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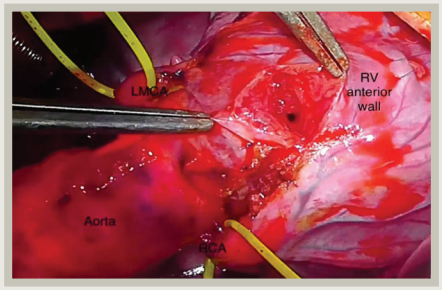

Figure 1. Proximal RCA and LMCA are released in the beating heart
LMCA: Left main coronary artery, RCA: Right coronary artery, RV: Right ventricle

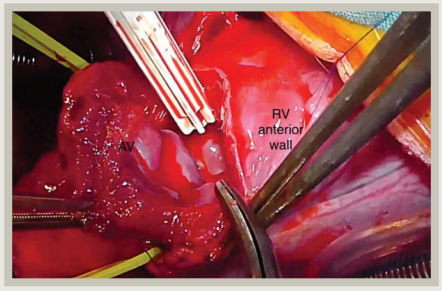

Figure 2. A curvilinear incision in the anterior wall of the RV was created to visualize the aortic valve
AV: Aortic valve, RV: Right ventricle

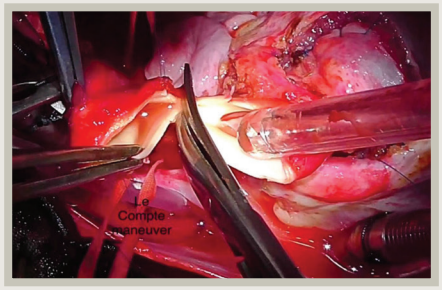

Figure 5. The aorta was transected for the Le Compte maneuver

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Journal History

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

Title: Cam ve Sakura Medical Journal

Official abbreviation: CSMJ, Csmedj

E-ISSN: 2791-8823

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Aims and Scope

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

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Peer Review, Publication Ethics and Malpractice Statement

B. DUTIES OF EDITORS:

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

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

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Instructions to Authors

c. Keywords

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

d. Original Article

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

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

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

Introduction

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

Materials and Methods

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

Results

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

Discussion

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

Study Limitations

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

Conclusion

The conclusion of the study should be highlighted.

e. References

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

i) Standard Journal Article

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

ii) Book

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

iii) Chapter of a Book

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

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

If more than one editor: editors.

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

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

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

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

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

Special Sections

Reviews

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

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

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

Case Reports

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

Clinical Images

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

Video Article

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

Technical reports

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

Diagnostic puzzle

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

Novel insight

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

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Instructions to Authors

Letters to the Editor

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

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

Revision Process

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

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

LIMITATION TABLE

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

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Editorial

Dear Colleagues,

We have just completed a 2 year period with the publication of the third issue of CSMJ in 2022. This is really important for us as we succesfully published all the issues of CSMJ as planned during this period. Therefore, I thank to all Editorial Board, authors, reviewers and readers. In this last issue, you will read 1 invited review, 4 original articles, and 1 technical report.

The review of this issue is about the importance of expanded disability status scale (EDSS) in multiple sclerosis (MS). EDSS has been widely used to evaluate the treatment efficacy in MS patients. In this review, a detailed approach for EDSS has been established and I believe that it will provide useful insights for neurologists and physicians dealing with MS. The first original study in this issue is about maternal and neonatal outcomes of pregnant women with COVID-19 from a tertiary perinatal referral center in Istanbul. The maternal epidemiological, clinical, laboratory, radiological and treatment features, and also maternal/neonatal outcomes of COVID-19 infection in this special population were established. The second study of this issue was performed to evaluate the presence of West Nile virus in blood donors. The main purpose of this study was to determine the necessity of routine screening of West Nile virus in blood donors. The third article in this issue includes the comparison of umbilical cord 25-OH Vitamin D levels between term and late preterm infants. The authors reported that with vitamin D levels reached to normal levels at postnatal fourth month with standard vitamin D replacement therapy. The last original study evaluated the risk factors for SARS-CoV-2 transmission in healtcare workers in intensive care units. In this issue, the first technical report of CSMJ was published. It describes the Nikoidoh procedure for a beating heart. I hope these manuscripts will provide valuable information for all readers.

In addition to J-Gate and Turk Medline indexes, CSMJ has been now indexed in EBSCO and Gale indexes within the second year publication period. We belive that it will be indexed in other national and international indexes with your support. Therefore, we are waiting your manuscripts for the future issues.

We wish a happy new year for all our colleagues and readers. We will be waiting your articles for the issues that will be published in 2023. We are also exciting to improve our contents and quality in 2023.

On behalf of Deputy Editors, Associate Editors and Editorial Secretary

Merih Cetinkaya

Editor in Chief

Cam & Sakura Medical Journal

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Expanded Disability Status Scale (EDSS) in Multiple Sclerosis

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ABSTRACT

Multiple sclerosis has an increasing prevalence and incidence. There are many articles showing that early treatment can prevent possible disability. Expanded disability status scale assessmenthas great importance both in pivotal studies and in clinical practice to evaluate treatment efficacy. For this reason, this review has been written to be well known and not to miss the details.

Keywords: Disability, EDSS, functional score, multiple sclerosis

CAM & SAKURA MEDICAL JOURNAL

Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system, affecting approximately 3 million people worldwide (1). It can be seen in almost any age range, although it is more common in the 20-40 age range and about 3 times more common in women. In our country, MS female/male patient ratio is 2.5/1 (2). The prevalence of MS is 41-61/100.000 (3).

The expanded disability status scale (EDSS) is the most commonly used scale in patients with MS. EDSS is a very effective method in reflecting disability (4). EDSS assessment is a non-linear assessment and is a scale in which MS is evaluated between 0 and 10, where normal neurological examination is 0 and MS-related death is 10 (5). Although EDSS is widely used in clinical studies and patient follow-up, it has some limitations. Increases of 1 point have different meanings in each point transition. The evaluation of functional systems (FS) is complex and subjective. It is insensitive and distant to the evaluation of cognitive functions and especially upper extremity functions between 4.0-6.5 EDSS. The contribution of cerebral functions to EDSS scores is very limited. In contrast, the contribution of pyramidal and cerebellar functions to the score is significant. EDSS includes an ambulation-based evaluation after 4.0 (6).

In an article published by Lublin (7) in 2014, the disease should be phenotyped according to active and progressive status. A numerical equivalent of disability has been adopted in terms of determining the degree of the disease, treatment change, or possible progressive process. For this reason, the EDSS is used in MS (8). In many pivotal studies, the primary endpoint is EDSS. Simultaneously, attack-related worsening and non-attack-related worsening are also determined by the increase in EDSS in patient follow-up (9).

Jean Martin Charcot described cognitive impairment in MS as markedly impaired memory, slowed conceptualization and impaired intellectual functioning (10). The EDSS was defined by

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Kurtzke (11). This article uses this article, which is still valid in clinical practice. In contrast to Charcot, they suggested that cognitive impairment in individuals with MS is seen in 3% of patients and that cognitive impairment occurs in patients with high rates of physical disability (11). This detail may perhaps explain the lack of emphasis on cognitive functions in the EDSS. Time is an important determinant of the nature of MS, so in a study investigating the predictive significance of time and cognitive status for EDSS, it was reported that although no cognitive test was predictive of EDSS in the early period, information processing speed was predictive of EDSS at 5-year follow-up, and both information processing speed and visuospatial ability were predictive of EDSS score at 6-8 years (12). Studies evaluating disease subtypes show that progressive MS is cognitively different from relapsing-remitting MS (13,14,15). In a study in which EDSS was categorized as <4 or ≥4, it was shown that the cognitive performance of the group with a low EDSS score was significantly better than the group with an EDSS ≥4 (16).

It is impossible to calculate the EDSS without knowing the functional scores. Although there are many digital calculation methods, these programs cannot perform some conversions. Functional scoring is explained in detail below. The tables were made by me and taken from the MS reference book (17).

Functional Systems

Pyramidal Functions

0. Normal

1. Abnormal findings without disability,

2. Minimal disability,

3. Mild or moderate paraparesis or hemiparesis; severe monoparesis,

4. Marked paraparesis or hemiparesis; moderate quadriparesis; or monoplegia,

5. Paraplegia, hemiplegia,

6. Quadriplegia.

The pyradimal function scoring table is given below (Table 1).

Table 1. Pyramidal functions scoring

One extremity	Score
Normal physical examination	0
Only if there are findings	1
If the motor force is 4/5	2
If the motor force is 2 or 3/5	3
If the motor force is 0 or 1/5	4
Two extremities	**Score**
If the motor force is 4/5	2
If the motor force is 3/5	3
If the motor force is 2/5	4
If the motor force is 0 or 1/5	5
Three extremities	**Score**
If the motor force is 4/5	3
If the motor force is 3/5	4
If the motor force is 2/5	5
Four extremities	**Score**
If the motor force is 4/5	3
If the motor force is 3/5	4
If the motor force is 2/5	5
If the motor force is 0 or 1/5	6

Cerebellar Functions

0. Normal,

1. Abnormal findings without disability,

2. Mild ataxia,

3. Middle truncal or limb ataxia,

4. Network ataxia, all extremities,

5. Inability to make coordinated movements due to ataxia.

The cerebellar function scoring table is given below (Table 2).

Table 2. Cerebellar function scoring

Body posture	Score
Normal physical examination	0
Only if there are findings	1
Romberg positivity	2
Moderate - hard	3
Hard	4
Walking	**Score**
Mild	2
Moderate - hard	3
Hard	4
Extremity	**Score**
Normal physical examination	0
Only if there are findings	1
Mild	2
Moderate	3
Hard (3-4 extremities)	4
Cannot act in coordination	5
Cannot be evaluated	X

Brain Stem Functions

0. Normal,

1. Findings only,

2. Moderate nystagmus or other mild disabilities,

3. Severe nystagmus, marked loss of extraocular power, or moderate disability of other cranial nerves,

4. Significant dysarthria or other significant disability,

5. Loss of the ability to swallow or speak.

The brain stem functions scoring table is given below (Table 3).

Table 3. Brain stem functions scoring

Extraocular movement score	Score
Only if there is a symptom [limitation in barely noticeable emergency obstetric hysterectomy (EOH) (no patient complaints)] 1	1
Mild (patient has complaints with limitation in EOH that is barely noticeable or incomplete paralysis in eye movements that the patient is not aware of)	2
Moderate (patient-aware incomplete paralysis of eye movements or complete loss of movements in one direction of gaze in both eyes)	3
Severe (complete loss of movements in both eyes when looking in more than one direction)	4
Nystagmus score	**Score**
Only signs or mild (gaze-evoked nystagmus)	1
Moderate (no nystagmus in primary position but persistent nystagmus at 30 degrees vertical/ horizontal gaze)	2
Severe persistent nystagmus in primary position or affecting vision, in all directions gaze	3
Complete internuclear ophthalmoplegia with very marked persistent nystagmus or persistent nystagmus in the abducting eye 3	4
Dysphagia score	**Score**
Only if there is a finding	1
Mild (difficulty drinking fluids)	2
Moderate (difficulty swallowing liquid solid foods)	3
Heavy (persistent difficulty swallowing, can eat puree)	4
Absent	5
Dysarthria score	**Score**
1 only if there is a finding	1
Mild (patient-aware dysarthria)	2
Moderate (dysarthria impairing intelligibility in everyday speech)	3
Heavy (unintelligible speech)	4
Complete loss (unable to speak)	5
Hearing Loss score	
7th cranial nerve	**Score**
Only if there are findings	1
Mild (facial weakness of which the patient is aware)	2
Moderate [incomplete facial paralysis (difficulty closing the eyes - must close them at night or difficulty closing the mouth - drooling)]	3
Heavy	4
5th cranial nerve	**Score**
Only if there are findings	1
Mild (patient-aware numbness)	2
Moderate [impaired sharp/crunch distinction in branches 1, 2, or 3 of the trigeminal nerve or trigeminal neuralgia (at least 1 pain attack in the last 24 h)]	3
Severe (inability to distinguish between sharp/ sharp or complete loss of sensation in all branches of the trigeminal nerve)	4

Sensory Functions (1982 Revision)

1. Decreased vibration or drawing only in one or both extremities,

2. Slightly reduced sensation of touch, pain, or position in one or both extremities, and/or moderately reduced, vibration in one or both extremities; or vibration deficit in 3-4 extremities alone (e.g. drawing shapes),

3. Moderate decreased sensation of touch, pain, or position in one or two extremities, and/or mainly loss of vibration; or mild touch, pain and/or moderate impairment of all proprioceptive tests in 3-4 extremities,

4. Markedly decreased sense of touch, pain, or loss of proprioception in one or two extremities, singly or in combination; or moderate loss of touch, pain and/or severe loss of proprioception in more than two extremities,

5. Loss of sensation (mainly) in one or both extremities; or moderate loss of sensation of touch, pain and/or proprioception in most of the parts of the body below the head,

6. Mainly loss of sensation in the sub-cranial parts.

The sensory function scoring table is given (Table given below 4, 5).

