 years old and above. Pfizer-BioNTech mRNA vaccine requires two doses, 21 days apart (19). Moderna (ModernaTX, Inc., Cambridge, MA, USA) is another form of mRNA vaccine that can be used in the United States of America and different countries.

ii- Inactivated Virus Vaccines

Such vaccine uses an inactivated virus of COVID-19 to activate an immune reaction. The inactivated vaccines do not include a live COVID-19 virus. Therefore, these vaccines may not cause the disorder. Aluminum hydroxide is used as an adjuvant in these vaccines. In Turkey, Coronavac (Sinovac, Beijing, China) is the first available inactivated vaccine for COVID-19 protection. The phase III trials reported the efficacy of Sinovac as 83.5%. The vaccine requires doses for twice. More common side effects are injection site reaction, headache, fatigue, chills, muscle pain, fever and joint pain. These side effects usually resolve within two days. Sinopharm (Sinopharm, Beijing, China) is another form of inactivated virus vaccine that can be used in different countries. Sinovac and Sinopharm are not confirmed for usage in the United States of America and some of the European countries (7). In Turkey, another form of inactivated virus vaccine named Turkovac (ERUCOV-VAC, Kayseri, Turkey) was applied for emergency use by the Turkish Minister of Health on 2021 November (20).

iii- Viral Vector Vaccines

These types of vaccines used viral vectors to deliver the spike protein mRNA into the host cell. A non-replicated modified version of adenovirus is used as a viral vector in such vaccine. The vaccine product finally contains SARS-CoV-2 spike protein and eliminated as an immune response with the same mechanism as mRNA vaccines (7). Oxford/AstraZeneca (AstraZeneca, Cambridge, UK) and Janssen (Janssen Biotech, Inc, Johnson & Johnson, New Brunswick, NJ, USA) are two forms of viral vector vaccines. The vaccine of Oxford/Astra Zeneca requires doses twice. The vaccine named Janssen requires a single dose (21). The reported efficacy of Janssen is 72% and Oxford/AstraZeneca is 63.1% from the phase III trials. The Janssen vaccine's side effects include injection site pain, myalgia, fatigue and headache. These side effects usually resolve within two days. On rare, this vaccine may cause thrombotic thrombocytopenic purpura, raduculitis, Guillain-Barré syndrome. The side effects of thrombosis cases have been noted in women. Pregnancy, oral contraceptives, hormonal therapeutics are thrombotic risk factors. Therefore, pregnant women have increased thrombosis risk with Janssen vaccine (22,23). In Turkey, there is no available viral vector vaccine for COVID-19 protection to date.

COVID-19 Vaccine Studies During Pregnancy

Women with pregnancy are generally excluded from COVID-19 vaccine studies, because of liability and safety concerns about mother and fetus. Systemic non-inclusion of this wide population from clinical studies means available very limited data on COVID-19 vaccines' safety and efficacy during pregnancy (24,25). Increasing evidence suggests that pregnancy-related COVID-19 risks substantially above the risk of non-pregnant woman. Pregnancy-related risks may be minimized and reduced by standard preventive strategies, including COVID-19 vaccines (26). Previous studies with non-COVID-19 mRNA-based vaccines on human, including influenza, rabies and Zika virus noted good safety and immunogenic profile in pregnant women (5).

To date, subsequent data from pregnant COVID-19 vaccinated women showed safety during pregnancy. There is no evidence of harmful effects on pregnancy, fetal development, parturition and postnatal development both directly and indirectly for the COVID-19 vaccines (27,28,29). After the vaccine administration during pregnancy; a maternal immune response, a reduced incidence of maternal COVID-19 and a reduced severe and critical infection of SARS-CoV-2 incidence was demonstrated. Also, the transfer of maternal vaccine-induced antibodies across the placenta to confer passive immunity against SARS-CoV-2 infection for fetus/newborn. Protective vaccine-induced antibodies have been demonstrated in umbilical cord serum after the 15th day of the first maternal COVID-19 vaccination (30).

Although pregnant women were not included from the vaccination studies and participants were warned to avoid pregnancy, 53 accidental pregnancy occurred in these trials. The miscarriage rates are comparable with the non-vaccinated groups vaccination does not have any effect on early pregnancy complications (31).

The CDC has recommended an application named V-safe after vaccination health checker for smartphones. The app includes pregnant people, to register adverse events following vaccination. The V-safe COVID-19 vaccine pregnancy registry has greater than 50,000 data from completed pregnancies. There are no obvious safety signals with congenital abnormalities, miscarriage, fetal growth, preterm labor, stillbirth and neonatal mortality (32). And also Vaccine Adverse Event Reporting System (VAERS) of the CDC has 154 pregnancy data. There was no excess observed in adverse and side effects compared with the CDC national birth data. The

Clinical Immunization Safety Assessment and Vaccine Safety Datalink of CDC have almost 40,000 pregnancy data. These data mostly for mRNA vaccines and have not shown adverse outcomes (33). Developmental and reproductive toxicity studies' early data have also not shown adverse effects for women reproduction, fertility, miscarriages, embryonal/fetal/postnatal development (17,34).

Shimabukuro et al. (35) studied the data on 35,691 vaccinated pregnancy from the registries of safety surveillance, including VAERS and V-safe. They noted fatigue, headache, injection site pain, myalgia and fever as common reactions to vaccines. The reactions were more common after the second vaccine dose. They reported that these patterns were similar in women who were not pregnant. Only vomiting and nausea were more slightly common in pregnant individuals compared with non-pregnant women after a second dose of vaccines (35).

In another study, 2,456 pregnant women who received COVID-19 mRNA vaccine before conception or before 20 weeks of getation have cumulative miscarriage risk of 12.8%. This is a similar rate in the general obstetric population (36). A different trial demonstrated that 13,000 miscarriages from 92,000 pregnant women had similar odds with and without mRNA COVID-19 vaccine exposure (29). Similar safety data were noted for viral vector vaccines (37).

Another study has noted poor pregnancy outcomes in non-vaccinated and infected women. COVID-19 related hospital admission was 77.4%, COVID-19 related critical care admission was 98%, perinatal death was 100% for the non-vaccinated at the time of SARS-CoV-2 infection. The perinatal death rate of COVID-19 vaccinated women was similar to obstetrics population rates (38).

In another study, the authors noted that mRNA vaccines caused a strong humoral immune response during pregnancy. Antibody responses were quickly developed after vaccine administration. This quick response was not shown with the natural infection of SARS-CoV-2. Reactogenicity and immunogenicity were similar in women with or without pregnancy. The authors also noted the passed preventive immunoglobulins (Ig) to the fetus/newborn by the placenta (39).

Lastly, Pfizer declared a global phase 2/3 study to evaluate the vaccine's immunogenicity, safety, and tolerability in pregnancy. This trial was placebo-controlled, observer-blind, randomized. It is planned to include 4,000 healthy women with pregnancy vaccinated between 24-34 weeks of gestation. The estimated completion date of the study is August 2022 (40). The other companies are planning similar studies.

Impact of COVID-19 Vaccination on the Fetus

Vaccination in pregnancy (e.g. pertusis, influenza, Zika) is a well known factor to protect to mother and fetus from infection (5). Experts suggest that mRNA based, viral vector and inactivated vaccines do not have indicative risk to newborn and fetus. There are directly no data that particles of vaccines pass the placenta and cross into fetal tissues. Trials on different vaccinations of lipid nanoparticle showed that they may not pass the placental barrier (41,42).

In Shimabukuro's study, pregnancy loss and adverse pregnancy results of small size for gestational age and preterm birth have similar incidences before the COVID-19 pandemic. They did not report any neonatal deaths (35).

Many experts suggest that vaccine-induced Ig antibodies can cross to the breastmilk and protect the infant against infection of SARS-CoV-2. A study noted the existence of vaccine-induced IgA in milk after four weeks of mRNA-based vaccine administration. They also reported IgA levels in milk were similar between vaccination and infection (43). Another study showed anti-spike antibody transfer via the placenta after maternal mRNA-based vaccination (44).

Hesitancy of COVID-19 Vaccination

The COVID-19 vaccines' acceptance level is inadequate to meet necessity for developing global immunity against SARS-CoV-2 infection. The number of infected individuals are affecting the herd immunity. The community level of vaccination to stop the pandemic needs to reach a level of 75% and above in a time period (45). WHO has categorized hesitancy of COVID-19 vaccination as one of the prior global health threat. It is critical to address and understand the reasons for vaccination hesitancy (46).

Skjefte et al. (46) noticed the causes for women with pregnancy to decline vaccines of COVID-19 in pregnancy as (i) not to sustain developing fetus to probable harmful effects, (ii) approve of the vaccines could be hurried for political causes, (iii) to have effectiveness and safety data during pregnancy.

Hesitancy for vaccination is a complex problem based on region, race, education level, ethnicity, social influence and pregnancy status (47). It is important to improve vaccine acceptance with effective and consistent public steps.

Choice of Vaccine

If both an mRNA and inactivated virus vaccine are available, pregnant are advised to select the vaccine beyond the benefits and risks. Some inactivated COVID-19 vaccines contain adjuvants. Insoluble aluminum salt, is one of the inactivated vaccine adjuvant, has a good safety profile (48).

Novel adjuvants containing vaccines are generally avoided during pregnancy. There is a lack of safety data of novel adjuvants. This theory must be balanced with the risk of COVID-19 pandemic, severe infection of SARS-CoV-2 and mortality risk in pregnancy.

CDC commends that pregnant with an early allergic and severe reaction to an mRNA-based vaccine's first dose, should not approve mRNA-based vaccines without evaluation by an immunology specialist (10).

Thrombosis is slightly more common in pregnancy, therefore pregnant people should be warned sensitive for the thromboembolic event's increased risk with Janssen vaccine (7).

Timing of the Vaccine

It is an appropriate advice that women planning pregnancy should be vaccinated as soon as possible. The current available COVID-19 vaccines do not have any effect on fertility. It is not necessary to receive a pregnancy test before vaccination. There is no data to delay pregnancy after vaccination for COVID-19. If a female has pregnancy after receiving the COVID-19 vaccine series' first dose, the secondary dose could be carried out at the exact time as non-pregnant persons (3).

Other Vaccine and Anti-D Ig Administration with COVID-19 Vaccines

A separation between other and COVID-19 vaccines is unnecessary. The vaccines of COVID-19 can be carried out at the same period as routine-administered vaccines. The immunoglobin of anti-D does not change the immun response to vaccines. A seperation period between the COVID-19 vaccines and anti-D Ig is also unnecessary. Standard protocols can be used for alloimmunization prevention with COVID-19 vaccines (3,8).

Lactation and COVID-19 Vaccines

Lactation should not effect timing of COVID-19 vaccines. Vaccine induced maternal serum antibodies of SARS-CoV-2 may pass into milk and can protect newborn with passive immunization. Although breastfeeding women excluded from vaccine studies, available COVID-19 vaccines are unlikely to get a risk to the lactated child. The vaccines do not contain infectious viruses and a minimal amount can pass into milk, but they are inactivated by the child's digestive system (49).