Table 4. Sensory functions

Position 1-2	Score
Mild	2
Moderate	3
Absent	5
Position 3-4	**Score**
Moderate	3
Hard	4
Absent	5
Figure drawings 1-2	**Score**
Mild	1
Absent	5
Figure drawings 3-4	**Score**
Mild	2
Moderate	3
Hard	4
Absent	5
Vibration 1-2	**Score**
Mild	1
Moderate	2
Absent	3
Vibration 3-4	**Score**
Light	2
Moderate	3
Hard	4
Absent	5
Pain 1-2	**Score**
Mild	2
Moderate	3
Hard	4
Absent	5
Pain 3-4	**Score**
Mild	3
Medium	4
Hard	5
Absent	6
Heat sensation 1-2	**Score**
Mild	1
Absent	5
Heat sensation 3-4	**Score**
Mild	2
Moderate	5
Absent	6

Table 5. Sensory functions converting scores

Vibration 3-4 moderate impairment + position 3-4 moderate impairment: 3 vibration 3-4 lost + position 3-4 lost: 4
Vibration 1-2 lost + pain-heat 1-2 lost + position 1-2 lost: 5 vibration 3-4 lost + pain-heat 3-4 lost + position 3-4 lost: 6

Bladder-bowel Functions

0. Normal,

1. Mild pause in urination (urgency), a feeling of urinary urgency or urinary retention,

2. Moderate urinary urgency, urinary urgency, urinary urgency, retention in the bowel or bladder, or rare incontinence,

3. Frequent urinary incontinence,

4. The need for almost continuous indwelling catheterization,

5. Loss of bladder function,

6. Loss of bladder and bowel function,

The bladder bowel function scoring table is given (Table 6 given below).

Conversion: Bladder-bowel FS grade 6-5

Table 6. Bladder bowel functions scoring

Catheter	Score	Converted
Intermittent	3	3
Always	5	4
Bowel	**Score**	**Converted**
Mild	1	1
Severe	2	2
Intervention	3	3
Missing	5	4
Bladder - incontinence	**Score**	**Converted**
Mild	1	1
Moderate (infrequent)	2	2
Moderate (frequent)	3	3
Missing	5	4

Visual (or Optical) Functions

0. Normal,

1. Scotoma with corrected visual acuity better than 20/30,

2. Maximum corrected visual acuity in the worse eye between 20/30-20/59,

3. Extensive scotoma in the worse eye, or a degree of visual field reduction but maximum-corrected visual acuity between 20/60 and 20/99,

4. Significant reduction in visual field and maximum-corrected visual acuity between 20/100 and 20/200 in the worse eye; maximum visual acuity 20/60 or less in grade 3 plus good eye,

5. Maximum corrected visual acuity less than 20/200 in the worse eye; maximum visual acuity 20/60 or less in grade 4 plus the better eye,

6. Fifth degree plus maximum visual acuity of 20/60 or less in the better eye.

The optical function scoring table is given (Table given below 7, 8).

Contribution of visual FS degrees to EDSS

6—4

5—3

4—3

3—2

2—2

1—1

Table 7. Optical functions scoring

Disk pallor	Score
0	0
1	1
Scotoma	**Score**
0	0
Small scotoma	1
Big scotoma	3

Table 8. Optical functions scoring 2 (visual acuity scoring)

Visual acuity		Score
Healthy eye	Damaged eye	
-	1.0	0
-	>0.67	1
-	0.67-0.34	2
-	0.33-0.21	3
-	0.2-0.1	4
<0.33	0.21-0.33	4
-	<0.1	5
<0.33	0.2-0.1	5
<0.33	<0.1	6

Cerebral (or Mental) Functions

0. Normal,

1. Mood disorder only (does not affect DSS score),

2. Slight decrease in mental function,3. Moderate impairment of mental function,4. Severe impairment of mental function (moderate chronic brain syndrome),

5. Dementia or chronic brain syndrome - severe or incompetent.

The mental function scoring table is given below (Table 9).

Table 9. Mental functions scoring

Mental	Score
Mood change	1
Mild	2
Moderate	3
Hard	4
Dementia	5
Fatigue	**Score**
Mild	1
Moderate - hard	2

Scoring

0.0: Normal neurological examination (grade 0 in all FS, including cerebral grade 1)

1.0: No disability, minimal findings (grade 1) in one FS (except cerebral grade 1)

1.5: No disability, minimal findings (grade 1) in more than one FS (except cerebral grade 1)

2.0: Minimal disability in one FS (one FS grade 2; others 0 or 1)

2.5: Minimal disability in two FS (two FS grade 2; others 0 or 1)

3.0: Moderate disability in one FS (fully ambulatory patient)

One FS grade 3, the others 0 or 1

Mild disability in 3 or 4 FS (3/4 FS grade 2, others 0 or 1)

3.5: Fully ambulatory patient, but moderate disability in one FS

One grade 3 + one or two FS grade 2

Five FS grade 2 (others 0 or 1)

4.0: Fully ambulatory patient (can walk around 500 metres unassisted and without rest) grade 4 severe disability in one FS (others 0 or 1)

Combination of lower grades, exceeding the limits of the previous steps

4.5: Can walk 300 meters without assistance or rest

The fully ambulatory patient unassisted for close to most of the day, able to work full time, grade 4 on one FS (others 0 or 1)

Combination of lower grades, exceeding the limits of the previous steps

5.0: Can walk approximately 200 meters without assistance or rest; the disability is severe enough to prevent him/her from fully conducting daily activities

Grade 5 in one FS (others 0 or 1)

Combinations exceeding low grades

5.5: Can walk approximately 100 meters without assistance or rest;

The disability was severe enough to prevent daily activities

Grade 5 alone in a FS (others 0 or 1)

Combinations exceeding low grades

6.0: Intermittent or unilateral fixed support required to walk approximately 100 meters with or without rest

Combinations of 3 or more degrees of impairment in more than two FS

6.5: Fixed bilateral support required to walk 20 meters without rest; combinations of 3 or more degrees of impairment in more than two FS

7.0: Cannot walk beyond 5 meters even with assistance;

Wheelchair-dependent

Turns the wheels by itself and can move into the wheelchair by itself

May spend approximately 12 h or more per day in a wheelchair

Grade 4 or more in one FS; rarely pyramidal grade 5

7.5: Cannot take more than a few steps;

Wheelchair-dependent

Assistance with the transition to a wheelchair may be required

Turns the wheelchair itself

Cannot spend the whole day in a standard wheelchair

Motorized wheelchair may be required

Grade 4 in more than one FS

8.0: Mainly bed/chair dependent, or can ambulate in a wheelchair

Can spend most of the day out of bed; can do most of his/her own work

Multiple grades 4 and above in FSs

8.5: Bedridden most of the day; can use arm(s) effectively to some extent

Multiple grades 4 and above in FSs

9.0: Hopelessly bedridden patient; can communicate and eat

Most of the FSs have a rating of 4 and above

9.5: Completely hopeless, bedridden patient; unable to communicate effectively or swallowing and eating impaired

10.0 Death

Practical Approaches to Ambulation

- Asymptomatic
- Can walk normally, but fatigue and exhaustion occur in situations requiring athletic performance
- Unassisted walks 300≤ >500 m (EDSS: 4.5-5)
- Can walk 200≤ >300 m without support (EDSS: 5)
- Can walk 100≤ >200 m without support (EDSS: 5.5)
- The unassisted walking distance was less than 100 m (EDSS: 6)
- Can walk more than 50 m with unilateral support (EDSS: 6)
- Can walk more than 120 m with bilateral support (EDSS: 6)
- Can walk up to 50 m with unilateral support (EDSS: 6.5)
- Can walk at least 5 and up to 120 m with bilateral support (EDSS: 6.5)
- Usually wheelchair-bound, cannot walk more than 5 m even with support, can switch to a wheelchair (EDSS: 7)
- Requires assistance for wheelchair use, cannot take more than a few steps even with support, requires assistance for transfer (EDSS: 7.5)
- Usually bed and chair bound, can spend most of the day out of bed, uses hands actively, needs help self-care (EDSS: 8)
- Spends most of the day in bed (EDSS: 8.5)
- Bedridden, able to communicate and feed (EDSS: 9.0)
- Bed-dependent, unable to communicate, feed and chew (EDSS: 9.5)

In Summary

- A FS 1 EDSS 1
- Multiple FS 1 (1+1+) EDSS 1.5
- One FS 2 EDSS 2
- Two FS 2 (2+2) EDSS 2.5
- A FS 3 or (2+2+2+2) or (2+2+2+2+2) EDSS 3
- A FS 3+2 or (3+2+2+2) or (2+2+2+2+2+2) EDSS 3.5
- An FS 4 or (EDSS; above 3.5) EDSS 4

• Unassisted 300-500 meters EDSS 4.5

• Unassisted 200-300 meters EDSS 5

• Unassisted 100-200 meters EDSS 5.5

From 6.0 points onward, the patient's need for support is recorded

• Unilateral support EDSS 6

• 2 sided support EDSS 6.5

From 7.0 onwards, wheelchair and gradual bed dependency

• Communicates bedridden after 8.5

• 9.5 EDSS cannot communicate

• 10.0 death

EDSS Calculation with Samples (18)

First, detailed patient examination of must be performed. Then the FS score is determined. Necessary changes are made in the systems that need conversion. The EDSS score is calculated based on a FS and ambulation.

Functional System Score Calculation

• Neurological examination: Visual acuity; left eye; 0.1 (20/200), right eye; 1.0 (20/20) visual FS score: 4 (after conversion: 3),

• Neurological examination: Visual acuity; left eye; 0.1 (20/200), right eye; 0.8 (20/25) left eye defects from childhood. Visual FS score: 1 (after conversion: 1),

• Neurological examination: Visual acuity; left eye; 0.05 (20/400), right eye; 0.8 (20/25) visual FS score: 5 (after conversion: 3),

• Neurological examination: Persistent nystagmus (primary) in the primary position, internuclear ophthalmoparasis (middle) in the left eye, clinically detectable dysarthria (mild) Brainstem FS score: 3,

• The patient has a clone in the right lower extremity, live deep tendon reflexes in the lower extremities, muscle strength is complete in all muscle groups. Pyramidal FS score: 1,

• The patient's right lower extremity 2/5 muscle strength, right upper extremity 3/5 muscle strength, live reflexes in lower extremities, plantar response extensor on the right. Pyramidal FS score: 4,

The patient cannot walk more than a few steps due to lower extremity ataxia. Have only trunkal ataxia when sitting. There is a mild tremor in the upper extremities cerebellar FS score: 4,

The patient had no complaints. Slightly reduced vibration sensation in the lower extremities. Other sensory examination findings were within normal limits Sensory FS score: 1,

• The patient had Lhermitte's complaint and mild depression sensory FS score: 0, cerebral system score: 1,

• Patient needs bladder catheterization several times a week, constipation problem is present, occasional manual intervention is required. Bowel and bladder FS score: 3 (after conversion: 3).

Conclusion

EDSS is a scoring system that is known by every neurologist but is not applied in practice. In this article, we want to address the EDSS approach in practice.

Ethics

Peer-review: Externally peer-reviewed.

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Maternal and Neonatal Outcomes of Pregnant Women with COVID-19 in İstanbul, Turkey: A Single-center, Descriptive Study

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CAM & SAKURA MEDICAL JOURNAL

What is known on this subject?

The coronavirus caused many unknown pneumonia cases that were clinically similar to viral pneumonia in Wuhan, a city in the Hubei Province of China, in December 2019. On January 30, 2020, the World Health Organization announced that the new coronavirus was a public health emergency of international concern. The virus spread rapidly worldwide and the number of cases began to increase in the other countries in February 2020. The first case in our country was announced on March 11, 2020. Until this date, the number of cases detected in the world was 125.900, but now (June 2) is 6.378 M. Currently, knowledge on the epidemiology and clinical features of pneumonia in pregnancy caused by coronavirus disease-2019 (COVID-19) is limited. Therefore, sharing clinical and epidemiological data on COVID-19 infected pregnancy is crucial for improving perinatal outcome. Effective obstetric therapy is required in these pregnant women and is key to optimizing the prognosis for both mother and child. Care should be individualized in determining the time of delivery, evaluating the C-section indications, preparing the delivery room to prevent infection, choosing the type of anesthesia and managing the newborn. Birth and treatment experiences are limited for pregnant women who have had the disease in the last 3 months.

What this study adds?

In our study, we define the epidemiological, clinical, laboratory and radiological features, maternal and neonatal outcomes and treatment of pregnant women confirmed to have severe acute respiratory syndrome coronavirus-2 infection.