Conclusion

Pregnant women should be offered the vaccination for COVID-19 where the benefits outweigh few potential risks. Women with SARS-CoV-2 infection and pregnancy are more likely to have severe disease, need intensive care, deliver preterm and because of these newborns are more likely to be hospitalized to neonatal unit. Vaccination can reduce these risks. Vaccination for pregnant women is a healthy and safe way to prevent infection of SARS-CoV-2 and should be considered. From the knowledge of similar prior non-COVID-19 vaccine trials' experience, reproductive and developmental toxicology trials from animals, datas from trials of humans and different advisory comitees of healthcare have published guidelines supporting vaccination for COVID-19 during pregnancy and breastfeeding.

Ethics

Peer-review: Externally peer-reviewed.

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

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Effects of Adjuvant Chemotherapy on Insulin Resistance in Patients with Early Breast Cancer

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What is known on this subject?

In the literature, a few studies have investigated the correlation between insulin resistance and cancer development. The presence of insulin resistance increases the risk of breast cancer. Also, there are studies showing interactions between insulin resistance and chemotherapy.

What this study adds?

This study confirmed that early breast cancer patients had a higher rate of insulin resistance. There was a statistically insignificant rise in fasting blood glucose levels throughout and after the chemotherapy procedure, which is probably due to the steroid impact. Homeostatic model assessment for insulin resistance score's mean values dropped.

ABSTRACT

Objective: To assess the effect of adjuvant chemotherapy on insulin resistance in patients with early breast cancer.

Material and Methods: Twenty-three non-diabetic patients were included. Patients were prospectively evaluated before, during, and after chemotherapy. Demographic, anthropometric, histopathological features, and treatment data were recorded. Blood samples were taken to evaluate fasting blood glucose, fasting insulin levels, and HbA1c. Homeostatic model assessment for insulin resistance (HOMA-IR) score measured using fasting blood glucose and fasting insulin levels.

Results: Overall, pre- and post-chemotherapy mean weights were comparable (70.17 kg vs. 71.43). Prechemotherapy mean HOMA-IR was 4.99 and significantly higher than the control group of the healthy population (p=0.008). The mean values of the HOMA-IR score before, during, and after chemotherapy were 4.99, 3.47, and 3.13, respectively. Although the mean HOMA-IR decreased after chemotherapy, these decreases were not statistically significant (p=0.089). The mean fasting glucose levels before, during, and after chemotherapy were 95.5, 101.9, and 94.1 mg/dL, respectively. Before, during, and after chemotherapy, the mean fasting insulin levels were 21.43, 13.32, and 13.28 µIU/mL, respectively.

Conclusion: In the study, we observed a higher rate of insulin resistance in patients with breast cancer. The mean values of the HOMA-IR score decreased during and after chemotherapy.

Keywords: Breast cancer, chemotherapy, HOMA-IR, insulin resistance

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Introduction

Breast cancer is the most common malignancy in females and the second most common cause of death from cancer (1). Palpable mass, axillary node, skin changes (erythema, thickening, or dimpling) are the most common symptoms of breast cancer. There are many risk factors for breast cancer, including reproductive factors (menarche age, menopause age, number of pregnancies, lactation), genetic factors (BRCA 1-2 mutations), and obesity (2). Breast cancer is treated in a multidisciplinary manner by surgical oncology, medical oncology, and radiation oncology.

Insulin resistance is decreased physiologic effects of insulin with normal serum concentration. Insulin resistance may be caused by many risk factors such as obesity, medications (glucocorticoids, contraceptives), insulin antibodies, and genetic defects in insulin-signaling pathways (3). It is measured using the euglycemic clamp technique and homeostatic model assessment for insulin resistance (HOMA-IR) score. Insulin resistance can be seen in 15.5%-46.5% of the general population (4). A few research has examined the correlation between insulin resistance and the development of cancer in the literature. The risk of breast, endometrial, colon, prostate, esophageal, liver, and kidney cancers increases with the presence of insulin resistance (5). Breast cancer risk is increased by approximately 10%-20% in patients with type 2 diabetes (6). Also, women with a familial history of breast cancer have a significantly higher frequency of insulin resistance (7).

There is essential evidence demonstrating the interactions between insulin resistance and chemotherapy. The insulin-like growth factor (IGF) is important for cell proliferation, differentiation, and growth. The IGF pathway is involved in the development of breast cancer (8,9). By suppressing apoptosis, IGF-1 prolonged cell survival in human breast cancer cells treated with methotrexate, 5-fluorouracil, and tamoxifen (10). Also, a study found that phosphatidylinositol-3 (PI-3) kinase was necessary for IGF-I rescue of doxorubicin-induced apoptosis, but both PI-3 kinase and MAP-kinase were required for IGF-I rescue of paclitaxel-induced apoptosis (11). A multi-center study showed that breast cancer patients with insulin resistance had a poor prognosis (12). Another study also showed that low-quality and high amounts of upper visceral fat tissue were related to insulin resistance and prognosis in patients with breast cancer (13). It has also been stated that hyperinsulinemia conditions due to transient hyperglycemia may reduce the effectiveness of chemotherapy (14). Only a few studies have evaluated interactions between insulin resistance and chemotherapy using measurement methods, including the HOMA-IR score. This study's goal was to assess the effect of adjuvant chemotherapy on insulin resistance in patients with early breast cancer.

Material and Methods

Patients and Study Design

Between October 2011 and September 2012, early-stage breast cancer patients were evaluated prospectively at Ankara University Medical Oncology Outpatients Clinics. The Ankara University Faculty of Medicine Ethics Committee (number 38-824) allowed this research, which was carried out in accordance with the Helsinki Declaration and good clinical procedure. Informed consent was obtained from all patients after the study procedures were explained. Patients without diabetes and did not use drugs that affect insulin metabolism were included in the study. The presence of diabetes mellitus (DM) in patients was determined using the standardized HbA1c method. Clinical data, pathological features (tumor type, tumor size, lymph node, grade, lymphovascular invasion, Ki67% levels), estrogen receptor (ER), progesterone receptor (PR), HER2/neu receptor status, and treatment approach (surgery type, radiotherapy, chemotherapy, and endocrine therapy) of the patients were recorded. Also, a history of family breast cancer and diabetes was noted. Immunohistochemistry was used in the examination of ER and PR status. Immunohistochemistry (score 3+) and *in situ* hybridization also used to detect HER2 overexpression. Tumor staging was done according to the 7th edition of the American Joint Committee on Cancer-TNM.

Patients were prospectively evaluated before, during (after 2-3 cycles of chemotherapy), and after chemotherapy (at least one month after the last chemotherapy cycle). Blood samples were taken from the patients with at least 8 h of fasting in the morning before chemotherapy to assess fasting insulin levels, fasting blood glucose, and HbA1c. Fasting blood glucose levels were evaluated using spectrophotometric method, fasting insulin levels were assessed by radioimmunoassay method, and HgA1c levels were assessed by high-performance liquid chromatography) method without waiting. Normal values for fasting blood glucose were accepted as 74-100 mg/dL, normal values for fasting insulin levels were 4-16 µIU/mL, and normal values for HbA1c were accepted as 4.4%-6% according to the laboratory's device validation of our institution. The height and weight of the patients were recorded in all visits. The formula for calculating the body mass index (BMI) is BMI: kg/m^2, where kg is a person's body weight in kilograms and m^2 is their length in meters squared. BMI is evaluated with World

Health Organization classification. With the model: Fasting glucose (nmol/L) x fasting insulin (μ/L)/22.5, the HOMA-IR score was computed using fasting insulin levels and fasting blood glucose. The diagnosis of insulin resistance was achieved with a HOMA-IR score >2.24, which is the mean level of the historical control group of a healthy population (15).

Statistical Analysis

Statistical analysis was performed using the SPSS version 20. Continuous variables are shown as median (minimum-maximum) values, whereas categorical variables are shown as numbers and percentages. A one-sample and paired-sample t-test used to detect statistical differences. Statistical significance was considered a p value from less than 0.05.

Results

The research enlisted the participation of twenty-three patients. Patients' median age was 45 years (range: 31-78). Sixteen (69.6%) patients were diagnosed as premenopausal, and the remaining were postmenopausal. The most common pathology was invasive ductal carcinoma (16; 69.6%). Twenty patients (87%) had ER and PR positive breast cancer, and five (21.7%) patients showed HER2 positivity. The mean BMI was 27.66 kg/m^2. While six (26.1%) patients had obesity (BMI >30 kg/m^2), 11 (47.8%) patients were overweight (BMI: 25-30 kg/m^2). Table 1 presents the clinic and pathological features of the patients.

Seventeen (74%) of the patients had undergone modified radical mastectomy. Fourteen (60.9%) patients received radiotherapy with a median 50 Gy in 25-28 fractions. The patients received different chemotherapy regimens, including anthracyclines, taxane, cyclophosphamide, and carboplatin. Also, the patients received dexamethasone 16 mg for premedication before taxane treatment. Table 2 presents the treatment approach of the patients

Insulin resistance was detected in 15 (65.3%) patients. Prechemotherapy mean HOMA-IR was 4.99 and significantly higher than the control group of the healthy population (p=0.008). The mean values of the HOMA-IR score before, during, and after chemotherapy were 4.99, 3.47, and 3.13, respectively. Although the mean HOMA-IR decreased after chemotherapy, this result was not statistically significant (p=0.089). The mean fasting glucose levels before, during, and after chemotherapy were 95.5, 101.9, and 94.1 mg/dL, respectively. The mean levels of fasting insulin before, during, and after chemotherapy were 21.43, 13.32, and 13.28 μIU/mL, respectively (Table 3). Overall, pre- and post-chemotherapy mean weights were similar (70.17 kg vs. 71.43).

Table 1. Clinicopathological characteristics of the patients

	Number of patients (n=23)	(%)
Median age, at diagnosis		
45 (range: 31-78)		
Family history		
Breast cancer	1	4.3
Diabetes	7	30.4
No	15	65.3
Body mass index kg/m^2		
<25	6	26.1
25-30	11	47.8
≥30	6	26.1
Menstruation status		
Premenopausal	16	69.6
Postmenopausal	7	30.4
HOMA-IR score, at diagnosis		
2.5<	15	65.3
2.5>	8	34.7
Histological type		
Invaziv ductal carcinoma	16	69.6
Mixed type	4	17.5
Tubular carcinoma	1	4.3
Micropapillary carcinoma	1	4.3
Invasive lobular carcinoma	1	4.3
pT status		
T1 (≤2 cm)	7	30.5
T2 (2-5 cm)	14	60.9
T3 (>5 cm)	2	8.6
pN status		
N0	7	30.4
N1 (1-3)	6	26.1
N2 (4-9)	7	30.4
N3 (≥10)	3	13.1
ER status		
Positive	20	87
Negative	3	13
PR status		
Positive	20	87
Negative	3	13
HER2 overexpression		
Positive	5	21.7
Negative	18	78.3

HOMA-IR: Homeostatic model assessment for insulin resistance, ER: Estrogen receptor, PR: Progesterone receptor

Discussion

In this study, compared with a healthy population, we observed a higher frequency of insulin resistance in early breast cancer patients. While insulin levels and HOMA-IR

Table 2. Treatment approaches of the patients

	Number of patients (n=23)	%
Breast surgery		
Lumpectomy + SNB[1]	3	13
Lumpectomy + AD	3	13
Modified radical mastectomy	17	74
Adjuvant radiotherapy		
Yes	14	60.9
No	9	30.1
Chemotherapy regimens		
3 FEC + 3 T	2	8.7
4 AC	6	26.1
4 AC + 4 T	10	43.5
3 AC + 3 T	2	8.7
6 TCb	3	13
Trastuzumab therapy		
Yes	5	21.7
No	18	78.3
Endocrine therapy		
Tamoxifen	18	78.4
Aromatase inhibitors	2	8.6
No endocrine therapy	3	13