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ABSTRACT

Objective: This study aimed to define the approach to pregnant women with coronavirus disease-2019 (COVID-19) and to determine the maternal and neonatal consequences of the disease.

Material and Methods: Maternal and neonatal outcomes of COVID-19 pregnant women are illustrated by looking at the following parameters: Real-time reverse transcription polymerase chain reaction test, complete blood count, D-dimer and ferritin concentration, lymphocyte count, aspartate aminotransferase, C-reactive protein, and alanine aminotransferase level, neonatal umbilical blood gas analysis, admission to the neonatal intensive care unit (NICU), and lung computed tomography images.

Results: Forty-three trimester pregnant women with a diagnosis of COVID-19 were included in the study. The most common complaint at admission was cough (50%), and the most common accompanying finding was shortness of breath and fever. The delivery method was 34 patients cesarean section and 6 patients vaginal delivery. Two neonates were admitted to the NICU due to respiratory distress. There were no maternal or infant deaths. The patients were hospitalized for approximately 5 days.

Conclusion: To sum up, our study is a preliminary study and there is a need for studies involving a much larger number of patients in terms of clinical features and follow-up treatment of pregnant women with COVID-19. In this regard, long-term patient follow-up results will be extremely important.

Keywords: COVID-19, maternal and neonatal outcomes, pregnant, obstetrics and gynecology

Introduction

The coronavirus caused many unknown pneumonia cases that were clinically similar to viral pneumonia in Wuhan, in December 2019 (1). On the World Health Organization declared that the new coronavirus was a public health emergency of international concern on January 30, 2020. The virus spread rapidly worldwide and the number of cases began to increase in the other countries in February 2020 (2). The first case in our country was announced on 11, 2020. Until this date, the number of cases detected in the world was 125.900, but now (June 2) is 6.378 M (3). Currently, knowledge on clinical features and the epidemiology of pneumonia in pregnant women induced by coronavirus disease-2019 (COVID-19) is restricted. Therefore, sharing clinical and epidemiological data on COVID-19 infected pregnancy is crucial for improving perinatal outcome.

Effective obstetric therapy is required in these pregnant women and is key to optimizing the prognosis for both mother and child. Care should be individualized in determining the time of labor, appraising the C-section indications, choosing the type of anesthesia, arranging the delivery room to avoid infection and controlling the newborn. Birth and treatment experiences are limited for pregnant women who have had the disease in the last 3 months (4).

Our research aimed to define the clinical, laboratory, epidemiological and radiological features, maternal and neonatal outcomes and treatment of pregnant women confirmed to have severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

Material and Methods

This retrospective, single-center study was conducted at University of Health Sciences Turkey, Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Turkey, between April and May 2020. The study protocol was approved by the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Ethics Committee and registered with ClinicalTrials.gov (NCT04337320) (decision no: 2020-09, date: 30.04.2020).

Our study criteria included pregnant women between 18 and 45 years old with a history of COVID-19-positive polymerase chain reaction (PCR) result. Patients with COVID-19-positive PCR who used systemic drugs as well as women with other endocrine and/or autoimmune disorders, pregnant women who had underlying lung disease were excluded from the study.

The demographic data of participants, including age, gravidity, parity, gestational week at admission were recorded. The samples from each patient were obtained to determine the complete blood count, alanine aminotransferase (ALT), C-reactive protein (CRP), aspartate aminotransferase (AST) levels, lymphocyte account and the concentrations of ferritin and D-dimer of blood. Simultaneously, neonatal umbilical blood gas analyses were also examined. Real-time reverse transcription-PCR test was applied to upper respiratory tract swab samples of all patients. We also requested lung computed tomography (CT) from all patients, except for 4 patients who did not wish to undergo any imaging tests. Six of the forty patients had normal vaginal delivery, others were delivered by the C-section and all newborn infants were admitted to the neonatology department for separation from the mother and for blood and PCR tests.

The primary outcome of our study was to compare maternal and neonatal results in pregnant women with a history of COVID-19-positive PCR result.

Statistical Analysis

Data analysis was performed by the SPSS version 20 for Windows (SPSS Inc., Chicago, IL). Continuous variables were expressed using means with standard deviations and categorical variables were expressed as numbers (%).

Results

Forty pregnant women with COVID-19 were included in the study. The demographic information of the patients is shown in Table 1. Two patients had a history of chronic disease (type 2 diabetes mellitus and hypothyroidism).

Most of the patients presented with cough complaints (50%). The most common symptoms accompanied by cough were fever and shortness of breath. A significant number of patients were asymptomatic (42.5%). While 15 patients needed nasal oxygen support during their hospitalization, 2 of our patients were hospitalized in the intensive care unit (ICU) due to serious respiratory problems. We divided the patients into groups according to the stage of CT findings. We detected 10 patients with mild involvement, 11 patients with moderate involvement and 8 patients with severe involvement. Lung CT findings and the clinical features of the patients are summarized in Table 2.

Laboratory findings of the pregnant on admission, such as complete blood count, coagulation tests, liver function tests, ferritin and CRP, were examined (Table 3).

Thirty-four of the patients had a C-section and six of them had a vaginal delivery. A patient with a previous C-section had severe AST (1560 U/L) and ALT (435 U/L) levels. Oxygen saturation under oxygen support was 94%. She had tachycardia (130 beats per minute) and shortness of breath. When she was 36 weeks of pregnancy, the decision was made by cesarean delivery. Four babies needed a neonatal ICU. Obstetric and neonatal characteristics are demonstrated in Table 4.

Forty-five percent of the patients received only hydroxychloroquine treatment. One patient was followed up without treatment. Low-molecular-weight heparin treatment (LMWH) was started for all patients. Patients with a D-dimer value above 2 mg/L were administered LMWH twice daily. The treatment options are shown in Table 5.

Discussion

The disease spread in our country in April and May. So far, 165.555 cases and 4.585 deaths have been reported in our country (5). This study is a descriptive study reporting the maternal and neonatal results of pregnant women with COVID-19 from a centre with an annual birth rate of more than 10.000.

This article reports the maternal and fetal results of 3rd trimester pregnant women who applied with COVID-19 in a tertiary center working as a pandemic hospital. 85% of patients gave birth by C-section. There was no maternal-fetal mortality or serious morbidity. Cough was the most common symptom, and 42.5% of patients were asymptomatic. As a general treatment approach of the country, the treatment was started by providing hydroxychloroquine within a short time after diagnosis.

Coronaviruses (CoV) are a major family of viruses that cause a diversity of illnesses by the common cold to more serious diseases such as SARS-CoV-2 and the middle east respiratory syndrome. Human beings can also be infected by inhalation of droplets scattered from the respiratory tract of the sick individuals or by contact with the surfaces contaminated with these aeroceles (6). Eighteen of our patients (45%) had a contacts with people who had a history of the disease.

Table 1. Demographic characteristics

Demographic characteristics	Study group (n=40)	Minimum - maximum	95% CI
Age	27.7±6.6	18-45	25.6-29.9
Gravidity	2.5±1.5	1-8	2.0-2.9
Parity	1.2±1.4	0-6	0.7-1.7
Gestational week of admission	37±2.7	29-41	36.1-37.9
Previous C-section (n, %)	9 (22.5%)	-	-
Chronic disease		-	-
Type 2 DM (n, %)	1 (2.5%)		
Hypothyroidism	1 (2.5%)		
Previous contact with COVID-19 patient	18 (45%)		

CI: Confidence interval, DM: Diabetes mellitus, COVID-19: Coronavirus disease-2019

Current evidence suggests that the severity of disease among pregnant women after COVID-19 infection is similar to non-pregnant adult COVID-19 cases, and there is no data showing that infection with COVID-19 during pregnancy has a negative effect on the fetus. Although rare, intrauterine transmission of SARS-CoV-2 has been reported (7). In our study, no vertical transition was detected as no infant had a positive PCR test.

In 2002-2003, there was a high maternal mortality rate in the SARS-CoV-1 outbreak (8). However, there has not been a similar situation in SARS-CoV-2 yet. However, more studies are needed on this subject. Looking at the current studies, it seems difficult to make clear comments (9,10). In Turkey, as of June 2, the overall mortality rate of the disease is 2.76%, and there are no published articles showing maternal mortality rates in pregnant women with COVID-19 (5). Similarly, no maternal and fetal deaths have been observed in our hospital too.

In terms of clinical findings in patients, the common symptoms at baseline were cough, fever, and difficulty breathing, and the rate of asymptomatic patients was 22 (11,12). Similar to current studies, laboratory tests were observed as low lymphocyte count, increased CRP and D-dimer (13).

The relatively high mortality of COVID-19 is making people feel anxious. Most of the women had C-section in our study, similar to the literature (14). The most common C-section indication was maternal request. This was followed by difficulty breathing and anxiety.

Table 2. Clinical features of the patients

Clinical features of the patients	Study group (n=40)	Minimum - maximum	95% CI
Symptom (n, %)		-	-
Asymptomatic	17 (42.5%)		
Fever	10 (25%)		
Cough	20 (50%)		
Shortness of breath	10 (25%)		
Fatigue	2 (5%)		
Anosmia	2 (5%)		
Body temperature (°C)	36.5±0.7	35.5-39	36.3-36.7
Heart rate (bpm)	94.7±15.1	69-136	89.8-99.5
Oxygen saturation	96.2±2.8	88-100	95.3-97.1
Systolic blood pressure (mmHg)	114.9±12.8	90-142	110.8-119
Diastolic blood pressure (mmHg)	70.7±9.9	50-89	67.5-74
Need for oxygen teraphy	19 (47.5%)		
Need for ICU (n, %)	2 (5%)		
Lung CT findings			
Refused investigation	4 (10%)		
No involvement	7 (17.5%)		
Mild involvement	10 (25%)		
Moderate involvement	11 (27.5%)		
Severe involvement	8 (20%)		

CI: Confidence interval, CT: Computed tomography, ICU: Intensive care unit

Table 3. Laboratory findings at admission

Laboratory findings on admission	Mean ± SD (n=40)	Minimum - maximum	95% CI
Hemoglobin (gr/dL)	11.4±1.4	8.4-15.3	11-12
Hematocrit (%)	34.3±3.5	25.7-45.2	33.2-35.4
Platelet count (10^3/µL)	222±70	102-468	200-245
D-dimer (mg/L)	3.1±2.7	1-14.9	2-3.9
Ferritin (ng/mL)	50.8±57	9.4-355	32-69.4
AST (U/L)	67.2±242	12-1560	-10.3-145
ALT (U/L)	32.3±69	5-435	10.2-54.4
CRP mg/L	31.4±52	0.7±292.6	14.6-48.3
Lymphocyte count (10^3/µL)	1.8±1.5	0.5±8.5	1.3-2.3

CI: Confidence interval, SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein

Table 4. Obstetric and neonatal characteristics

Obstetric and neonatal characteristics	Study group (n=40)	Minimum - maximum	95% CI
Delivery route (n, %)		-	-
C-section	34 (85%)		
Vaginal	6 (15%)		
C-section indications (n, %)			
Multiple pregnancy	2 (5.8%)		
Previous C-section	9 (26.4%)		
Maternal hypoxia	3 (8.8%)		
Maternal request	15 (44.1%)		
Malpresentation	2 (5.8%)		
Fetal distress	3 (7.5%)	-	-
Premature birth (n, %)	15 (37.5%)		
Birth weight (gram)	2955±656	1255-4000	2745-3165
5th minute APGAR score	8.8±0.6	6-9	8.6-9
Umbilical cord pH	7.38	7.2-7.4	7.37-7.39
Need for NICU	4 (10%)	-	-
Positive neonatal PCR test	0		

CI: Confidence interval, NICU: Neonatal intensive care unit, PCR: Polymerase chain reaction

Table 5. Treatment options

Treatment options	Study group (n=40)	Minimum - maximum
None- observation (n, %)	1 (2.5%)	-
LMWH	40 (100%)	
Hydroxychloroquine (n, %)	18 (45%)	
Hydroxychloroquine + azithromycin (n, %)	7 (17.5%)	
Hydroxychloroquine + azithromycin + oseltamivir (n, %)	7 (17.5%)	
Hydroxychloroquine + lopinavir/ritonavir (n, %)	4 (10%)	
Hydroxychloroquine + azithromycin + lopinavir/ritonavir (n, %)	3 (7.5%)	2-12
Duration of hospitalization (days)	5.4±2.5	

LMWH: Low-molecular-weight heparin treatment

Lung CT findings are important for the diagnosis of pneumonia in pregnant women with COVID-19. In patients who had mild involvement in CT, multiple patchy frosted glass areas are peripherally located rather than parenchyma, and lesions increased as the disease progresses. According to the study by Li et al. (15), extensive pulmonary consolidations are observed in cases of severe involvement, "white lungs" may appear on the radiogram, but pleural effusion is rare.

For treatment, hydroxychloroquine is usually used along with a second-generation macrolide. There is not enough data to know if it plays a role in treatment, but it is widely used. It can also cause QT prolongation and ventricular arrhythmias, which may pose a certain risk of critical patients (1,16). Among the 40 patients we examined, no cardiac side effects related to drug use were observed. Additionally, heparin has been suggested to be added to treatment by some specialized consensus due to the risk of disseminated intravascular coagulation and venous thromboembolism. Heparin treatment has been related to good prognosis, mostly in severe COVID-19 cases with high D-dimer concentrations (17). Lopinavir, another treatment option, is a protease inhibitor used to treat HIV along with ritonavir. In one of a randomized study with 199 patients by Cao et al. (18), 99 of these patients were evaluated in the group receiving lopinavir-ritonavir and 100 in the standard care group. According to this study, it was observed that there was no additional benefit of lopinavir-ritonavir treatment beyond standard care in adult patients diagnosed with heavy COVID-19. Oseltamivir is an approved neuraminidase inhibitor for treating influenza. Since the epidemic in China occurred during the peak season of influenza, oseltamivir was added to the treatment of patients. In fact, this agent plays no role for treating COVID-19 after influenza (19). We applied LMWH and hydroxychloroquine to pregnant women as standard treatment. We observed one of our patients without treatment because she was asymptomatic and laboratory values were normal. Initially,

we added oseltamivir to the treatment of 7 patients because of the seasonal period. We used lopinavir/ritonavir treatment in patients who needed oxygen therapy and had severe involvement findings on lung CT. We have created our treatment algorithm according to the "COVID-19 guide", which is updated regularly by our health ministry since the disease first appeared in our country. Changes in treatment arise from this (20).

Study Limitations

The most important advantage of this study is that it is single-centered and covers 40 patients. Similarly, the number of patients was generally kept lower in other articles planned. Nevertheless, this study has some limitations. All patients included were in the third trimester, it is still unknown how the fetuses of pregnant women whom infected with COVID-19 in the first and second trimesters will be affected. More studies are needed to the maternal and neonatal long-term results of the pandemic.

Conclusion

According to our experience, the clinical features of pregnant women with COVID-19 in the third trimester are similar compared to non-pregnant adults. According to our study, no vertical transition was observed. Maternal and fetal results seem favorable to non-COVID-19 pregnant women. Long-term results and comparative studies are required.

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Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Ethics Committee and registered with ClinicalTrials.gov (NCT04337320) (decision no: 2020-09, date: 30.04.2020).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.P., M.Ç., Concept: M.A.T., Design: M.A.T., Data Collection or Processing: P.Y.B., A.B., O.K., Analysis or Interpretation: A.A., Literature Search: M.A.T., O.K., S.Y.S., Writing: İ.P., M.A.T.

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Are We Missing West Nile Virus in Turkish Blood Donors?

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What is known on this subject?

While donor selection is made in blood donors (BD) in Turkey, West Nile virus screening tests are not performed. In some countries in the world, this virus screening is mandatory for every donor. Is this screening test necessary for our country?

What this study adds?

Although Istanbul is a city on bird migration routes, the frequency of West Nile virus was found to be negative among BDs.

Therefore, it can be suggested not to perform screening for West Nile viruss in BDs in Turkey.

ABSTRACT

Objective: In countries with the West Nile virus (WNV) presence, blood bank screen donated blood for WNV to reduce contamination risk. Despite surveillance studies in Turkey, which is currently a sporadic region for WNV, it remains unclear whether routine WNV screening is necessary. The aim of this study was to investigate whether WNV screening is necessary in Turkey by analyzing WNV seropositivity in blood donors (BD) in Istanbul, which houses more than one-fifth of the country's population.

Material and Methods: This cross-sectional research was conducted between April 2020 and December 2020 as a joint study by the University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital and University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey. A total of 552 healthy BDs who applied to the blood center of these two hospitals and accepted participation were included in the study.

Results: Among the donors, 522 were male and 30 were female, and the median age of the volunteers was 37 (range 22-61) years. The city of residence was Istanbul 507 (91.8%) volunteers, while 45 (8.2%) lived in other cities. The initial WNV immunoglobulin G (IgG) results of 528 (95.7%) volunteers were negative and 24 (4.3%) were equivocal. Tests with equivocal results were repeated and all repeat tests showed negativity.

Conclusion: We did not detect WNV IgG positivity in any BD participating in our study. Our results demonstrate that WNV screening is unnecessary in Turkey. However, to prevent contamination risks, such studies must be conducted and repeated frequently after the emergence of sporadic diseases that can be transmitted by blood.

Keywords: Blood donors, infections transmitted by transfusion, West Nile virus, West Nile virus immunoglobulin G

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Introduction

West Nile virus (WNV) is an enveloped positive- sense RNA virus from the Flavivirus family. It is classified in the Japanese encephalitis serocomplex of the Flavivirus genus (1). The first isolation of the WNV was in the West Nile Region of Uganda in 1937. After this date, it has caused epidemics in different parts of the world (2). WNV circulation is a zoonotic cycle of transmission between various species of birds and primarily Culex mosquitoes (3), whereas mammals are dead-end hosts and demonstrate the clinical symptoms of WNV infection (4). People are often infected with mosquito bites (5). However, scientific studies have shown that WNV can also be transmitted from person to person through intrauterine exposure, breastfeeding, blood transfusion, organ transplant, and occupational exposure (3,4). Since 80% of WNV infections are asymptomatic, there is a high risk of transmission to blood product recipients without screening for WNV (5).

In the 1960s, the first studies on the existence of arboviral infections began in Turkey (6). In studies conducted between 2007 and 2010, WNV seropositivity in blood donors (BDs) was found to be 9.4% in the Southeast and 0.56% in the Central Anatolia regions of Turkey (7,8). The first cases of acute human WNV infection in Turkey were documented in 2010 in a cluster of 47 individuals who had presented with encephalitis-like symptoms, which was ultimately defined as an epidemic (6). Before these cases, reporting of WNV infections in Turkey was not mandatory, but this event triggered the inclusion of WNV into the list of notifiable diseases and Turkey was defined as a sporadic region for the disease. Concern about the transmission of WNV by blood transfusion is increasing in the United States (US) and Europe. Today, in some countries where WNV cases are endemic, screening for WNV has started in all blood and organ donors to reduce the risk of transmission of this microorganism through blood and blood products and organ transplantation (3,9). Despite surveillance studies for WNV in Turkey, it remains unclear whether routine WNV screening in BDs is required in the country.

This study aimed to investigate whether WNV screening is necessary in BDs in Turkey, which is currently a sporadic region for WNV, by detecting WNV seropositivity frequency among BDs in Istanbul, which houses more than one-fifth of the country's population.

Material and Methods

Study Design

This cross-sectional study was conducted between April 2020 and December 2020 as joint research by University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital and University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey. The study was initiated with the approval of the University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (2020.07.136, no: KAEK/2020.07.136) and was performed out according to the BD selection criteria guidelines of the Ministry of Health. Additionally, informed consent was obtained from each volunteer donor included in the study for infectious disease screening in blood products. Routine safety tests, anti HIV-1 antibody, anti HIV-2 antibody, HIV p24 antigen, anti HCV antibody, HBsAg and syphilis total antibody levels were measured.

Study Population

A total of 552 healthy volunteers who applied to the blood center of the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital or the University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital as BDs were included in the study. The volunteers for the study were selected from the donor group who applied from April 2020 to December 2020, the months during which WNV has been detected most frequently (10).

Serological Screening

The blood samples were centrifuged at 2500 rpm for 15 min and then stored at -70 °C until measurements were performed. All samples were analyzed quantitatively for WNV immunoglobulin G (IgG) using commercial microplate enzyme-linked immunosorbent assay (ELISA) kits (West Nile IgG ELISA, DRG Instruments, Germany, Catalogue number: EIA 4519) according to the manufacturer's instructions as follows. Briefly, all specimens and reagents were brought to room temperature (20-25 °C) and gently mixed. The positive, negative controls were assayed in duplicate and test samples were assayed in duplicate. WNV-derived recombinant antigen (WNRA) and normal cell antigen (NCA) were readily-bound to wells. Serum samples and positive and negative controls were diluted using 1:300 sample dilution buffer. Fifty µL of diluted serum samples and controls were added to the wells. The strips were covered and incubated at 37 °C for one hour (NUVE EN-500, Turkey). After the incubation, the strips were washed 6 times with the wash buffer. An automatic washwell plate washer (Robonik, India) was used for the wash buffer. Then, 50 µL of HRP-conjugated solution was added to each well. A second 1-hour 37 °C incubation was performed and strips were again washed 6 times. Incubation with 150 µL EnWash

(provided in the kit) was performed at room temperature for 5 min. After another washing step, 75 µL TMB substrate was added to each well. Finally, it was incubated for 10 min at dark room temperature. Fifty µL of stop solutionwas then added to each well, and the plates were read immediately at 450 nm (Robonik, India).

Data Analysis and Validity Criteria

The mean optical density of two sample replicates with WNRA was evaluated for each sample and assay control, two sample replicates were calculated with NCA. The WNRA/NCA ratio (immune status ratio, ISR) was then calculated. The same calculation was performed for the positive and negative controls. Any negative control WNRA/NCA ratio greater than 1500 was accepted for repeating the test procedure. Any positive control WNRA/NCA ratio less than 3000 was accepted to indicate that the test procedure must be repeated. We used WNR reverse transcriptase polymerase chain reaction (RT-PCR) for nucleic acid identification as a supplemental test when needed.

Interpretation of the Results

Results were interpreted as follows:

Negative: WNRA/NCA ratio (ISR) ≤2 are seronegative for WNV IgG,

Equivocal: WNRA/NCA ratio (ISR) of 2-3 is equivocal and should be retested,

Positive: WNRA/NCA ratio (ISR) ≥3 are seropositive for WNV IgG and should be confirmed by supplemental testing.

Statistical Analysis

All analyses were performed on SPSS v25 (SPSS Inc., Chicago, IL, USA). Data are given as median (minimum - maximum) for continuous variables and as frequency (percentage) for categorical variables.

Results

Five hundred and twenty-two male and 30 female volunteers with a median age of 37 (range 22-61) years were included in our study. five hundred and seven (91.8%) volunteers were from Istanbul and 45 (8.2%) volunteers were from other cities. Anti HIV-1 antibody, anti HIV-2 antibody, HIV p24 antigen, anti HCV antibody, HBsAg and syphilis total antibody were negative in all volunteers. All specimens met the assay validity criteria. WNV IgG results of 528 (95.7%) volunteers were negative and 24 (4.3%) were equivocal (Table 1). The tests of 24 volunteer serums with equivocal results were repeated and repeat tests were negative for all of these subjects. Thus, all volunteers included in the study were found to be negative for WNV IgG.

Discussion

WNV is one of the most common arboviruses in the world (2). In the last two decades, there have been many changes in the epidemiology of the WN virus and it has caused endemic outbreaks in many countries. WNV is a Flavivirus that has since emerged as a public health issue (4,8). Interest in WNV has been increasing since 2002, when it was determined that it could be transmitted through blood transfusion and organ transplantation. Efforts to reduce the risk of virus transmission are important in blood recipients, particularly patients who receive multiple transfusions and those who are immunocompromised (11). Our knowledge of its recent epidemiology in Turkey is not Japanese. Tests previously used to distinguish WNV from other Flavivirus strains in Turkey had lower specificity. WNV seroprevalence rates were also based on these experiments (7,12,13). Although blood centers in many countries around the world have made WNV screening a routine the necessity of screening is still unclear for Turkey. To provide data on this topic, we evaluated the presence of WNV IgG antibodies, which is one of the most frequently used

Table 1. Summary of volunteers' characteristics and laboratory measurements

Age	37 (22-61)
Gender	
Male	522 (94.6%)
Female	30 (5.4%)
City	
Istanbul	507 (91.8%)
Other	45 (8.2%)
Anti HIV-1 positivity	0 (0.0%)
Anti HIV-2 positivity	0 (0.0%)
HIV p24 positivity	0 (0.0%)
Anti HCV positivity	0 (0.0%)
HBsAg positivity	0 (0.0%)
Syphilis positivity	0 (0.0%)
WNRA	0.083 (0.062-0.234)
NCA	0.070 (0.051-0.093)
ISR	1.246 (0.710-2.786)
Negative (≤2)	528 (95.7%)
Equivocal (2-3)	24 (4.3%)
Positive (≥3)	0 (0.0%)

Data are given as median (minimum - maximum) for continuous variables and as frequency (percentage) for categorical variables

serological methods for screening WNV, in serum samples taken from BDs who applied to the blood bank of two hospitals in Istanbul. We did not detect WNV IgG positivity in any of BDs that we included in our study.