SNB: Sentinel node biopsy, AD: Axillary dissections, MRM: Modified radical mastectomy, FEC: Fluorouracil + epirubicin + cyclophosphamide, CA: Adriamycin + cyclophosphamide, T: Trastuzumab, TCb: Docetaxel + carboplatin, T: Docetaxel

Table 3. The mean values of insulin resistance parameters before, during, and after chemotherapy

	n	Mean	SD	p value
Body weight-1 (kg)	23	70.17	11.82	0.126
Body weight-3		71.43	11.94	
FBG-1 (mg/dL)	23	95.5	10.88	0.073
FBG-2		101.9	18.73	
FBG-1	21	95.4	11.35	0.614
FBG-3		94.1	9.89	
Insulin levels-1 (µIU/mL)	23	21.43	20.78	0.075
Insulin levels-2		13.32	7.68	
Insulin levels-1	21	21.23	21.61	0.09
Insulin levels-3		13.28	7.44	
HbA1c-1 (%)	23	5.38	0.36	0.054
HbA1c-2		5.51	0.42	
HbA1c-1	21	5.40	0.32	0.162
HbA1c-3		5.30	0.30	
HOMA-IR-1	23	4.99	4.54	0.134
HOMA-IR-2		3.47	2.52	
HOMA-IR-1	21	4.92	4.70	0.089
HOMA-IR-3		3.13	1.90	
HOMA-IR-1*	23	4.99	4.54	0.008

**Test value: 2.24, 1: Before chemotherapy, 2: During chemotherapy, 3: After chemotherapy, FBG: Fasting blood glucose, HOMA IR: Homeostatic model assessment insulin resistance, SD: Standard deviation; n: Number*

decreased after chemotherapy, BMI and fasting glucose levels were comparable. Chemotherapy is associated with clinically significant weight gain. In a study of 3,088 breast cancer patients, chemotherapy-associated statistically significant weight gain was observed (16). Body weight gain after chemotherapy usually ranges between 1 and 6 kg (17). In a study by Makari-Judson et al. (18) in which 95 patients with early-stage breast cancer were included, an average of 0.4 kg increase in body weight was detected in the 6th month after adjuvant chemotherapy, while this increase increased to an average of 0.9 kg in the 12th month. It has been stated that weight gain may be associated with the effect of dexamethasone used during chemotherapy and the deterioration of insulin resistance (18). Overall, pre- and post-chemotherapy mean weights in our study were similar (70.17 kg vs. 71.43), not statistically significant.

Prechemotherapy mean HOMA-IR was 4.99 and significantly higher than the historical control group of the healthy population (p=0.008). Insulin resistance was detected in 15 (65.3%) of patients in our study. In a published study by Capasso et al. (19), insulin resistance was found in 49% of breast cancer patients. Similarly, Lawlor et al. (20) showed that hyperinsulinemia is positively linked with breast cancer in a cross-sectional study of 3868 women aged 60-79 years. In another study by Duggan et al. (21) in which 527 patients with early-stage breast cancer were evaluated, it was shown that with an increase in HOMA-IR score, survival due to breast cancer and all-causes decreased.

We found an increase in blood glucose levels during chemotherapy among patients who received dexamethasone. Similarly, Hickish et al. (22) found that blood glucose levels increase during chemotherapy. Also, hyperglycemia may result in transient hyperinsulinemia. Transient hyperglycemia may also affect the efficacy of chemotherapy by perturbations of the tumor microenvironment (14). Conversely, we did not find that transient hyperinsulinemia was associated with hyperglycemia. Some studies found increased HOMA-IR in breast cancer patients who received chemotherapy (18,23,24) but these changes tended to return to baseline in the 12th month (18,25). A study including 128 breast cancer patients without a history of DM was found β-cell dysfunction and insulin resistance after systemic treatment (26). In another study by Chala et al. (27), a statistically significant decrease

was found in 2-hour insulin levels in OGTT tests performed before and after chemotherapy.

Study Limitations

This study had some limitations. The number of patients was small, and therefore no differentiation was made for insulin resistance change according to chemotherapy groups. The patients had naturally taken steroids for premedication before the chemotherapy session.

Conclusion

In conclusion, we observed that patients with early breast cancer had a higher rate of insulin resistance. During and after the chemotherapy protocol, there was a statistically insignificant increase in fasting blood glucose levels, which is thought to be related to the steroid effect. However, the mean values of the HOMA-IR score decreased. These decreases can be explained by chemotherapy's influence on the insulin pathway or more attention to nutritional status. Our study provides important data even though the number of patients is small due to the limited number of studies in the literature. However, further studies that included many patients needed to verify these results. There are limited studies examining insulin resistance and cancer development. Further translational studies must be conducted to elucidate the pathophysiological mechanisms leading to cancer development.

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Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine Ethics Committee (number 38-824) allowed this research.

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.D., Y.Ü., H.O., Design: İ.D., Y.Ü., H.O., Data Collection or Processing: İ.D., Y.Ü., Analysis or Interpretation: İ.D., Y.Ü., H.O., Literature Search: İ.D., Y.Ü., H.O., Writing: İ.D., Y.Ü.

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Intubation Biomarkers in COVID Critical Care Patients

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What is known on this subject?

The coronavirus disease-2019 pandemic is an important cause of mortality worldwide and has created a serious burden for intensive care units. Many biomarkers have been studied and found valuable in terms of mortality and are used routinely. Many biomarkers have been researched and proved to be useful in predicting death, and they are now routinely used.

What this study adds?

In this study, in addition to the increase in acute phase reactants compared to the laboratory data of intubated patients admitted to the intensive care unit, we found higher I-granulocyte and neutrophil lymphocyte ratio ratios.

ABSTRACT

Objective: The coronavirus disease-2019 (COVID-19) pandemic is an important cause of mortality worldwide and has created a serious burden for intensive care units (ICU). Many biomarkers have been studied in terms of mortality and are used routinely. This study aims to look at the laboratory data of patients transferred to the intensive care as well as the laboratory data on the day of intubation to try to figure out which biomarkers can help predict the intubation procedure.

Material and Methods: Patients in the COVID ICU had their records retrospectively reviewed. The study comprised patients who received oxygen therapy at the time of admission and had a positive polymerase chain reaction (PCR) test in the ICU, as well as patients who were endotracheal intubation after 24 h due to respiratory distress and/or other complications. Patients' information was gleaned from the hospital's computer database and patient files. The data of patients hospitalized in the COVID ICU were reviewed retrospectively. Patients who received oxygen therapythe firstirst admission with PCR test positive at ICU and patients who were intubated after 24 h due to respiratory distress and/or other accompanying reasons were included in the study. The data of the patients were obtained from the hospital computer database and patient files.

Results: Lactate dehydrogenase, fibrinogen, ferritin, D-dimer, international normalized ratio (INR), WBC, neutrophil, neutrophil lymphocyte ratio (NLR), I-granulocyte, Sequential Organ Failure Assessment score ($p<0.001$) and pro-C, urea, INR, hemoglobin, lymphocyte scores were compared when the patients were intubated upon admission. There was a statistically significant difference in the values ($p<0.05$).

Conclusion: Acute phase reactants (AFR) increase in COVID-19 pneumonia. In the follow-up of the disease, it can be used in I-granulocytes with NLR as well as the increase in AFR.

Keywords: COVID-19, PLR, I-granulocyte

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic is a leading cause of death worldwide, and it has put a strain on intensive care units (ICU). Many biomarkers have been researched and proven to be useful in predicting death, and they are now frequently employed. This study aims to look at laboratory data from patients who are admitted to the ICU as well as laboratory findings on the day of intubation to determine whether any biomarkers can assist in predicting the intubation phase.

Material and Methods

This retrospective analysis-comprised patients who were followed up in adult ICU in a tertiary hospital center due to COVID-19 between October 1, 2020 and February 1, 2021. After the study was accepted by the hospital's ethical approval, the documents of patients coming to the ICU during the times stated were scanned retrospectively Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (ethical permission number: 2021-58, date: 14.04.2021).

The study's inclusion criteria were 1-) cases in which COVID-19 has been validated through polymerase chain reaction (PCR) testing; 2-) patients who have been diagnosed with acute respiratory distress syndrome (ARDS) according to the Berlin criteria; and 3-) patients aged 18 and over.

Criteria for exclusion: 1-) Patients under the age of 18; 2-) patients without ARDS (n=5); 3-) patients who are pregnant (n=5); 4-) patients with concurrent malignancy (n=5); 5-) patients with a history of organ transplantation and/or immunosuppressive drugs (n=8); 6-) patients with a radiological diagnosis with a negative COVID-19 PCR test (n=7); 9-) ICU patients who were intubated at the time of admission and/or patients who were intubated within the first 24 h of admission to the ICU (n=24). Patients with ARDS with COVID-19 pneumonia (n=154) were involved in the research.

Patients who had a positive PCR test and required high-flow nasal oxygen therapy, non-invasive mechanical ventilation, reservoir mask, nasal cannula mask, or a combination of these at first admission. Patients were also included in the trial if they were intubated after at least 24 h for respiratory distress and/or other reasons. To gather information on the patients, the hospital's computer database and patient files used. The patients' age, gender, concomitant disease status, and laboratory results on the day of admission to the ICU and day of intubation were all studied. The Sequential Organ Failure Assessment score (SOFA) and the Acute Physiology and Chronic Health Evaluation scores were also recorded at the time of admission to the ICU.

Statistical Analysis

The SPSS program used to conduct statistical analysis on the study data. To see if the continuous data fit the normal distribution, one sample Kolmogorov-Smirnov test employed. According to their distribution, quantitative variables were presented as mean and standard deviation or medians in our study (Table 1). Categorical variables were represented using numbers and percentages (Table 1). For continuous data that fit a normal distribution, the Student's t-test used to compare two different groups, whereas the Mann-Whitney U test used for those that did not (Table 2).

Table 1. Sociodemographic and clinical the research population's features n=154

	Mean ± SD/n	%/min-max
Age	63.07±14.57	18-85
BMI (kg/m^2)	28.06±4.98	18-42
Gender		
- Male	86	55.8%
- Female	68	44.2%
Comorbidities		
- Diabetes mellitus	58	37.66%
- Hypertension	55	35.7%
- COPD	18	11.68%
- Coronary artery disease	23	14.9%
- Chronic renal failure	9	5.84%
- Neurodegenerative disease	15	9.74%
- Liver failure	3	1.9%
- Heart failure	4	2.59%
PaO_2/FiO_2 admission		
- Moderate ARDS	81	52.59%
- Severe ARDS	73	47.41%
APACHE score	18.50±8.79	7-29
SOFA score at admission	6.32±2.95	4-20
LOS	18.38±12.65	2-55
Lenght of stay in hospital	18.40±12.62	2-73
Mechanic ventilation days	14.47±10.65	1-54
Intubation days	3.03±1.41	2-6

COPD: Chronic obstructive pulmonary disease, ARDS: Acute respiratory distress syndrome, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment score, LOS: lenght of stay in ICU, ICU: Intensive care unit, BMI: Body mass index, SD: Standard deviation, min: Minimum, max: Maximum

To examine categorical data between two groups, the chi-square test was used (Tables 2, 3).