Over the past two decades, the geographic distribution of WNV has significantly expanded, and considerable changes in its epidemiology, virulence, and host species have been observed. This classically self-limiting disease with mild symptoms is showing a change toward being an agent causing major epidemics with morbidity and mortality in thousands of human and animal cases. Therefore, surveillance for this infection is important to ensure a safe blood supply in the future (5). Several studies have been conducted in many countries to estimate WNV seropositivity in the donated blood pool. Some studies conducted around the world reported the incidence of WNV in BDs as 5% in Iran, 3.7% in Italy and 4.4% in Northern Cyprus. However, 8.2% of positives in Iran and 18.1% of positives in Italy were confirmed by immunofluorescence testing (IFA) and plaque reduction neutralization testing (PRNT). Additionally, 78.8% of positives in northern Cyprus were confirmed by PRNT (1,14,15). In studies using serum samples from different blood donation centers in Turkey, the rate of WNV IgG seroprevalence was reported as 1.0%-2.5%. In one study from Turkey, 2821 serum samples from BDs were tested. WNV IgG was positive in 0.9% of them, and 41 of them were found to be indeterminate (16). In a similar study by Sahiner et al. (17) in Ankara, the capital of Turkey. The presence of WNV RNA in serum samples from 729 healthy BBs was investigated by RT-PCR. 702 BDs (96.3%) were located in Ankara. Five hundred ninety six (78%) of the donors had a high probability of contact for arboviral infections (e.g., outdoor activity, mosquito, and tick bites). WNV RNA was not detected in any serum samples (17). Similarly, in another study conducted at Hacettepe University Hospital in Ankara, 1200 BD serum samples were analyzed between April and December 2009. As a result, the positivity rate of WNV and IgG, which was detected by ELISA in BDs had been found to be 1.6%, and half (0.8% of total) had been confirmed via the gold standard method, PRNT (18). Biçeroğlu et al. (19), in their 2015 study, investigated WNV RNA by qRT-PCR and anti-WNV IgG by ELISA in the sera of 438 BDs from the western provinces of Turkey. The WNV RNA test was evaluated as negative in all blood samples. Eleven (2.51%) samples were positive for anti-WNV IgG (19). In another study conducted in 2516 BDs in Central Anatolia, it was found to be positive in 0.5% and was also confirmed by PRNT (8). The first case of WNV originating from Istanbul was diagnosed in 2017 at the Istanbul Faculty of Medicine, and the patient had meningoencephalitis associated with WNV (20). In our study, a significant majority of the donors were from Istanbul. We found WNV IgG was negative in all of these 552 randomly selected participants. The low percentages found in a significant majority of other studies on BD in Turkey and in our study suggest that, currently, routine WNV screening is not required for blood donation in Turkey.

WNV was first identified in humans in the USA in 1999 (21). However, in 2002, the number of WNV increased in humans. Later, WNV was identified in the USA, which was transmitted through transfusions of red cells, platelets, or fresh frozen plasma. This has led to 23 confirmed WNVs being recognized as a viruses that can be transmitted by blood and blood products (3,22). As such, under pressure from the Food and Drug Administration, WNV NAT tests for blood screening were developed by diagnostic kit manufacturers in the summer of 2003 (3). In the European Union (EU) there was a major outbreak of 352 neuroinvasive diseases associated with WNV in 1996, with 17 deaths from the disease in Romania (23). In the European Region; WNV infections, which resulted in death, continued to be seen with the same characteristics, despite precautions being taken. In 2010, there were 262 cases in Greece, of which 197 were neuroinvasive. All 33 resulted in death. All cases were confirmed for WNV (24). Some measures used to prevent contamination of blood products were to delay or restrict blood donation from individuals returning from other countries with human transmission (25). Some EU transfusion centers have decided to perform WNV NAT testing instead of delays or restrictions (3,26). World Health Organization; Apart from European countries, it has been reported that WNV outbreaks have been detected in many Eastern Mediterranean countries such as Turkey, Greece, Palestine, Israel and Egypt (1,3). In a study conducted in Turkey in July-November 2010, a study was conducted on individuals presenting with at least one of the clinical signs or symptoms such as meningitis, encephalitis, meningoencephalitis, myelitis of unknown cause. IgG and IgM antibody tests were performed to identify WNV in patient serum samples. As a result, 47 cases of WNV were identified, of which 12 were confirmed by PRNT and reported as definite and 35 as probable. Fourty were CNS symptoms and 7 were non-neuroinvasive infection cases. The overall incidence of WNV infections was reported as 0.19 cases per 100.000 population (6). This case cluster was defined as an epidemic and WNV became one of the notifiable diseases in Turkey (20). Studies conducted in Turkey show that WNV infection is seen sporadically, and mostly the infection is asymptomatic. Simultaneously, it shows that WNV infection in Turkey mostly circulates in various regions, including central, western, southern and southeastern Anatolia (27).

Studies have shown that WNV infection has an incubation period of 3-14 days. Patients infected with this virus may present with simple nausea, vomiting, headache and fever, and this constitutes only 20% of infected individuals. Additionally, 80% of WNV infections may develop asymptomatically (3). Finally, in 1% of patients, especially the elderly and those with suppressed immune systems, it causes neurological disease with a fatality rate of approximately 10% and high morbidity (2,28). Neurological disease may manifest with severe symptoms such as viral encephalitis, meningitis, seizures and long-term sequelae such as altered mental status, lethargy, cranial nerve palsy, acute flaccid paralysis, and movement disorders (3,29). The early stages of WNV infection have been described in detail. During this period, it can be transmitted through infected donors through blood and blood products. It is therefore important to develop algorithms to screen and confirm infected donors, to decide when it is safe for such donors to continue donating blood and to assess the risk of transfusion (30). Serological tests (IgM, IgG and IgG avidity by ELISA method) are most commonly used when identifying WNV infections in humans. However, this infection can also be detected using methods such as IFA, PRNT, rRT-PCR, immunohistochemistry, and virus isolation from cultured cells (1). Because of short duration of viremia (1-11 days), low level of circulating virus (usually <100 pfu/mL), and late appearance of clinical symptoms, the main method for diagnosing active WNV infection is the detection of specific IgM antibodies in serum or cerebrospinal fluid by serological tests (3,31). IgM antibodies appear shortly after the onset of symptoms. It can be caught if tested by ELISA or hemagglutination inhibition methods during this period. However, IgM-positive samples should be confirmed with PRNT, which is considered the gold standard diagnostic method for Flavivirus serology (32). The PRNT test has also been adopted by the EU WNV infection case definition (33). However, seropositivity should be interpreted with caution due to frequent cross-reactivity with other Flavivirus species (3). IgM cannot be detected in serum for a long time. therefore, it is difficult to detect in serum. Rarely, it can remain positive in the blood for up to 500 days after infection. In these situations, IgG antibody measurements can be used to detect false positives due to persistent IgM antibodies. Otherwise, it may lead to an erroneous BNW diagnosis (3,34). IgG avidity determination has been proposed to distinguish active WNV infection from persistent seropositivity at previous exposures. The serum of individuals who have been exposed to WNV for 6 months or longer demonstrates a high avidity for IgG antibodies (34,35). For these reasons, in our study, as in many similar studies (8,16,18), we used the WNV IgG test to evaluate BDs in terms of WNV infectivity.

Study Limitations

There were some limitations to our study. First, the small number of volunteers and the inclusion of BDs who applied to the blood centers of only 2 hospitals in Istanbul may have limited the generalizability of the results for the whole of Turkey. Secondly, the fact that only WNV IgG was used as a screening test in the study may have caused false negative results in carrier donors who were in active infection period and had asymptomatic disease. Although it seems like a limitation that PRNT, ELISA IgG avidity, RT-PCR tests and IFA were not performed in our study, these tests were not considered necessary since there were no WNV IgG-positive volunteers. Studies with a larger number of volunteers from more centers with more test diversity are necessary for precise assumptions about the subject.

Conclusion

In conclusion, we did not detect WNV IgG positivity in any of the BDs participating in our study. Since WNV is not endemic to Turkey, it is not seen as a risk of blood donation. Our data show that it is not necessary to include WNV in routine tests before blood donation. However, to prevent contamination risks, such studies must be conducted and repeated frequently after the emergence of sporadic diseases that can be transmitted by blood.

Ethics

Ethics Committee Approval: The study was initiated with the approval of the University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (2020.07.136, no: KAEK/2020.07.136).

Informed Consent: Informed consent was obtained from each volunteer donor included in the study for infectious disease screening in blood products.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Z.Ş., N.G., N.C., Concept: K.Z.Ş., N.C., Design: K.Z.Ş., N.G., Data Collection or Processing: K.Z.Ş., N.G., N.C., Analysis or Interpretation: K.Z.Ş., N.G., Literature Search: K.Z.Ş., N.G., Writing: K.Z.Ş.

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ORIGINAL ARTICLE

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Comparison of Umbilical Cord and Postnatal Fourth Month Serum 25-OH Vitamin D Levels of Late Preterm and Term Infants

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What is known on this subject?

Vitamin D is one of the fat-soluble vitamin that is steroidal in structure, that can affect the organism throughout life. The effect of vitamin D is not only to maintain bone metabolism by regulating calcium balance but also additional benefits have reported such as to prevent inflammation and regulating the immune system.

What this study adds?

Although the cord blood vitamin D levels of late preterm infants are reported to be similar in late preterm and term infants, vitamin D deficiency was notably high in both groups.

It was observed that with oral 400 IU vitamin D3 replacement, vitamin D levels increased significantly and returned to normal levels at postnatal 4th month.

ABSTRACT

Objective: Our aim was to compare vitamin D levels of late preterm and term babies measured at birth and at postnatal 4th month.

Material and Methods: One hundred four late preterm infants (group I) and 118 term infants (group II) were enrolled in the study. Maternal age, parity, morbidities related to pregnancy, educational status, sun exposure, dressing style and use of multivitamin supplements were recorded. Gestational age, birth weight, height, head circumference, sex of infants were also recorded. Umbilical cord blood was collected from all participants and cord blood 25-OH vitamin D levels were measured. Oral vitamin D 3 supplementation (400 IU) was started on postnatal 15th day for all babies. Vitamin D measurements were repeated at the postnatal fourth month. Serum 25-OH vitamin D concentrations were measured by chemiluminescence assay. The results were evaluated statistically.

Results: Mean umbilical cord 25-OH vitamin D levels of groups I and II were 7.6±6.6 ng/mL and 7.5±6.5 ng/mL, respectively (p=0.835). Eighty-four percent of infants in group I and 78% of infants in group II had severe vitamin D deficiency (<10 ng/mL). Cord blood vitamin D levels in both groups did not differ in terms of sun exposure (p=0.595). A statistically significant increase in 25-OH vitamin D levels was seen after vitamin D supplementation in both groups (p<0.05). Also, 25-OH vitamin D levels at postnatal 4th month of life between the two groups did not differ (group I 34.4±8.7 ng/mL vs. group II 38.9±12.7 ng/mL; p=0.306).

Conclusion: Although the umbilical cord 25-OH vitamin D blood levels of late preterm infants were similar to term infants', a high incidence of vitamin D deficiency in the umbilical cord blood was observed in both groups. Late prematurity did not pose an additional risk factor for vitamin D deficiency. After four months of oral replacement therapy, repeated serum vitamin D-level measurement confirmed significantly increased vitamin levels, almost reaching normal values.

Keywords: Vitamin D, late preterm, newborn, neonatology

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Introduction

Vitamin D is one of the fat-soluble vitamin that is, which is steroidal in structure and can affect the organism. The effect of vitamin D is not only to maintain bone metabolism by regulating calcium balance, but also additional benefits have reported such as to prevent inflammation and regulating the immune system (1,2).

Maternal vitamin D deficiency has been shown to be an important health problem in developing countries recently. It has been reported that there is an inverse relationship between maternal vitamin D deficiency and fetal growth, ossification, enamel hypoplasia, and neonatal Ca balance.

It was shown that there is a direct correlation between cord blood levels and the mother's serum concentrations of 25-OH vitamin D in the first eight weeks of life, whereas sunlight or oral vitamin D3 supplementation is more effective on vitamin D serum levels after that (3).

The daily requirement of vitamin D for term infants has been determined as 400 IU. The amount of vitamin D amount in breast milk can only meet a very small part of this requirement (12-60 IU/liter) (1-3).

Neonates born between 34th and 36th gestational age are called late preterm. Although not as much as very low birth weight (VLBW) babies, late preterm babies experience sepsis, jaundice, hypoglycemia, respiratory, and feeding difficulties more often and their mortality rates are higher compared to term babies. One can predict that if the factors affecting mortality and morbidity are better determined, problems that may arise in these babies can be better coped with (4,5). Studies on the daily vitamin D requirement and maternal levels of vitamin D of late preterm infants who are chronologically between VLBW and term infants are limited.

In this study, our aim is to compare the umbilical cord serum and 4th month vitamin D levels of late preterm and term infants who were born in our clinic. Moreover, it is one of our goals to reveal whether daily vitamin D supplementation is sufficient and how much vitamin D is needed in late preterm babies compared to term babies.

Material and Methods

Between January 2013 and April 2013 infants who born in our hospital and followed up in the neonatology clinic after birth were enrolled in this study. Babies were divided into two groups as "late preterm babies born at 34 0/7-36 6/7 weeks" and "term babies those born at 37 0/7 and above". Group I was defined as late preterm babies and group II as term babies. A total of 222 cases, including 104 late preterm cases and 118 term cases, constituted the study group. Babies born before 34 weeks, with known chronic diseases and without parental consent were excluded from the study.

The study was planned in accordance with the Declaration of Helsinki after obtaining permission from the University of Health Sciences Turkey, Zeynep Kamil Maternity and Children's Training and Research Hospital, Ethical Committee (decision no: 034, date: 15.02.2013). Parents of the babies were informed about the study and their consent were obtained. For data collection, information about the mother (age, previous of pregnancies, education level, breast milk usage, and breastfeeding information in the first four months, vitamin usage during pregnancy, sun exposure, preeclampsia), and the baby (gestational week, delivery type, body weight, laboratory, and clinical characteristics) was gathered.

In both groups, blood was drawn from the umbilical cord for vitamin D levels. In both groups, 400 IU vitamin D3 supplement was initiated enterally after the postnatal 15th day. Blood samples were drawn again for blood 25-OH vitamin D levels who came for control at the age of four months.

Gathering and Collecting Blood Samples

1 mL blood sample was taken from the umbilical cord and then later from the antecubital vein of the babies who were in the study, into biochemistry tubes with gel. The samples were centrifuged at 5000 rpm for 5 min at +4 °C. The serums were separated and stored at -30 °C until the day of the study.

Analyzing Blood 25-OH Vitamin D Levels

Samples were analysed consecutively, on the Liaison device using the DiaSorin kit (Diasorin Inc. Northwestern Ave-Stillwater, USA) by the chemiluminescent immunoassay method at the biochemistry laboratory of the hospital.

If, 25-OH vitamin D levels >32 ng/mL defined as normal, between 20 and 32 ng/mL defined as insufficiency, <20 ng/mL defined as deficiency (<10 ng/mL severe deficiency, 10-20 ng/mL moderate deficiency) (5).

Statistical Analysis

The statistical analyses were obtained using the SPSS version 11.5 (Statistical Package for the Social Sciences for Windows) program. Student's t-test or Mann-Whitney U tests were used to compare means between groups, chi-square and Fisher's exact tests were used to compare ratios, and Wilcoxon test was used to evaluate dependent-repeated measurements. Additionally, Pearson correlation analysis was used in the evaluation of two quantitative data. If p value is less than 0.05, it is considered as statistically significant.

Results

The socio-demographic characteristics of the mothers according to the groups are shown in Table 1.

Of the cases in group I, 45 (43%) were female, 59 (57%) were male, and of the cases in group II, 67 (57%) were female and 51 (43%) were male. Gestational weight of the patients were; in group I, small for gestational age (SGA) (n=18), appropriate for gestational age (AGA) (n=80), large for gestational age (LGA) (n=6) and in group II; SGA (n=11), AGA (n=93), LGA (n=14). 74% of group I cases and 69% of group II cases were delivered by cesarean section. There was no difference between the groups regarding the weight of the patients at birth and gender (p>0.05).

The median weight of group I cases was 2390 grams (range 1520-3850 grams), and median height was 45 cm (range 37-50 cm); in group II cases, the median weight was 3410 grams (range 1990-4520 grams), and the median height was 50 cm (range 43-54 cm). There was a significant difference between both groups (p<0.01).

Table 1. Socio-demographic status of patients' mothers

Parameter	Group I n-%	Group II n-%	p
Maternal age (mean ± SD years)	28.5±5.5	28.8±5.7	0.840
Gestational diabetes (yes)	6-5.7	8-6.7	0.324
Early membrane rupture (yes)	2-1.9	-	0.285
Preeclampsia (yes)	7-6.6	-	**0.004**
Profession and homemaker	94-90.4	98-83.1	
Other	10-9.6	20-16.9	0.120
Education level**			
Illiterate	2-1.9	5-4.2	
Primary school	77-74	74-64.7	0.292
High school	21-20.2	31-26.3	
University	4-3.8	8-6.8	
Vitamin use in pregnancy			
Yes	73-70.2	78-66.1	
No	31-29.8	40-33.9	0.565
Vitamin use ng/mL in pregnancy			**0.001**
Yes	8.6±7.3	8.8±7.3	
No	5.4±3.7	4.8±3.7	
Gravity			
≤3	80-86.5	103-87.3	
>3	24-13.5	15-12.7	0.613
Parity			
≤2	72-69.2	87-73.8	0.578
>2	32-30.8	31-26.2	

***Chi-square and Fisher's exact tests, SD: Standard deviation*

While umbilical cord serum 25-OH vitamin D levels of babies whose mothers had used a vitamin supplement during pregnancy in group 1 and group 2 were 8.6±7.3 ng/mL and 8.8±7.3 ng/mL, these measurements were found to be 5.4±3.7 ng/mL and 4.8±3.7 ng/mL for the babies whose mothers had not used a vitamin supplement during pregnancy in group 1 and group 2, respectively. Umbilical cord serum 25-OH vitamin D levels are higher in both groups I and group II in patients whose mothers are under multivitamin supplement (p<0.01).

The umbilical cord blood vitamin D level was <20 ng/mL in 94.5% (n=69) of group I infants and 92.3% (n=72) of group II infants whose mothers were using vitamins; it was <20 ng/mL in 100% (n=31) of group I infants and 100% (n=40) of group II infants whose mothers did not use vitamins. Umbilical cord vitamin D level was <10 ng/mL in 83% (n=60) of group I infants and 88% (n=68) of group II infants whose mothers were using vitamins; it was <10/ng/mL in 80% (n=25) of group I infants and 58% (n=23) of group II infants of mothers who did not use vitamins. Although vitamin D usage during pregnancy increased the level of vitamin D, it did not prevent vitamin D deficiency (p=0.753).

Table 2 shows the vitamin D levels and the incidence of vitamin D deficiency and insufficiency according to the groups.

Vitamin D levels were re checked at the age of four months in 70 infants in group I and 76 infants in group II. The mean vitamin D level of group I was 34.4 ±8.7 ng/mL, and the mean vitamin D level of group II was 38.9±12.7 ng/mL at the age of four months. It was found that vitamin D level was <10 ng/mL in 3.9% and <20 ng/mL in 7% of group I infants. Vitamin D levels were found to be <10 ng/mL in 6.9% and <20 ng/mL in 10.5% of group II infants. There was no statistically significant difference between groups by the means of mean vitamin D level (p>0.05) (Table 2).

With the administration of vitamin D in both groups, the vitamin D levels at the 4th month were increased statistically significantly compared to the vitamin D level in the umbilical cord blood (Wilcoxon test, p=0.02 for group I and p=0.01 for group II).

In the group I, 46% of cases were fed with breast milk, 50% with breast milk and formula, and 4% with only formula. In group II, 63.2% of cases were fed only breast milk, 31.6% with breast milk and formula, and 5.3% with only formula. The enteral feeding types of both groups were similar (p=0.455). Vitamin D levels were also similar at the 4th month according to the feeding types (Table 3).

Table 2. Serum vitamin D level in umbilical cord blood and fourth postnatal month

Initial		Group I n=104	Group II n=118	p
Vitamin D level (ng/mL); mean ± SD		7.6±6.6*	7.5±6.5**	0.835
Vitamin D level (ng/mL); median (range)		6.1 (0.1-30)	5.1 (0.1-28)	0.790
Deficiency; n (%)	**<10 ng/mL**	85 (81.7)	91 (77.7)	0.773
	10-20 ng/mL	15 (14.5)	21 (16.5)	0.696
	<20 ng/mL	100 (96.2)	112 (94.2)	0.753
Insufficiency; n (%)	**20-32 ng/mL**	4 (3.8)	6 (5.8)	0.751
The fourth month		**n=70**	**n=76**	
Vitamin D level (ng/mL); mean ± SD		34.4±8.7*	38.9±12.7**	0.890
Vitamin D level (ng/mL); median (range)		40 (7.2-95)	45 (6-95)	0.740
Deficiency; n (%)	**<10 ng/mL**	3 (3.8)	5 (6.9)	0.280
	10-20 ng/mL	2 (3.2)	3 (3.4)	0.990
	<20 ng/mL	5 (7)	8 (10.5)	0.439
Insufficiency; n (%)	**20-32 ng/mL**	4 (5.7)	5 (6.9)	0.812

*Wilcoxon *p=0.02, **p=0.01, SD: Standard deviation*

Table 3. Comparison of serum vitamin levels according to the patient's nutritional status

	Group I	Group II	p
Breastfeeding n, median (range) ng/mL	32-38 (16-80)	48-40 (6-75)	p>0.05
Breastfeeding + formula n, median (range) ng/mL	35-40 (7-90)	24-38 (8-70)	

Tablo 4. Comparison of serum vitamin levels according to the patient's birth weight

	Group I n (%)			Group II n (%)			p
Vitamin D level	**SGA**	**AGA**	**LGA**	**SGA**	**AGA**	**LGA**	
<10 ng/mL	15 (83)	66 (82)	4 (66)	8 (72)	74 (79)	9 (64)	0.714
10-20 ng/mL	2 (11)	11 (14)	2 (34)	3 (28)	15 (16)	3 (22)	0.840
20-32 ng/mL	-	2 (3)	-	-	3 (3)	1 (7)	0.910
>32 ng/mL	1 (6)	1 (1)	-	-	1 (1)	1 (7)	0.860

AGA: Appropriate for gestational age, LGA: Large for gestational age, SGA: Small for gestational age

When infants' mothers sun exposure, in infants with and without severe vitamin D deficiency in infants (<10 ng/mL) were compared; although those with <10 ng/mL had less weekly sun exposure (<10 ng/mL 5.7±4.4 h; >10 ng/mL 6.0±3.5 h), there was no statistically significant difference (p=0.658).

The mothers of 65 (63%) infants in group I and 77 (65.2%) infants in group II were wearing hijab. Severe vitamin D deficiency was determined at the sample of umbilical cord blood of 55 (84%) newborns in group I and 61 (80%) newborns in group II.

However, severe vitamin D deficiency was found in the umbilical cord blood samples of 30 (77%) babies in group I and 30 (73%) babies in group II of mothers who were not wearing hijab. There was no statistically significant difference between the groups in terms of dressing style and severe vitamin D deficiency (p>0.05).

There was no statistically difference between the umbilical cord vitamin D deficiency severity and birth weight in late preterm and term infants (p>0.05) (Table 4).

Discussion

In this study, umbilical cord and fourth month 25-OH vitamin D levels in late preterm and term infants were compared. In both groups, a high rate of vitamin D

insufficiency and deficiency was detected at the cord serum level. It was observed that with the same amount of vitamin D supplementation given to both late preterm and term cases, vitamin D levels were notably normalized in the 4th month. With these features, our study is one of the limited number of studies on this topic in the literature.

Although it varies in different countries, vitamin D deficiency is seen at a rate of 20%-85% during pregnancy in worldwide (6). In studies conducted in Turkey, the prevalence of vitamin D deficiency varies between 67.5%-90% (7,8). However, most rates reported previously included term newborn infants and their mothers.

In our study, vitamin D deficiency was found in 96.2% and severe vitamin D deficiency in 81.7% of late preterm infants. In term infants, vitamin D deficiency was found in 94.2% and severe vitamin D deficiency in 77%. Vitamin D levels were within normal limits in only one infant among both groups. This may be because our hospital generally serves a patient population with low socio-economic status and the study was conducted during winter.

If the vitamin D storage of the mother is sufficient, the baby has sufficient vitamin D levels for about 3 months. Particularly in the third trimester of pregnancy, 25-OH vitamin D is transferred from mother to baby. In a study conducted in India, fifty newborns with low calcium levels were examined and it was observed that 26% (n=13) of them were infants who were only breastfed and did not receive vitamin D supplementation. It was also been observed that the mothers of these babies had low levels of vitamin D (9).

In our study, the frequency of mothers receiving vitamin D supplementation was similar. In both groups, umbilical cord vitamin D levels were significantly higher in babies whose mothers used vitamins. However, the use of vitamin D did not reduce the rate of vitamin D deficiency in either groups. The low vitamin D levels of the mothers despite suppression generally during pregnancy may be related to the small amount of vitamin D in the multivitamin content used in our country (400 IU) and the insufficient intake of vitamin D through food sources. This is because the milk and dairy products in our country are not enriched with vitamin D or it may be related to other factors.