Results

The sociodemographic and clinical characteristics of the study population has been described in Table 1. Eighty six (55.8%) of the patients were of male gender. Fifty five (35.7%) of the patients had hypertension, 58 (37.66%) had diabetes mellitus, 18 (11.68%) had chronic obstructive pulmonary disease, 23 (14.9%) had coronary artery disease, 15 (9.74%) had neurodegenerative disease, and 9 (5.84%) had chronic renal failure. The patients' average number of mechanical ventilator days was 14.47±10.65, their intensive care days were 18.38±12.65, and their hospital days were 18.50±8.79. The patients' average intubation day was 3.03±1.41. Additionally, laboratory data on the day the patients were admitted to the ICU and day they were intubated were compared and statistically significant results were obtained (lactate dehydrogenase, fibrinogen, ferritin, D-dimer, international normalized ratio (INR), white blood cell, neutrophil, neutrophil lymphocyte ratio (NLR), I-granulocyte, SOFA score ($p<0.001$), procalcitonin, blood urea nitrogen, INR, hemoglobin, lymphocyte ($p<0.05$) (Table 2). Comparison of laboratory data on the day of admission to the ICU and day of intubation.

Table 2. Laboratory results from the day of admission to the intensive care unit and the day of intubation n=154

	Admission to intensive care	Intubated	p value
Glucose (mg/dL)	192.12±108.51	199.25±11.65	0.450
BUN (mg/dL)	74.99±65.57	96.27±107.02	0.03
Creatinine (mg/dL)	1.6±1.43	1.57±1.40	0.29
AST (U/L)	83.46±296.94	154.96±560.14	0.94
ALT (U/L)	71.80±88.77	135.16±551.92	0.37
Fibrinogen (mg/dL)	641.45±699.43	500.08±215.96	0.000
INR	1.21±0.56	1.27±0.57	0.02
D-dimer (mg FEU/mL)	3.36±4.89	5.69±5.41	0.000
LDH (U/L)	509.43±398.23	731.42±816.84	0.000
Ferritin (ng/mL)	1427.56±1868.67	1749.2±1994.81	0.03
WBC (10^9/L)	11.38±8.52	15.13±8.99	0.000
HB (g/dL)	11.88±2.44	11.08±2.59	0.007
Platelet	243.39±122.56	231.76±125.69	0.36
Lymphocyte (10^9/L)	0.98±1.21	0.84±1.41	0.007
Neutrophil (10^9/L)	10.05±8.57	14.55±11.79	0.000
CRP (mg/L)	137.24±91.42	145.54±275.24	0.18
PCT (ng/mL)	4.89±31.71	3.56±9.31	0.008
NLR	20.34±30.17	32.72±40.27	0.000
PLR	442.08±406.24	495.11±400.94	0.169
I-granulocyte (10^9/L)	0.45±0.620	1.10±8.97	0.000
Mortality	140 (80.92%)	34(24.28%)	0.000
SOFA	6.52±2.83	10.11±3.4	0.000

BUN: Blood urea nitrogen, LDH: Lactate dehydrogenase, AST: Aspartate transaminase, ALT: Alanine aminotransferase, WBC: White blood cell, HB: Hemoglobin, PCT: Procalcitonin, CRP: C-reactive protein, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, I-granulocyte: Immature granulocyte, SOFA: Sequential Organ Failure Assessment score

The treatments and complications that occurred throughout the intensive care follow-up are summarized in Table 3. Tocilizumab was used in 13 (8.4%) of the patients, anakinra in 22 (14.3%), dexamethasone in 40 (26%) of the patients, plasmapheresis in 22 (14.3%) of the patients, stem cell therapy in 2 (1%) of the patients, pulse methylprednisolone in 66 (42.9%) of the patients, and intravenous immunoglobulin therapy in 17 (9.7%). In 73 (47.4%) of the patients, secondary bacterial infection developed. Positivity in culture in 46 (29.9%) patients. A total of 132 patients (85.8%) died. Septic shock was observed in 103 (66.9%), diabetic ketoacidosis 21 (13.6%), acute renal failure 52 (33.1%), elevated liver enzymes 11 (7.1%), and pulmonary thromboembolism 3 (1.9%) of the patients.

Table 3. Medical treatments and complications

	Total (n=154)
Dexamethasone	40 (26%)
Tocilizumab	13 (8.4%)
Anakinra	22 (14.3%)
Stem cell therapy	2 (1.3%)
Methylprednisolone pulse therapy	66 (42.9%)
IVIG	17 (9.7%)
Secondary bacterial infection	73 (47.4%)
Positivity in culture	46 (29.9%)
Septic shock	103 (47.4%)
Mortality	132 (66.9%)
Acute renal failure	51 (33.1%)
Diabetic ketoacidosis	21 (13.6%)
Elevated liver enzymes	11 (7.1%)
Deep vein thrombosis	2 (0.06%)
Pulmonary embolism	3 (1.9%)
Plasmapheresis	22 (14.3%)

IVIG: Intravenous immunoglobulin

Discussion

COVID-19 has various clinical manifestations, including asymptomatic pneumonia, ARDS, and even mortality. As a result, determining the seriousness of COVID-19 and implementing effective early therapies are critical steps in lowering mortality. Lymphocytosis is a common complication of viral infections. By collecting and neutralizing viruses, lymphocytes safeguard the body. A drop of lymphocyte count was seen in COVID-19 patients in our study. Because the angiotensin-converting enzyme 2 receptor is expressed in lymphocytes, one possible explanation for this observation is direct infection and death of lymphocytes by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). The importance of NLR in the diagnosis and prognosis of viral infection has been highlighted in numerous research. NLR, for example, has abetter sensitivity than neutrophil and lymphocyte counts alone, according to Han et al. (2), and can be employed as a preferred diagnostic technique to screen patients infected with influenza virus. Furthermore, NLR has been linked to chronic hepatitis B virus infection and can be used to predict recurrence (3,4) Lymphocytes play a major role in the immunological response triggered by a viral infection (5).

Systemic inflammation inhibits cellular immunity, decreasing CD4+ T lymphocytes and an increase in CD8+ suppressor T-cells (6). Thus, virus-induced inflammation increases NLR. High NLR may indicate COVID-19 progression. In this context, in our study, we found the NLR on the day of intubation to be higher and statistically significant than the NLR on the day of admission to the ICU ($p<0.001$). Neutrophils, along with mononuclear cells, are the first cells infected with SARS-CoV-2 and attracted to the alveoli, recruited by interferons, interleukin-6 (IL), IL-1, and other cytokines with a C-C motif chemokine ligand-2 motif. Cytokines cause immature granulocytes (I-granulocytes) to be produced and released by the bone marrow, which subsequently returns to the endothelium of the lungs, producing further inflammation and ARDS. In COVID-19-related hyperinflammation, neutrophils are thought to transform into immature forms, leading to degranulation, cytokine production, and increased interferon response (7,8,9). The NLR was linked with disease severity and organ dysfunction in a study of 42 critically ill persons with COVID-19 (10). Septic patients have higher I-granulocyte levels than patients with severe SARS-CoV-2 infection, according to previous research. Found that patients with ventilator-associated pneumonia had a significant peak in both absolute I-granulocyte counts and I-granulocyte percentages compared to those who did not (11).

COVID-19 patients with severe disease exhibited greater immature granulocyte levels but lower lymphocyte and platelet counts than COVID-19 patients without severe disease, according to a morphological analysis of 27 COVID-19 positive and 18 COVID-19-negative patients (12). In our investigation, the difference in I-granulocyte levels between intubated and non-intubated groups was statistically significant ($p=0.001$). As a result, I-granulocyte and NLR may be indicators of illness progression and the process leading to intubation.

The retrospective aspect of this study is one of its many flaws. Because the physician decided to intubate, the time it took to intubate varies. Furthermore, the causes of death have not been thoroughly investigated. More research is needed to determine if the onset of symptoms, the length of hospitalization, and the pharmacotherapies used affect the patient's clinical outcome.

Conclusion

In COVID-19 pneumonia, acute phase reactants (AFRs) known to rise. It can be employed in I-granulocytes with NLR as well as the increase in AFR in illness follow-up. The information obtained from a complete blood count is useful in clinical practice since it is affordable and quick to obtain. The use of these indicators in normal blood testing can aid clinicians in monitoring and predicting COVID-19 severity and prognosis.

Ethics

Ethics Committee Approval: Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (ethical permission number: 2021-58, date: 14.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

19

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Evaluation of the Route of Transmission and Clinical Course of SARS-CoV-2 Infection in Healthcare Workers at Istanbul Medipol University Hospital

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What is known on this subject?

Hospital workers are considered to be at high-risk in the coronavirus disease-2019 pandemic. Besides environmental and individual factors, inevitable contact with infected cases and exposure to high virulence concentrations makes healthcare workers susceptible to severe disease course and even death. Though the source of transmission may be predictable, this study targeted the most common source of infection for optimal protection.

What this study adds?

The main transmission route of the infection among hospital workers was found to be in-hospital. More intensive training and education should be given to the hospital staff who do not comply with infection control guidelines and to those without sufficient knowledge on transmission routes of severe acute respiratory syndrome coronavirus-2. Supervision on proper implementation of social distancing and hospital infection control policies, screening of asymptomatic patients and evaluation of personal protective equipment quality and accessibility is suggested.

ABSTRACT

Objective: Healthcare workers (HCW) have been the occupational group at highest risk of coronavirus disease-2019 infection despite early availability of guidelines for infection control, administrative management, and application of required conditions on field since the beginning of the pandemic. In this survey study our aim is to investigate environmental and individual factors which facilitate transmission of the virus among HCW in order to target preventative measures to be taken in the future.

Material and Methods: This current study is a single center based retrospective study conducted by analysing 446 telephone surveys conducted on HCW in Medipol Mega University Hospital who tested positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) between 15.03.2020-14.01.2021. Demographic details, comorbidities, department of work, occupation, symptoms, clinical course, choice of pulmonary imaging, use and availability of personel protective equipment (PPE) as well as adherance to social distancing rules was determined.

Results: Among the 3,013 HCW's at our hospital, 877 (29%) were tested positive for SARS-CoV-2, of which 446 were included in the survey. It was shown that 337 (85%) of those included in the study were adherent to the infection prevention protocols. Despite the high application of preventative measures at our hospital in-hospital transmission rates were still found to be high. In-hospital transmission was observed to be in groups of workers simultaneously among different departments of the hospital. The source of transmission was unknown in 33.78% of our HCW. Advanced age and those with comorbidities were found to have higher rates of severe infection. Infection rate was low in pregnant HCW due to the granted administrative leave.

Conclusion: Overall transmission of the infection among HCW is seen to be substantially in-hospital. More extensive training and education should be given to hospital staff who do not comply with infection control guidelines as well as to those who are unable to identify the source of transmission. Supervision of the implementation of hospital infection control policies, screening of asymptomatic cases as well as evaluation of PPE quality is valuable in the protection of HCW. In the event of a pandemic, elderly healthcare workers and those who have comorbidities may benefit from working in secluded environments within the hospital due to the severe course of disease seen in this group of patients.