In the northern hemisphere, vitamin D production in the skin begins to decrease starting from autumn in regions north of the Tropic of Cancer (10,11). Studies have found that the vitamin D levels of babies born in summer/autumn periods are higher than those born in winter/spring periods (10,11). Similar to the results in a study by Ustuner et al. (12) in 79 pregnant women in the third trimester who had their pregnancies mostly during the winter months, vitamin D levels were found to be lower. In another study of 171 cases involving prepubertal girls, it was observed that serum 25-OH D levels did not change and could not reach the values measured in the summer months when vitamin D supplementation was given between October and February (13). In a study conducted in Finland, 2 groups were selected, pregnant and non-pregnant women, and serum 25-OH D levels of pregnant women who had their pregnancies mostly during winter months were found to be lower than those of non-pregnant women. In the summer, no difference was observed between the groups. Based on this result, it has been suggested that mothers should be given vitamin D supplementation in winter (14).

The seasonal effect could not be evaluated because most of the case group were babies born in the winter-spring period, in our study. However, the fact that the vitamin D level was <20 ng/mL in most cases in both groups may indirectly indicate that the vitamin D level is seasonally low in winter.

Conditions such as increasing urbanization, dark skin color, covered clothing, not using the vitamin support given during pregnancy, low socio-economic level, and die poor in vitamin D and calcium may cause changes in maternal vitamin D level.

In a study conducted with breastfeeding mothers and their babies in Asia, the effect of socio-economic level on blood vitamin D levels was investigated. The serum 25-OH D level was found to be significantly lower in mothers with high economic income and their babies compared to mothers with low income and their babies. This has been attributed to the fact that those with high incomes do not go out to the sun as much (15). In a study conducted in our country, it was found that 57% of mothers of infants with rickets were illiterate (16). Contrary to this information, in another study, no correlation was found between serum 25-OH D3 levels in infants and the socio-economic status of the mother (17). In our study, the rate of illiterate mothers was 1.9% in group I and 4.2% in group II. There was no correlation between the education level of the mothers and the serum 25-OH D level of the babies.

Serum 25-OH D3 levels were found to be low in 70% of the mothers wearing covered clothing and their babies in a study conducted in Saudi Arabia (17).

In our study, no significant relationship was found between the level of education and vitamin D level. The mothers of the babies in the groups were similarly dressed in covered clothing. No significant difference was found between clothing style and umbilical cord blood vitamin D levels compared with other studies. This may be due to the

low level of vitamin D in most of the cases and the fact that they were born in the winter months.

The main source of vitamin D in humans is sunlight. Any factor that prevents the sun's rays from reaching the skin reduces the synthesis of vitamin D (1,2,18). Holick (19), in their study, found that the most important factors affecting the synthesis of vitamin D in the skin were the size of the skin area exposed to sunlight and the time interval during the day. In our study, no correlation was found between the duration of sunlight exposure and vitamin D level. Weekly sun exposure times were similar in both groups.

In a study, they could not find any correlation between serum 25-OH D levels, height and weight values of infants (20). Giapros et al. (21) examined 128 late preterm in 102 AGA and 26 SGA types, and reported similarly low vitamin D levels in SGA and AGA infants in the early period (SGA 20±7 ng/mL; AGA 21±11 ng/mL), and normal vitamin D levels at the 6th month in both groups (45±14, 47±10 ng/mL). In our study, the results were compatible with the literature.

The optimal level of vitamin D is debatable (22,23,24,25,26,27,28). It has been suggested that the target level of vitamin d should be the level that suppresses PTH, which is published as 40 ng/mL (7). The serum 25-OH D concentration required to prevent osteomalacia is more than 15 ng/mL, while the serum 25-OH D concentration required to improve neuromuscular performance is 38 ng/mL (22). The concentration of serum 25-OH D found to reduce the risk of colon cancer by 50% is 33 ng/mL, and the level of 25-OHD decreasing the risk of breast cancer by 50% is 52 ng/mL (23,24).

In a study, they reported that daily use of 3000 IU vitamin D, which is recommended for pregnant women, brought the serum 25-OH D level to >35 ng/mL in 97% of the cases (25). In infants who are not exposed to sun light, 1000-2000 IU vitamin D support should be given daily by planning according to their body mass. Halicioglu et al. (8) were stated that daily vitamin D needs should be reviewed, especially in infants whose mothers have vitamin D deficiency. However, it was stated that the risk of intoxication might be increased by giving high doses (1,2).

In our study, after 400 IU/day vitamin D was given to all subjects, the repeated blood samples showed that vitamin D level at the 4th month was found to be >20 ng/mL in 93.1% of group I and 89.5% in group II. Vitamin D treatment increased the level of 25-OH vitamin D statistically significantly.

Study Limitations

The main limitations of this study is that it was conducted in a single center with a limited number of cases. Other shortcomings are that the infants-constituting the study group were born in the winter and the cord blood was collected in the initial period and then the cases were checked in the fourth month.

Conclusion

As a result, although the cord blood vitamin D levels of late preterm infants were similar to term infants, a high level of vitamin D deficiency was found in the cord blood of both groups. Repeated vitamin D-level control in the fourth month showed that vitamin D levels increased, increased significantly and returned to normal levels with oral 400 IU vitamin D3 replacement. Infants with vitamin D deficiency should be administered vitamin D prophylaxis immediately after birth as soon as feeding is tolerated.

Ethics

Ethics Committee Approval: The study was planned in accordance with the Declaration of Helsinki after obtaining permission from the University of Health Sciences Turkey, Zeynep Kamil Maternity and Children's Training and Research Hospital, Ethical Committee (decision no: 034, date: 15.02.2013).

Informed Consent: Parents of the babies were informed about the study and their consent were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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The Risk Factors for SARS-CoV-2 Transmission in Healthcare Workers of Secondary Level Intensive Care Units

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What is known on this subject?

The infection risk in the departments with a high of aerosol release and the risk factors affecting the infection were not determined, even though a few studies were performed to evaluate this job security problem.

What this study adds?

We evaluate the risk factors for the severity of the infection in the healthcare workers of the intensive care unit in which there are many viral aerosol-generating procedures.

ABSTRACT

Objective: Health workers are at the front line of the coronavirus disease-2019 (COVID-19) outbreak response during the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemics, the healthcare workers have been the most affected people by the infection overall the world. Eleven times higher risk for the severe infection in the healthcare workers in the current studies, especially in departments with a higher among of viral aerosols. This information would be useful to formulate job security policies and minimize occupational transmission. We evaluate the risk factors for the SARS-CoV-2 transmission in the healthcare workers of secondary level intensive care units (ICU) in which there are many viral aerosols because of the use of a non-invasive mechanic ventilator and high flow nasal oxygen treatment.

Material and Methods: Fourty healthcare workers of secondary level ICU with a capacity of 16 patients were included in our study between November and December 2020. The risk factors and incidence of COVID-19 infection were evaluated by making a questionnaire.

Results: 25% of the healthcare workers (n=10) were infected by SARS-CoV-2. The infected ones were remarkable with younger age, less experienced, and long duty hours ($p<0.05$). There were no significant differences between the gender, daily duty hour, smoking, marital status, body weight, history of cardiopulmonary resuscitation, duration of rest after the duty of the two groups ($p>0.05$).

Conclusion: As a result, younger age, less experience and longer duty hours were the risk factors for COVID-19 infection. Our study can be useful to ensure that all necessary preventive and protective measures are taken to reduce occupational risks of SARS-CoV-2 transmission to healthcare workers.

Keywords: Healthcare, worker, COVID-19, risk, factor

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Introduction

During the syndrome coronavirus-2 (SARS-CoV-2) pandemics the healthcare workers have been the most affected people by the infection overall the world. Eleven times higher risk for severe infection in the healthcare workers than in society was reported in the current studies (1). The World Health Organisation (WHO) classified the department of the healthcare workers with a history of cardiopulmonary resuscitation (CPR) and those who perform the treatment of the patients releasing aerosols because of the use of a non-invasive mechanic ventilator (NIMV) and high flow nasal oxygen (HFNO) treatments as "very high risk" in the classification of job security (2). In the early phases of the pandemics, several studies have reported a lack of personal protective equipment, low control of the infection, comorbidities, harsh working conditions associated with higher infection risk in the healthcare workers (3). The infection risk in the departments with a high of aerosol release and the risk factors affecting the infection was not determined, even though a few studies have been performed to evaluate this job security problem (4). We evaluate the risk factors for the severity of the infection in the healthcare workers of the intensive care unit (ICU) in which there are many viral aerosol-generating procedures.

Material and methods

Subjects

We conducted a retrospective cohort study with 40 healthcare workers of a secondary level ICU with a capacity of 16 patients between November and December 2020. The risk factors and history of coronavirus disease-2019 (COVID-19) infection were evaluated by making a questionnaire. In the ICU, there was 1 nurse per every 3 patients in all working periods. The nurses were working with a routine of 24 h working and after that 48 h resting. Medical doctors did not have any working routine. The patients were hospitalized in the ICU with a capacity of 16 negative air pressured rooms for each patient. In severe respiratory failure, those patients were supported with a non-invasive mechanical ventilator and high flow oxygen therapy.

According to the guidelines of the Ministry of Health, only symptomatic healthcare workers were tested with COVID-19 polymerase chain reaction (PCR). Symptomatic and PCR negative ones were evaluated by thorax computed tomography (CT). PCR-positive ones were accepted as infected. The healthcare workers with a history of COVID-19 infection before working in the ICU and the ones who refuse to answer the questionnaire were excluded. A questionnaire with 25 questions was sent to them via a web link. The demographic data and history of COVID-19 infection were recorded. Subjects were separated as infected and non-infected.

The study protocol was approved by the Istanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinical Research Ethics Committee (decision no: 2021-97, date: 11.03.2021).

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median (range) and categorical data as percentages as appropriate. Differences between the groups were assessed using a Student's test. Categorical data were compared using the X^2 test: A p value of <0.05 was accepted as significant. Data analysis was performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

The median age was 32.2±8.8 (23-55). 65% of the subjects (n=26) were female. His median working experience was 8.2 years (1-33). Daily duty hours varied between 8 and 24 h. The median duration of rest after the duty was 35.1 hours (0-48). 87% of the subjects had a history of CPR existed. The demographic data of the subjects are shown in Table 1.

Table 1. Demographic data

Total	n=40
Median age (mean ± SD)	32.2±8.8 (23-55)
Female/male	26 (65%)/14 (35%)
Marital status married/single	14 (35%)/26 (65%)
Comorbidities	1 (2.5%)
Smoker	15 (37.5%)
Smoking pack/year	3.4±6.7 (0-30)
Position distribution specialist/ assistant doctor/nurse	21 (52.5%)/4 (10%)/15 (37.5%)
Working experience (years)	8.2±8.5 (1-33)
Daily working duration (hours)	17.4±7.8 (8-24)
Duration of resting after work (hours)	35.1±15.8 (0-48)
COVID-19 infection	10 (25%)
COVID-19 severity mild/middle/ severe	4/6/0
History of cardiopulmonary resuscitation	35 (87.5%)

SD: Standard deviation, COVID-19: Coronavirus disease-2019

25% of the subjects (n=10) were infected. Nine subjects were COVID-19 PCR positive and 1 subject was diagnosed with thorax CT. When 60% of the infected subjects had mild covid-19 infection, 40% of them had moderate COVID-19 infection. There was not severe pneumonia which necessitated hospitalization. The median duration of hospitalization was 14.3±3.5 days (10-20).

The median period between SARS-CoV-2 transmission and beginning to work in the ICU was 22.3±9.5 days (7-30). The household transmission rate was 25%.

The infected healthcare workers had significantly younger age, lower working experience, longer monthly duty hours, and there was not any significant difference between marital status, median body weight, smoking, daily duty hours, history of CPR of the two groups. 46.7% of the nurses (n=7/15), 12%of the doctors (n=3/25) were infected. The infection risk was significantly higher among the nurses (Table 2).

Discussion

When in the early phase of the SARS-CoV-2 pandemics, several studies reported a higher infection risk in the healthcare workers than society (5), the severity and mortality were lower in the healthcare workers. When the infection risk was higher for the nurses, older age and male doctors were remarkable with a higher mortality (5). Another study found the infected healthcare workers to be 84% female and 54% nurses (6). We did not find any significant differences between the genders of the two groups. Half of the nurses were infected and 70% of the infected subjects were nurses.

In our study, the median age of all subjects was 32.2 years and the median age of the infected healthcare workers was 25.7, lower than that in the previous studies. Our comorbidity rate was 2.5% and lower than other studies which were evaluated to be related to lower median age. In our study, there were not any subjects with severe pneumonia necessitating hospitalization. This finding is consistent with the lower severity and mortality in younger patients without comorbidities, as reported in several studies (7).

It is known that non-invasive mechanical ventilators and high-flow nasal oxygen treatment reduce the risk of intubation in severe pneumonia with respiratory failure (8,9,10).