Keywords: COVID-19, healthcare workers, SARS-CoV-2, personal protective equipment

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Introducion

In December 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel virus causing acute respiratory distress, quickly spread across the world after its initial emergence in China. Causing great concern to people of all countries, the World Health Organization (WHO) declared a pandemic on the 11th of March 2020 in an attempt to protect global health by increasing all preventative measures taken against the virus. The SARS-CoV-2 pandemic poses a serious threat to public health by causing physical, psychological, economical, social disturbances as well as loss of lives. The occupational group at highest risk of suffering the consequences of this pandemic has healthcare workers (HCW) (1). The total number of HCW who have been infected by the virus and lost their lives at the beginning of the pandemic is unknown. What is common among the data presented from different countries is the increased prevalence of SARS-CoV-2 infection among HCW compared to the general population. The prevalence of SARS-CoV-2 infection among HCW in China is 3.46-28.9% (2,3), 12.9% in Massachusetts (USA) (4), between 10.6-20% across various studies in Italy (5,6), 38% in the city of Madrid (Spain) (7), 14% in accordance with the Health Ministry of Spain (8), and reported to be 14.5% in the United Kingdom (9). The WHO reports 3% of the world population in April 2020 to be HCW, and at least 14% of SARS-CoV-2 infections to be in HCW. According to these statistics 1 in every 7 SARS-CoV-2 cases is a healthcare worker (10).

Due to the availability of epidemiological studies on this topic in our country, this study is based on reliable data provided by the Health Ministry of Turkey on the relationship between SARS-CoV-2 infection and HCW. The Health Ministry revealed that HCW constituted 6.3% of the 117,589 SARS-CoV-2 cases seen by 29th of April 2021 (11). On 2nd of September 2020, 29,865 of the 273,301 cases were HCW and 52 HCW had lost their lives to the infection (12). The Health Ministry further revealed that by 10th of December 2020, the number of infected HCW had passed 120,000, and that more than 10% of HCW were infected with 216 lives lost (13). In the 25th of February edition of The Turkish Thorax Society, it was revealed that a total of 28,138 lives were lost in Turkey to the SARS-CoV-2 pandemic of which 380 were HCW. According to these data, at the same date 1 of 74 of the lives lost to SARS-CoV-2 was unfortunately a healthcare worker (14).

HCW play an active role in the diagnosis, treatment and observation of the SARS-CoV-2 infection. In the SARS-CoV guidelines published by the T.C. Health Ministry of Turkey, routes of transmission, diagnostic methods, strategy and protocols to be followed in the management of SARS-CoV-2-positive patients and those with close-contact is described in detail, with regular updates made accessible to all healthcare institutions.

Studies on the incidence of infection among HCW, screening, clinical course, and radiological findings found in literature, however the precise route of transmission among HCW has been difficult to determine during a pandemic. This study aims to investigate the route of infection among HCW to target further preventative measures that can be taken. We identify environmental and individual risk factors contributing to the spread of the disease, and to provide recommendations based on the variable risk factors. In addition to this we observed the different factors, which affect the clinical course of the disease among our HCW to improve preventative measures that may be taken.

Material and Methods

This is a single center based retrospective study with written informed consent forms and is approved by both the Health Ministry (2020-06-22T16_19_42) as well as the Istanbul Medipol University Institutional Review Board (04.03.2021/286).

Data obtained between the date of the first case of SARS-CoV-2 infection in a healthcare worker at our hospital and the first Synovac vaccination was included in this study. Thus, data screening was retrospectively conducted on positive SARS-CoV-2 PCR tests between 15.03.2020-14.01.2021 in the occupational medicine records of HCW at our hospital.

Of the 3013 HCW at our hospital 2127 are female (70.59%) and the remaining 886 are male (13.80%). At our hospital, we have 312 medical doctors (10.35%), 739 nurses (24.52%), 416 patient assistants (13.80%), 140 translators (4.64%). According to the occupational medicine records, in the duration of the aforementioned dates 877 of our HCW (29%) were found to have a positive SARS-CoV-2 test. Of these people, 446 [326 (73.09%) female, 120 (26.91%) male] who gave informed consent were included in the study. Those who did not respond to the survey or were unable to be contacted due to changes in their contact information were excluded from the study.

A telephone survey was conducted on our infected HCW. Data on demographic details, comorbidities, department of work, occupation, symptoms in the duration of the disease, clinical course, the choice of pulmonary imaging were collected from the hospital information system and surveys. In addition the survey also consisted of data on whether the HCW believed to be infected in-hospital or outside of the hospital, the availability of personal protective equipment (PPE) inside the hospital

and how well they adhered to social distancing rules such as wearing a surgical mask and standing at a 1 meter distance from others. Compliance to using PPE (surgical mask, coveralls, gloves, goggles/face shields) when in contact with an infected patient and using gloves, goggles/face shield, coverall and FFP2, N95, or other equal protective masks during aerosol generating procedures was also questioned in the survey. Education on hand hygiene, social distancing, usage of PPE and other standard infection prevention and control precautions were given online to all employees working at the hospital.

The clinical course of SARS-CoV-2 can be graded to be mild, moderate, serious and critical based on the symptoms of the infected individual (15). Mild cases commonly experience symptoms such as fever, myalgia, fatigue, headache and throat ache without any radiological findings. Moderate cases may have fever, respiratory symptoms, and radiological findings indicative of pneumonia. Cases with greater than 50% pneumonic infiltration within the first 24-48 hours after diagnosis are excluded in this group. Serious cases include at least one of the following symptoms; dyspnea, tachypnea (respiratory rate >30/min) or arterial oxygen saturation <93% in room air or PaO_2/FiO_2 >300 mmHg. Critical cases are identified by respiratory failure, septic shock, or multiorgan failure.

On thorax computed tomography, typical findings such as ground glass opacities, crazy paving pattern, irregular multifocal consolidation and/or interstitial changes with peripheral distribution were deemed pozitif for SARS-CoV-2 pneumonia in the context of the pandemic.

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 software (Chicago, IL). Normally distributed continuous variables were expressed as mean ± standard deviation and categorical variables were reported as counts and percentages.

Results

Our level III hospital located in the Bagcilar district of Istanbul, an area with the highest rate of SARS-CoV-2 infection, our HCW were exposed to this infection to a large extent (infection rate among hospital workers 29%). The highest number of infected HCW in our hospital was seen in November 98 cases (11.17%), followed by October and December (Figure 1).

Occupational medicine records show the occupation of the infected HCW to be 89 (10.14%) doctors, 261 (29.76%) nurses/midwives, 34 (3.87%) laboratory technicians, 12 (1.36%) anestezia technicians, 16 (1.82%) radiology technicians, 168 (19.15%) patient consoulers, 31 (3.53%) translators, 20 (2.28%) administrative staff, 76 (8.66%) office staff, 65 (7.41%) technical health staff, and 105 (11.55%) miscellaneous staff (Figure 2). The age range of our HCW: 7 (1.57%) aged >20, 311 (69.73%) aged 21-30 (69.73%), 80 (17.94%) aged 31-40, 37 (8.30%) aged 40-51, 11 (2.47%) workers aged <51. It was observed that 129 of our HCW (28.92%) worked in the SARS-CoV-2 infection wards, while 317 (71.07%) did not.

Nine (2.01%) of the HCW were pregnant. Of these pregnant women 4 underwent a c-section, whereas one had a spontaneous vaginal delivery at term without any complications. Among those who had a c-section, one was a surgical nurse who was being treated in the intensive care unit and had a premature delivery due to the disease. The remaining 4 pregnant cases are being followed up with no complications related to the infection.

Among the HCW who were infected, 79 (17.71%) of the cases were found to have chronic diseases whereas 367 (82.28%) did not. 10 (2.24%) had hypertension, 7 (1.56%) had diabetes mellitus, 4 (0.89%) had chronic kidney disease, 24 (5.38%) had asthma, 7 (1.56%) had heart disease, 5 (1.12%) had autoimmune disease, 1 (0.22%) had cirrhosis, 1 (0.22%) had cerebrovascular disease, 3 (0.67%) had hematological disease and 17 (3.81%) had other miscellaneous diseases. One hundred ten (24.66%) were smokers, 336 (75.33%) were non-smokers.

Our healthcare professionals were asked the question, "How do you think you infected?" and answered "Infected

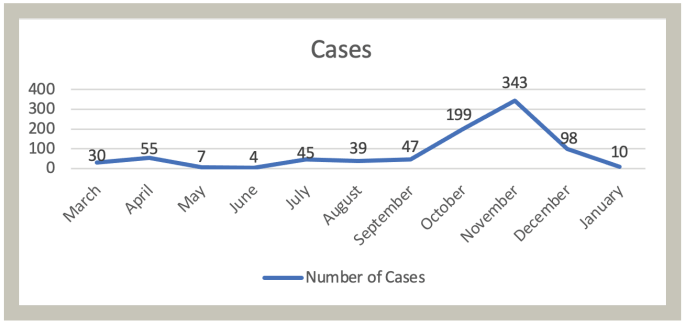

Figure 1. Monthly distribution of cases at the hospital

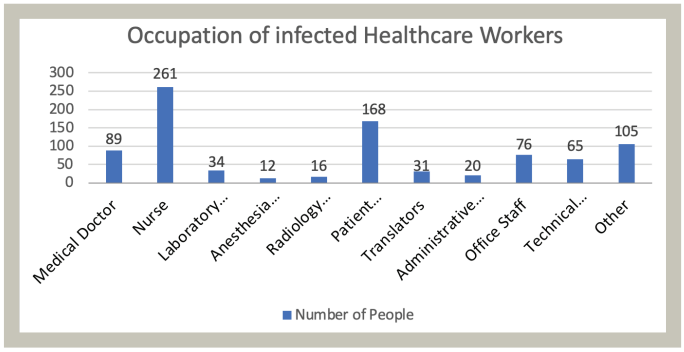

Figure 2. Occupational title of infected healthcare workers

from a patient inside the hospital by 170 of the cases (38.11%)", "infected by hospital staff" by 83 (18.60%) of the cases, infected from a patient outside the hospital by 74 (16.59%) of the cases, and "I don't know" by the remaining 119 (26.68%) (Figure 3).

Three hundred eighty nine (87.21%) of the HCW reported maintaining a 1-meter distance and wearing a medical mask when in contact with people who are not sick, while 57 (12.78%) did not. Three hundred thirty seven (85.10%) confirmed using surgical masks, gowns, gloves, goggles/face shield when in contact with infected patients, while 59 (14.90%) were not complient.

While performing aerosol generating procedures, 128 (77.58%) HCW used N95 or FFP2, or equivalent mask, gloves, goggles/face shields, apron, 37 (22.42%) did not. Access to PPE was said to be "sufficient" by 299 (69.21%) HCW, "insufficient" by 22 (5.09%), and "partially sufficient" by 111 (25.69%).

Among the HCW who responded to the survey, symptoms of SARS-CoV-2 infection were observed to be fever in 191 (43.61%) of the cases, cough in 184 (42.01%), shortness of breath in 118 (26.94%), muscle-bone pain in 291 (66.44%), nausea-vomiting in 56 (12.79%), abdominal pain in 44 (10.05%), diarrhea in 90 (20.55%), loss of taste (ageusia) and loss of smell (anosmia) in 244 (55.71%), sore throat in 154 (36.16%), nasal discharge in 102 (23.29%), and lastly various other symptoms were experienced by 22 (5.02%) of the workers (Figure 4).

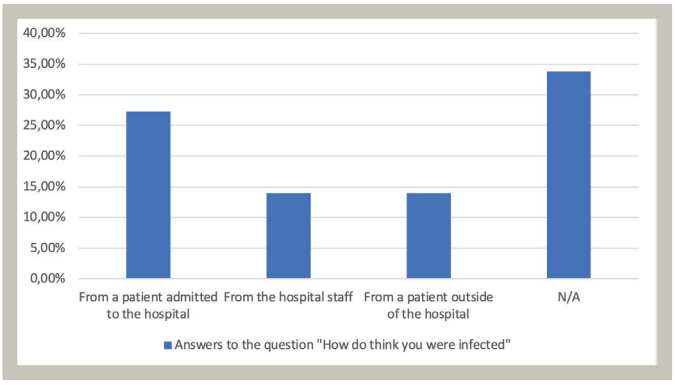

Figure 3. Route of transmission

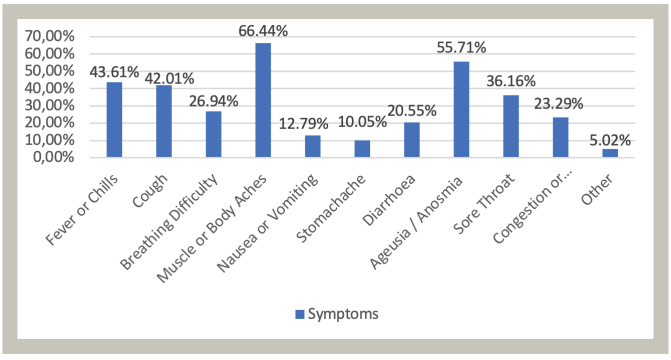

Figure 4. Symptoms of infected healthcare workers

Four hundred thirty one (96.63%) of our HCW were treated in the outpatient clinic while 5 (1.12%) were admitted into the hospital for inpatient care. Nasal oxygen therapy was given to 4 (0.89%), reservoir mask therapy to 1 (0.22%), and high flow oxygen therapy to 3 (0.67%) of our healthcare professionals. Intensive care treatment was required for 2 (0.44%) of the workers. According to the severity of the symptoms, 362 of the cases were classified to be mild, 78 moderate, 4 severe and 2 were considered critical.

Among the HCW who had a prescription for the management of their chronic diseases 6 (1.34%) were using corticosteroids, 7 (%1.56) were using immunosuppressants, and 6 (1.34%) were using angiotensin-converting-enzyme -inhibitor containing antihypertensive drugs.

The preferred pulmonary imaging modality was chest X-ray in 54 patients (13.43%), thorax tomography in 116 (28.86%), and lung ultrasonography in 5 (1.24%). Two hundred and twenty seven (56.47%) of the HCW did not undergo any imaging.

Discussion

In a study conducted in two referral hospitals in Italy, the rate of SARS-CoV-2 infection among hospital workers was reported to be 11.3% (16). Similarly, this rate was reported to be 11.1% (17) in a hospital in Madrid, Spain. Data from various countries were evaluated in the August 2020 edition of Chou et al. (18) review of "the epidemiology and risk factors of coronavirus infections in HCW." It has been observed that the frequency of SARS-CoV-2 in HCW varies between 1.9% and 12.6% (18). However, the rate of SARS-CoV-2 infection among the staff of our hospital is 29%, which is quite high compared to the rate seen in other countries. This may be associated with multiple factors such as the location of the hospital being in a region with the highest cases in Istanbul, the fact that most of the hospital staff reside in the same area and the active role that the hospital played in serving SARS-CoV-2 patients during the pandemic.

At our hospital 29.76% of the cases were nurses, 19.15% were patient assistants, 10.14% were doctors. These data are supportive of literature (19) which has shown nurses to be the healthcare subgroup to be most infected by the virus.

From March 2020 to January 2021, the incidence of infection at our hospital had fluctuating peaks which were seen to be parallel to the number of cases in the country. As the number of cases increased in the country, so did the

number of SARS CoV-2-positive HCW (Figure 1, 5).

In a large epidemiological study by the Chinese Center for Disease Control and Prevention (CDC), 80.9% of patients were reported as milemoderate 13.8% as severe and 4.7% as critical. The mean age of the patients in the study was 47 (15). Among our hospital staff, 81.16% of those infected were mild, 17.48% moderate, 0.89% severe, and 0.44% were critically infected. Fortunately, we have not had a case resulting in death. Most of the infected HCW at our hospital were between the ages of 21-30 (with the average age of our employees being 29). The number of people with chronic diseases among them was 17.71%. The average age of the HCW at our hospital requiring inpatient treatment was 41.7, of which 40% had coexisting chronic diseases. The lower rate of comorbidities as well as the younger age of our employees can explain the decreased rate of serious/critical cases and increased rate of mild cases seen at our hospital.

In a study of more than 370,000 confirmed cases of coronavirus disease-2019 (COVID-19) reported to the CDC in the United States, symptoms were found to be cough 50%, fever 43%, myalgia 36%, headache 34%, shortness of breath 29%, sore throat 20%, 19% diarrhea, 12% nausea/vomiting, <10% loss of smell or taste, 7.6% abdominal pain and 6.1% runny nose (20). It is emphasized in the study that the complaints of anosmia-ageusia was probably under-reported. Myalgia (60%) and loss of smell and taste (55%) were more common among our hospital staff. Other symptoms were found to occur at similar rates.

The chronic diseases seen among the COVID-19 cases reported to the CDC in the United States were as follows; 32% had cardiovascular disease (including hypertension), 30% had diabetes mellitus, 18% had lung disease, and lastly 11% were pregnant at the time of infection. In our study, 3.80% had cardiovascular disease (including hypertension), 1.56% had diabetes mellitus, 5.38% had lung disease, and only 2% were pregnant. The rate of our pregnant group is low due to the administrative leave granted to pregnant women after their 24th gestational week.

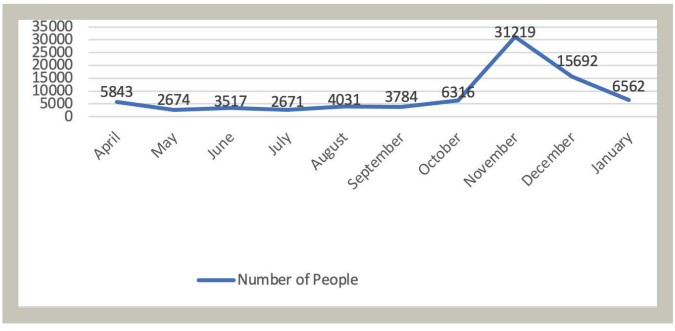

Figure 5. Monthly distribution of the 100 thousand cases seen in our country

Since the average age of our employees is young, the rate of chronic diseases is not compliant with literature.

According to the results of "COVID-19 survey in the hospital workers", a multicenter study conducted by the Turkish Infectious Diseases and Clinical Microbiology Specialization Association in our country, an average of 14.7% people do not know the possible source of transmission. In our hospital, 56.71% of our HCW were infected inside the hospital, 16.59% outside the hospital, and 26.68% were unable to detect the source of transmission. The fact that the source of transmission is not known by healthcare professionals requires more detailed investigation. The rate of inaccessibility to PPE was 5.09%, and the rate of applying protective measures as required in the hospital was 85.10%. With these results, our in-hospital contamination rate is high despite the precautions taken by our employees. This may be due to asymptomatic carriers that can be found in all environments. The spread of the virus in the hospital was seen to be as groups among various departments. Table

Table 1. Classification of infected healthcare workers according to hospital department

Month	Classification of infected healthcare workers according to the hospital department
April	Operating room (4), emergency (4), 6th floor patient service (6), cardiovascular surgery service (5), biochemistry (4), training nurse (4)
July	Biomedical (7), security (8), archive (4), neonatal intensive care (5), international patient services (9), pediatric polyclinic (5)
August	Archive (5), blood collection (2), IVF (2), neonatal intensive care (3), international patient services (6), operating room (4)
September	Dental service (5), 3rd patient floor service (6), cardiovascular surgery (5), 6th floor (4), cardiovascular surgery (3), general intensive care (5)
October	Medical directorate (4), 4th floor patient service (5), 6th floor service (4), baby room (8), call center (4), angio room (8), interventional radiology (5), gynecology and obsetetrician polyclinic (5), pharmacy (7), 8th floor patient service (4), 7th floor patient service (4), child polyclinic (9), radiology polyclinic (6)
November	Emergency (14), 5th floor (27), physical therapy (12), operating room (11), eye polyclinic (5), ENT (3)*, call center (9), IVF (4)**, VIP services (6), neurology service (4), dental polyclinic (6), dental service (6), chemotherapy (8), international patient services (17), oncology service (3), medical directorate (4)
December	Radiology (4), 6th floor (4), 8th floor patient service (7), support services (6), emergency (4), corporate marketing (4), sterilization (2), dental polyclinic (4)

ENT: Ear nose throat, IVF: In vitro fertilization***

1 shows that 27 people from our 5th floor ward, 12 people from the physical therapy department, 9 people from the call center, and 17 people from the international relations department were infected simultaneously within their units. It can be understood that HCW apply protective measures when in contact with patients however are less compliant with these rules (such as 10-15 min of eating and drinking breaks) in their social working environment. Here, it can be thought that HCW in the same department may be a source of contamination amongst themselves and cause separate epidemics within their departments.

Conclusion

Hospital workers are deemed a high-risk group during the pandemic. The main transmission route of the infection among hospital workers is most probably in-hospital. More intensive training and education should be given to the hospital staff who do not comply with infection control guidelines and to those without sufficient knowledge on transmission routes of SARS-CoV-19. Supervision on proper implementation of social distancing and hospital infection control policies, screening of asymptomatic patients and evaluation of PPE quality and accessibility is suggested.

Ethics

Ethics Committee Approval: The Health Ministry (2020-06-22T16_19_42) as well as the Istanbul Medipol University Institutional Review Board (04.03.2021/286).

Informed Consent: Written informed consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.P., Concept: G.P., Design: F.M., Data Collection or Processing: G.P., Analysis or Interpretation: G.P., İ.P., Literature Search: G.P., Writing: G.P., H.K.A.

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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After COVID-19 Infection Extended Intensive Care Process and Assessment of its Cost

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What is known on this subject?

Prolonged intensive care unit stays get more costs to the hospitals.

What this study adds?

Complicated coronavirus disease-2019 cases prevent the effective use of intensive care units. Additionally, these cases cause cost increases.

ABSTRACT

Objective: In coronavirus disease-2019 (COVID-19), the length of stay (LOS) in the intensive care unit (ICU) is about a month. In this case series, we assessed the reason for the long LOS in ICU and the cost analysis.

Material and Methods: The study was designed retrospectively. We investigated 533 patients and identified 9 patients with a hospital stay of more than 30 days.

Results: Generally, 9 patients were admitted to the ICU with clinical findings that were not specific for COVID-19. During the ICU follow-up, we observed that secondary infection and acute respiratory distress syndrome developed in all the patients. Simultaneously, we determined that the prolonged ICU stay caused additional costs.

Conclusion: In the terms of COVID-19 pandemic; the prolongation LOS in ICU leads to cost increase and negative affects the health system.

Keywords: ICU, prolonged LOS, COVID-19, cost

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Introduction

Coronavirus disease-2019 (COVID-19) is an infection with a high morbidity and mortality, requiring hospitalization and intensive care unit (ICU), at the same time creating a serious burden on the health budget. Generally, patients admitted to the ICU from the pandemic clinic or the emergency department to provide invasive or non-invasive mechanical ventilator support due to advanced respiratory failure. A major part of the patients leave the ICU within the first month. In this case series, we assessed the reason for the long hospitalization of patients with long-term ICU and the medical cost.

Material and Methods

During November 2020 and February 2021, we investigated 533 patients that we followed up in our unit due to COVID-19 and identified 9 patients with a hospitalization period of more than 30 days. An informed approval form was obtained from all patients. Approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (no: 2022.01.36, subject number: KAEK/2022.01.36).

Age, gender, days of ICU stays and mortality of the patients were recorded. Also, complication that depend on prolonged in the ICU of the patients were recorded. Cost analysis was performed for each patient with prolonged hospitalization. Cost analysis was done with current hospital billing unit data The average cost was calculated. The statistical data were not used in case of the patient number was 9.

Results

Two of the patients were female and 7 were male and the age range ranged from 36 to 73 years (Table 1). The first thing that stood out in these patients was that they were admitted to the ICU clinical findings that did not support COVID-19. Among these patients who were hospitalized in the ICU for more than 30 days due to COVID-19, 3 patients had regression in Glasgow Coma scale, 2 patients had respiratory arrest, 1 patient had hepatic failure associated with acute respiratory distress syndrome (ARDS), 2 patients were admitted from the emergency department with an ischemic cerebrovascular disease (Table 2). One patient was taken over from the pandemic due to clinic respiratory failure. COVID-19 positivity was detected in polymerase chain reaction (PCR) tests. During the ICU follow-up, all patients developed secondary infection and ARDS, while deep vein thrombosis in 1 patient, pneumothorax in 1 patient, arrhythmia in 1 patient, neurological disorder in 2 patients, and acute renal failure in 1 patient. All 9 the patients were followed up on a mechanical ventilator with tracheostomy. Among these patients, the minimum number of ICU hospitalization days was 33, while the maximum was 395 days. While 3 patients who were followed up and treated in the ICU were transferred to the clinic, 6 patients died. In the calculation that made with the fees which were determined by the Republic of Turkisch Ministry of Health during the study period, we determined that the treatment expenses of these patients were 74060±10863.4 TL.

Table 1. Demographic characteristics

Age	55.88±11.83 (36-73)
Gender F/M	2/7
LOS in ICU	82.66±117.75 (33-395)
Mortality	66%

LOS: Lenght of stay, ICU: Intensive care unit, F: Female, M: Male

Table 2. Complications in patients with prolonged stay in ICU

Secondary infection and ARDS	9 patients
Neurological disorder	3 patients
Deep vein thrombosis	1 patient
Pneumothorax	1 patient
Arrhythmia	1 patient
Acute kidney disease	1 patient

ICU: Intensive care unit, ARDS: Acute respiratory distress syndrome

Discussion

Patients with COVID-19 usually admit to the hospital with symptoms of fever, weakness, and cough (1). In studies of the first period of the pandemic, the average hospital stay of these patients was 4-53 days in China, while it was reported as 4-21 days in other countries (2,3,4,5). The data in these studies are in the first period of the disease and in the following periods, studies with different results have been revealed with the updating of the information about the disease and the treatment practices.

With the rapid spread of COVID-19 in the world, clinicians tried determining the criteria for the effective and ethical use of hospital beds. Additionally, to the high mortality rate in patients with advanced age and co-morbidities, the length of hospital stay may be long (6). Especially, it has tried developing estimation models for ICU length of stay, but it is seen that the estimation models for the number of hospitalization days at the patient level are not very sufficient (7). Complex models with multiple parameters may also not be sufficient (8,9). In

addition to studies considering parameters such as age, Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology II scores, there are also studies evaluating the clinical picture of ARDS and multiple organ failure (MOF). With these parameters, prolonged ICU length of stay estimations can be made (10,11,12). The length of stay in the ICU does not only depend on epidemiological and physiological parameters. ICU resources and access to treatment may also affect the length of stay (13).

This study, in which we evaluated our patients who were hospitalized in the ICU for more than 30 days, we saw that patients were transferred from other hospitals with diagnoses other than COVID-19 since our hospital is 4th level hospital. However, the PCR tests of all patients were positive. Simultaneously, we observed that the patiens had MOFs during the transfer. Therefore, we tought that the longer ICU stay in our patient group is because patients were admitted to the ICU with COVID-19 complications. Secondary infections and ARDS (2) were most frequent complications that had caused hospitalization due to COVID-19. Arrhythmia, shock, acute cardiac injury, acute kidney injury (1) was also developed. Similarly, ARDS and secondary infections were observed in our patients during their follow-up.

The cost of COVID-19 to the health system is another important dimension of this epidemic. It has been determined that a symptomatic COVID-19 case in the USA can lead to an average of $3,045 direct medical costs during its course (14). In our study, the prolonged hospitalization and the struggle with complications constitute the reason for this increase in costs. According to a cost-effectivity study conducted in COVID-19 patients in South Africa; according to the normal service hospitalization; it was observed that there was a difference of about 3 times (15). Another study from the USA, it was stated that the cost increased in parallel with the length of stay in the ICU and comorbidity (16).

Study Limitations

There are some limitations to our study. First, the study was retrospective. Secondly, the number of patients was small.

Conclusion

Although it is ideal to complete the treatment of the patient before complications that develop during the COVID-19 ICU, it is not always possible. The prolongation of the process also leads to negative cost analysis and affects the health system.

Ethics

Ethics Committee Approval: Approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (no: 2022.01.36, subject number: KAEK/2022.01.36).

Informed Consent: An informed approval form was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ö., B.İ.F., M.Ü., Concept: A.Ö., Design: A.Ö., G.T., Data Collection or Processing: A.Ö., B.İ.F., M.Ü., Analysis or Interpretation: A.Ö., M.Ü., G.T., Literature Search: A.Ö., B.İ.F., Writing: A.Ö., G.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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Management of Patient by a Pulmonary Embolism Response Team in the Emergency Department

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What is known on this subject?

The treatment of pulmonary embolism (PE) remain one of the great challenges of emergency medicine. The management of patient with PE requires a multidisciplinary approach. A detailed treatment algorithm should be developed with the collaboration of emergency medicine, cardiology, interventional radiology, and thoracic surgery experts.

What this case report adds?

We believe that establishing Pulmonary Embolism Response Team is essential in terms of beginning the most appropriate treatment faster and reducing mortality.

ABSTRACT

Pulmonary embolism (PE) occurs when the pulmonary arterial system is blocked by a thrombus. Mortality is attributed to the right ventricle failure due to the increased pressure load. In this case, patient was successfully treated with catheter-mediated local thrombolytic therapy by a Pulmonary Embolism Response Team (PERT). A 70-year-old male patient was transferred to our emergency department for further evaluation and treatment, with a prediagnosed PE. Consultant physicians (PERT) of cardiology, pulmonology, interventional radiology, and thoracic surgery were called to the emergency department and evaluated the patient. After a deliberate discussion, PERT members reached a consensus on catheter-mediated thrombolytic therapy for the patient. The patient had no symptoms or complaints over that one-month period. We believe that establishing a PERT is essential in terms of beginning the most appropriate treatment faster and reducing the mortality.

Keywords: Pulmonary embolism, Pulmonary Embolism Response Team, emergency medicine, catheter-mediated thrombolytic therapy

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Introduction

Pulmonary embolism (PE) occurs when the pulmonary arterial system is blocked by a thrombus. Deep vein thrombi are frequently involved in the etiology. PE has a wide presentation and is among the main causes of the mortality. Mortality is attributed to the right ventricle failure due to the increased pressure load. The clinical management of the patients with PE has been rapidly changing over the years. In the absence of hemodynamic instability at presentation, the clinical management plan should be done according to the initial assessment. If the probability of the PE is high in clinical evaluation or the patient has a high PE risk score, CT pulmonary angiogram is recommended as soon as possible (1). When a massive PE is proved, thrombolytic therapy is administered if there is no contraindication. Contraindications for thrombolytic therapy include active bleeding, hemorrhagic or cryptogenic stroke, central nervous system tumors, history of ischemic stroke in the last six months, and major trauma/surgical intervention/head trauma in the last three weeks (2).

The treatment of PE remains one of the great challenges of emergency medicine. The management of the patient with PE requires a multidisciplinary approach. A detailed treatment algorithm should be developed with the collaboration of emergency medicine, cardiology, interventional radiology, and thoracic surgery experts. Hereby, we presented a case who was diagnosed with a massive PE in which systemic fibrinolytic therapy was contraindicated. In this case, patient was successfully treated with a catheter-mediated local thrombolytic therapy by a Pulmonary Embolism Response Team (PERT).

Case Reports

A 70-year-old male patient was transferred to our emergency department for further evaluation, and treatment with a prediagnosis of PE. Upon arrival, it was documented that he was admitted to the previous healthcare facility with the shortness of breath and receiving radiotherapy for his brain tumor for a month. In the initial assessment, the patient was awake, cooperative, and oriented. Glasgow Coma scale was 15/15. Vital signs recorded as following: BP: 90/50 mmHg, pulse: 90/min, SpO_2: 92%, RR: 26/min. In the physical examination, the full review of systems was normal except for tachypnea. Lab results showed increased troponin which is 129 ng/L and high D-dimer level. Other tests were found to be normal (Table 1). In CT pulmonary angiogram, the thrombus located in the bilateral pulmonary arteries was seen (Figure 1). Thereupon, PERT was alerted. Consultant physicians in cardiology, pulmonology, interventional radiology, and thoracic surgery were called to the ER and evaluated the patient. In the echocardiography, the right ventricle was dilated, and its functions were reduced. After a detailed evaluation, the patient was diagnosed with a massive PE. However, thrombolytic therapy was contraindicated due to the patient's intracranial tumor. After a deliberate discussion, PERT members reached a consensus on catheter-mediated thrombolytic therapy for the patient.

Table 1. Lab results

WBC	10.29 10^9/L	INR	1.04
Potassium	3.93 mmol/L	aPTT	24.6 sc
Sodium	141 mmol/L	D-dimer	7.71 µg/mL
Troponin T	129 ng/L	pH	7.35
Creatinine	1.18 mg/dL	pCO_2	43.0 mmHg

WBC: White blood cell, INR: International normalized ratio, aPTT: Activated partial thromboplastin time

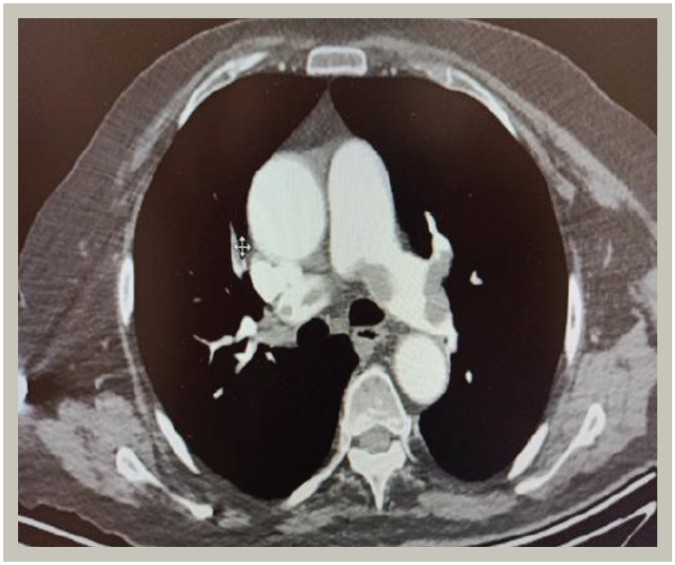

Figure 1. CT pulmonary angiogram
CT: Computed tomography

After reaching the pulmonary arteries through a catheter introduced to the right femoral vein, the thrombolytic agent was administered to the right and left main pulmonary arteries. During the procedure, a total of 10 mL of tissue plasminogen activator (tPa) was injected in both pulmonary arteries. Afterwards, pig tail catheter was placed in the left main pulmonary artery due to a high thrombus load (Figure 2), and continuous infusion of 1 mL/hour tPa treatment for 15 hours started. During the procedure vital parameters remained stable; BP: 110/70/mmHg, HR: 85 bpm, SpO_2: 94%. The patient tolerated the procedure well without any complications. Throughout the following 24 hours, the patient

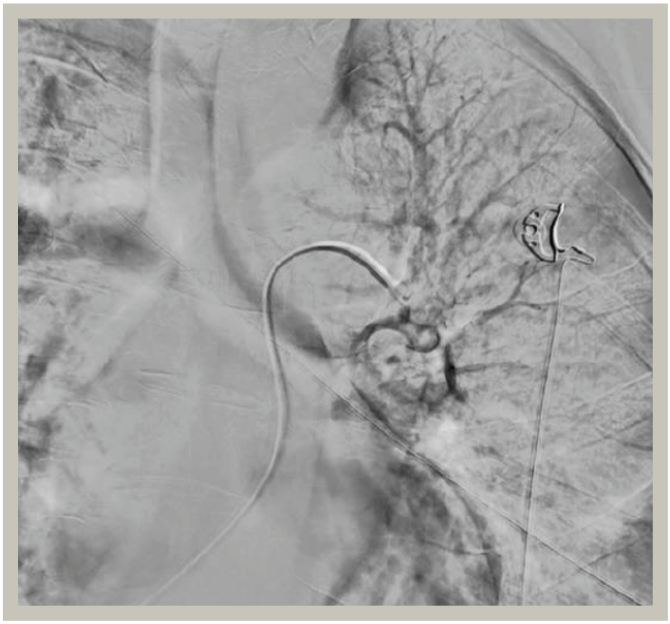

Figure 2. Pig tail catheter was placed in the left main pulmonary artery

was monitored in the intensive care unit. Then, transferred to the pulmonology department as his clinical status started to improve. After the successful in-hospital treatment, medical treatment and outpatient clinic follow-ups were planned. Telephonic follow-ups were made once a week for a month. The patient had no symptoms or complaints over that one-month period.

Discussion

There are several treatment strategies for PE in the literature. In a massive PE, systemic thrombolytic therapy is recommended as the first-line treatment (3). However, as in our case, there is a limited number of clinical studies in the medical literature recommending other treatment options, that could be selected for patients whom systemic thrombolytic therapy is contraindicated. Lately, catheter-mediated thrombolytic therapy has been suggested when favorable outcome is not able to be reached with a systemic thrombolytic therapy or if there is any type of contraindications for a systemic therapy (4). Our case is a PE case with an intracranial tumor who received catheter-mediated thrombolytic therapy.

In a prospective observational study conducted by Kuo et al. (5), no major complications, hemorrhagic stroke, and major hemorrhage followed by a catheter-mediated thrombolytic therapy was reported in 101 patients with PE. They stated that catheter-mediated thrombolytic treatment could be used safely in PE.

In a multicenter study conducted by Bloomer et al. (6), a catheter-mediated thrombolytic therapy was shown to be safer, like the study of Kou et al. (5). Also, Bloomer et al. (6) recommended catheter-mediated thrombolytic therapy for fewer side effects and higher treatment efficiency.

Since there are several treatment options in PE, the treatment algorithm is quite complex, and it is challenging to decide which treatment is the best. Current guidelines recommend building a "PERT" in the centers where PE treatment is delivered (7). In addition, it is stated that PERT should involve a wide variety of the specialties such as: Emergency medicine, critical care, cardiology, internal medicine, and the radiology (8). In the current literature, it is shown that PE managed with PERT results in the reduced time to diagnosis, time to anticoagulant therapy, the length of the hospital stays, and the mortality rate (9,10). In this case, we successfully treated our patient with PE with the collaboration of PERT members.

Patients diagnosed with PE requires immediate medical attention in the emergency department. To deliver a maximum value to the patients with PE, we believe that establishing the PERT is essential in terms of beginning the most appropriate treatment faster and reducing the mortality.

Ethics

Informed Consent: Patient consent was obtained for the article to be published.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Ş., K.S., Ö.K., Concept: K.Ş., M.K., R.G., Design: K.Ş., R.G., Data Collection or Processing: K.Ş., K.S., Literature Search: K.Ş., R.G., Writing: K.Ş., B.A.

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

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Treatment of Isolated Penile Fournier's Gangrene: A Case Report and Current Literature Review

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What is known on this subject?

Fournier's gangrene (FG) is rapidly progressive necrotizing fasciitis of genital, perineal and perianal regions. FG is occurs mainly in the perineum and scrotum. Isolated penile involvement is much rarer.

What this case report adds?

Data on isolated penile FG are extremely limited. In the literature, there are very few case reports of FG of the isolated penis. We think that it will contribute to these case reports. We also saw that different choices were made as a treatment such as radical or partial penectomy. In this case report, we have contributed to the trend of partial penectomy treatment by treating with partial penectomy.

ABSTRACT

Fournier's gangrene (FG) is rapidly progressive necrotizing fasciitis of genital, perineal and perianal regions. Usually seen in patients with accompanying predisposing factors. Here, we report a case of FG with isolated penile necrosis in a 70-year-old diabetic male patient with a permanent foley catheter who presented to the emergency department with the complaint of blackish discoloration and purulent discharge in the penis for 4 days. Examination of external genital area showed ulcerated and necrotic lesions on the glans and shaft of the penis and scrotum and testes were normal. Broad spectrum intravenous antibiotics were given and surgical debridement was performed. A penectomy was performed and a neo-mea was created. In the presence of FG of the penis, early diagnosis and aggressive surgical treatment increases the chance of survival.

Keywords: Fournier's gangrene, penectomy, penis, necrotizing fasciitis

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Introduction

Fournier's gangrene (FG) is rapidly progressive necrotizing fasciitis of genital, perineal and perianal regions. It is a disease with high mortality if untreated rapidly. This is usually observed in patients with accompanying predisposing factors (1,2,3).

FG mainly occurs in the scrotum and can spread to the perineum, penis and abdominal wall, but it is very rare that it first occurs in the penis (4). Here, we present FG of the isolated penis and its successful treatment.

Case Report

Seventy years old male presented in emergency with complaint of blackish discoloration and purulent discharge in the penis and increased body fever. Penile lesions started 4 days ago, fever started one day ago.

The patient was living with a permanent foley catheter and his catheter was renewed 1 month ago. He had had diabetes mellitus (DM) and coronary arterial disease for about 20 years. The patient's DM poorly controlled. It was learned from the history of the patient, that bypass surgery was recommended to the patient because three coronary vessels were obstructed, but the patient refused the operation because his surgical performance was low.

The patient's temperature was 39.8 °C, pulse 95 beats/min, blood pressure 105/65 mm of high, respiratory rate 20 breaths/min. Examination of the external genital area showed ulcerated and necrotic lesions on the glans and shaft of the penis (Figure 1). The scrotum and testes were normal. In laboratory examination, white blood cell: 22.000/dL, C-reactive protein: 250 mg/L, procalcitonin: 6 mg/dL, blood sugar: 450 mg/dL. Blood urea and serum creatinine levels were normal.

Figure 1. Necrotic tissues in the penis before surgery

After making the diagnosis of FG, broad-spectrum intravenous antibiotics were given, and emergency surgery was performed for surgical debridement and gangrenous tissue excision.

Cavernosal tissues were checked after the necrotic penis glans was excised. Necrosis was also observed in the cavernosal tissue and we decided to perform penectomy. The corpus cavernosum and urethra were separated and resected from the proximal of both cavernosal bodies and sutured. A partial penectomy was performed. After resection, the remaining urethra was spatulated and neo-mea was fixed on the penile stump (Figure 2). A suprapubic catheter was placed at the end of the procedure.

In the postoperative period, the patient did not have a fever. Insulin treatment was initiated to regulate blood sugar. Both blood glucose and other laboratory findings decreased dramatically after surgery. The dressing was repeated twice a day for 10 days and was operated for reconstruction after wound healing.

The skin flaps on the wound margins were closed primarily approximated to each other. The patient was discharged 5 days later with his foley catheter removed. After the catheter was removed, it was checked that the patient could sit and urinate. Suprapubic cystostomy was removed 3 weeks later.

Discussion

FG is an extremely rare disease that occurs in 1.6 cases per 100,000 men each year (0.02%-0.09%). Although it can be seen in women, it often occurs in men (2,5).

DM, advanced age, alcoholism, chronic steroid use, HIV infection, malnutrition and other conditions that suppress the immune system are predisposing factors for FG (1,2,3). In addition to these factors, traumatic conditions such as

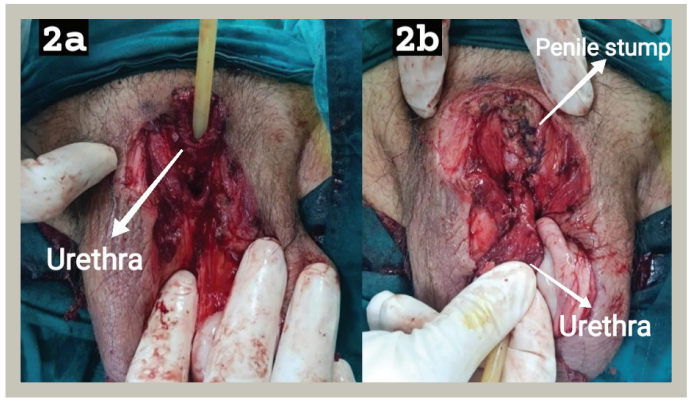

Figure 2. (a) Separation of the urethra and both cavernosal bodies. (b) Penile stump after resection of cavernosal bodies

urethral catheterization, cavernosal injections and penile trauma may accompany the FG of the penis (4). Human bite, penile self-injection with cocaine, abrasion of the penis during oral sex, urethral stricture, and DM have been observed as predisposing factors for penile FG in the literature (6,7,8,9). The patient we presented; had predisposing factors such as DM, coronary artery disease and urethral catheter.

FG, which occurs mainly in the perineum and scrotum, isolated penile involvement is less common. This is probably due to the rich blood flow to the penis. In the literature, the FG of the penis consists of data shared as case reports (4,6,7,8,9,10).

FG is diagnosed by clinical examination. The treatment included aggressive surgical debridement and antibiotic therapy. Early diagnosis and early surgical treatment are critical for preventing mortality. Generally, the agent is polymicrobial, so broad spectrum antibiotics should be initiated. Surgical treatment should include excision of all necrotic and infected tissues. Predisposing factors, if any, should also be treated, such as blood sugar control.

Partial penectomy may be sufficient for limited FG in the penile glans, while total penectomy is required in advanced necrosis. In this study, since there was necrosis up to the proximal cavernosum, partial penectomy was performed and neo-mea was created.

In the presence of FG of the penis, early diagnosis and aggressive surgical treatment increase the chance of survival.

Ethics

Informed Consent: Permissions were obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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