Although HFNO treatment has been performed for non-hypercapnic respiratory failure in ICUs for many years, in the early phase of the SARS-CoV-2 pandemics the treatments, which release viral aerosols -like NIMV and HFNO- were not suggested due to the transmission risk (11). Later the studies showed the efficiency and reliability of those treatments and became the first option in the guidelines for treating severe COVID-19 pneumonia with respiratory failure (12,13). Besides, some studies showed no association between high flow oxygen therapy and increased risk of infection in healthcare workers (14). The factors related to the patients' symptoms like cough and sneeze affect the aerosol release (15). The transmission risk is affected by the of the pathogen, environmental factors like air flow (16).

It has been reported that HFNO and NIMV release aerosols bigger than 10 µm, the relative risk for the transmission to healthcare workers is 2.2 for NIMV and 0.6 for HFNO and it is being reduced by the use of negatively pressured rooms and appropriate protective equipments (4).

Our findings follow those studies and lower infection rates in our study might be related to the existence of negatively

Table 2. Clinical features of the infected and non-infected subjects

	COVID (+)	COVID (-)	p value
Age	25.7±3.3	34.4±9.0	0.005
Gender (female/male)	6/4	20/10	0.70
Marital status married/single	8/2	18/12	0.44
Working experience (years)	2.4±3.4	10.2±8.9	0.01
Daily working duration (hours)	20.8±6.7	16.2±7.9	0.11
Monthly working duration (hours)	228.8±35.2	171.3±62.7	0.009
Duration of resting after work (hours)	40.8±11.5	33.2±16.7	0.19
Position doctor/nurse	3/7 (12%/46.7)	22/8 (88%/53.3)	0.008
History of cardiopulmonary resuscitation (yes/no)	9/1	26/4	0.1
Smoking pack/year	2.0±3.8	3.8±7.4	0.48
Median weight	72.8±20.7	68.7±16.4	0.54

COVID: Coronavirus disease

pressured rooms and careful use of personal protective equipment. Besides, the infection rate of healthcare workers with no specification of departments was 57.4% in a study of the Turkish Thoracic Society which performed by questionnaire (17).

In a study in France, only 1 nurse from 44 healthcare workers of an inpatient clinic with 14 rooms with HFNO was infected. There was a household transmission in the family of the infected healthcare worker (18). In our study in 25% of the infected subjects, there was a household transmission and it seemed to be associated with being single in 65% of the subjects. Daily duty hours longer than 10 h and suboptimal hand hygiene after contact with patients were linked to COVID-19 increases the risk of healthcare workers' infection risk (19). The high infection rate of the nurses is related to longer duty hours and is following those studies.

In our study, the history of CPR was not a risk factor of COVID-19 infection in the healthcare workers. The relative risk was 0.63 for a history of CPR in a previous study (19). Duty hours were longer in the infected subjects. We did not evaluate the use of personal protective equipment and suboptimal hand hygiene in our study but enough existence of the personal protective devices seems to increase the compliance of the healthcare workers with the preventions against the transmission.

Another study in our country found 7.1% of 703 patients to be infected. Working at the departments where COVID-19 patients were treated, working as cleaning staff, being in contact with the COVID-19 patients closer than 1 meter, staying and eating in the same room with the other healthcare workers without any protective equipment, suboptimal hand hygiene after contacting with patients were linked to COVID-19, contact with a COVID-19 case in the family was the risk factors (20). This study emphasized the control of paying attention to the prevention of healthcare workers (20). We implicate the relationship between the high infection rate of the nurse and not paying attention to the protective preventions in the social area. WHO suggests working plan management for healthcare workers, especially in ICU: Duty hours 8 hours/5 days or 10 hours/4 days, taking a break per 1-2 hours, resting for minimum 10 h between shifts (2). Even though the duty hours were longer in the infected group, there was no significant difference between daily duty hours and resting durations after the duty of the two groups.

In the quarantine period (14 days) after the infection, the lack of those healthcare workers causes major labor loss. Reducing the duty hours of nurses was suggested to prevent labor loss and reduce the infection risk (21). Protection of the healthcare workers, reducing mortality and morbidity are important to prevent secondary transmission and labor loss (7).

Study Limitations

Our limitations are that our study is designed single-center, retrospectively with a small sample size. Our sample included only symptomatic healthcare workers, with no control group. Also, we could not separate household transmission or hospital transmission.

Conclusion

As result, our study showed that personal protective equipment and the existence of negatively pressured rooms reduce the infection risk of healthcare workers, especially in the departments where aerosol releasing treatments like NIMV and HFNO have been performed. Taking effective preventions would be important to the effectiveness of use of labor.

However, we think that our study emphasizes the risk factors for infecting the healthcare workers in secondary level ICUs.

Ethics

Ethics Committee Approval: İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinical Research Ethics Committee (decision no: 2021-97, date: 11.03.2021).

Informed Consent: An informed consent form was signed by each subject included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.B., H.S.Ö., Design: A.B., S.Y., C.A., G.Ü., Data Collection or Processing: A.B., H.S.Ö., G.Ü., Analysis or Interpretation: A.B., S.Y., Literature Search: H.S.Ö., G.Ü., Writing: A.B., C.A.

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

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Nikaidoh Procedure for a Beating Heart: A Technical Note

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What is known on this subject?
The Nikaidoh procedure is a complicated surgery that has only been performed for 100 patients to date.

What this techinical reports adds?
Performing the Nikaidoh procedure on a beating heart provides advantages.

ABSTRACT

Aortic root translocation is a surgical choice offering potential advantages for combinations of transposition of the great arteries (TGA), pulmonary stenosis (PS), and ventricular septal defect (VSD). Six patients were included in this analysis. All of them were diagnosed with TGA, PS, and VSD and all of them underwent the Nikaidoh procedure. In 2 of these 6 cases (33.3%), aortic translocation was performed on a beating heart. Performing aortic root translocation on a beating heart is probably useful in reducing the cross-clamp time and the mortality rate, as well as preventing coronary malposition.

Keywords: Aortic translocation, pediatric cardiovascular surgery, beating heart, Nikaidoh procedure

Introduction

The cases of six patients are addressed in this report. Their mean age was 25.5±8.73 months and mean body weight was 11.5±2.42 kg. They were all diagnosed with simultaneous transposition of the great arteries (TGA), pulmonary stenosis (PS), and ventricular septal defect (VSD) and all of them underwent the Nikaidoh procedure. Half of the patients (n=3) had a history of right modified Blalock-Taussig shunt (m-BT shunt) and underwent shunt take-down and right pulmonary artery (PA) reconstruction simultaneously. Aortic translocation was performed on a beating heart in 33.3% of the cases (n=2). The mean cross-clamp time was 124 (range: 82-167) min while mean cardiopulmonary bypass time was 228.16 (range: 220-234) min. Of these patients, 16.6% (n=1) needed support in the form of extracorporeal membrane oxygenation. Aortic insufficiency was not observed in any case during the early or middle period. The early mortality rate was 16.6% (n=1). The body weight of that patient was less than 10 kg and he had the longest cross-clamp time. While 66.7% of patients underwent right ventricular outflow tract (RVOT) reconstruction with a transannular patch, 33.3% (n=1) underwent a conduit replacement procedure performed between the right ventricle (RV) and PA. The mean hospital stay was 10.33±1.86 days, mean duration of intensive care was 3.67±1.86 days, and these values were significantly shorter for patients for whom the Nikaidoh procedure was applied to a beating heart. Neurological complications were not observed in any cases.

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The mean duration of follow-up was 58.4±24.75 months. The rate of reoperation among patients who survived was 20%. The patient who underwent RV-PA conduit replacement needed surgery again 4 years later due to conduit degeneration. No reoperation occurred during follow-up for patients who underwent reconstruction with a transannular patch.

There are three main groups of surgical procedures for the complex forms of these cases. These are the réparation à l'étage ventriculaire (REV), Rastelli, and Nikaidoh procedures (1).

The Nikaidoh procedure entails aortic translocation with a biventricular outflow tract. It has gained popularity recently (2,3). The Nikaidoh procedure originally consisted of translocating the aortic root in a direct posterior fashion, involving the resectioning of the infundibular septum while leaving the coronary arteries in place. The RVOT is reconstructed with the largest possible quantity of autologous tissue to ensure some extent of growth potential. Conduit replacement may be required in cases where this procedure is impossible (4). Nikaidoh (3) subsequently described surgical modifications to the approach.

The most important advantage offered using the Nikaidoh procedure is that it provides a correction closer to normal anatomy. This reduces any risks of left ventricular outflow tract (LVOT) or RVOT obstruction and minimizes the rate of reoperation (5). This report was drafted to share our experiences with patients operated on with the Nikaidoh procedure because of the combination of TGA, PS, and VSD.

Technical Report

Before beginning these operations, it is of the utmost importance to establish a clear picture of the patient's cardiac anatomy, including full information about the following:

- Spatial relationships of great vessels,
- Location and size of the VSDs,
- Coronary anatomy,
- Pulmonary annulus size,
- Presence of any abnormal atrioventricular valve attachments,
- Size of the right ventricle (6).

The chest is entered via standard median sternotomy, and a large section of the pericardium is extracted to used to close the VSD and reconstruct the RVOT. The coronary anatomy is examined to ensure safe removal of the aortic root from the right ventricle, and the main PA and its branches are mobilized. Arterial cannulation is applied to all patients at the level of the proximal aortic arch to permit more effective aortic mobilization and bicaval cannulation is used to initiate cardiopulmonary bypass at 32 °C. The proximal right coronary artery and left main coronary arteries are released in the beating heart (Figure 1). To begin, a curvilinear incision is made in the anterior wall of the right ventricle, parallel to the aortic annulus, to facilitate proper visualization of the valve (Figure 2). Subsequently, the aortic root is dissected from the RV circumferentially. The size and location of the VSD are evaluated (Figure 3). The main PA is proximally transected while ensuring that its length is preserved. The posterior aspect of the aortic root is then sutured to the pulmonary annulus in the beating heart (Figure 4). Cross-clamping is applied to the aorta and antegrade custodial cardioplegia is induced. Via the right pulmonary vein, a left ventricular vent is inserted. The aorta was transected for the Le Compte maneuver (Figure 5).

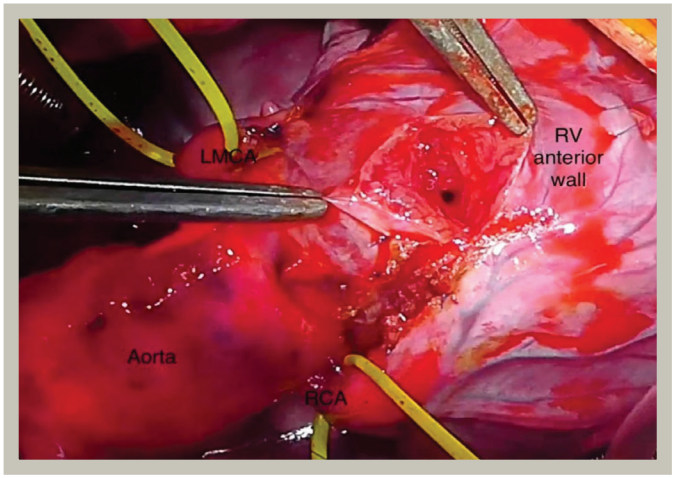

Figure 1. Proximal RCA and LMCA are released in the beating heart

LMCA: Left main coronary artery, RCA: Right coronary artery, RV: Right ventricle

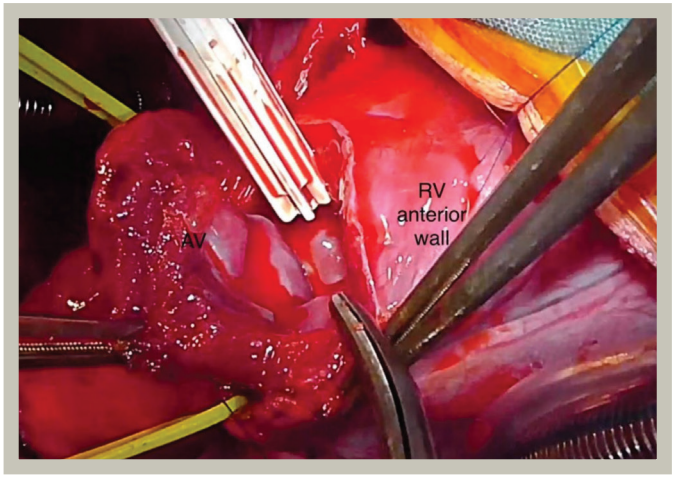

Figure 2. A curvilinear incision in the anterior wall of the RV was created to visualize the aortic valve

AV: Aortic valve, RV: Right ventricle

Figure 3. The size and location of the VSD is evaluated

VSD: Ventricular septal defect

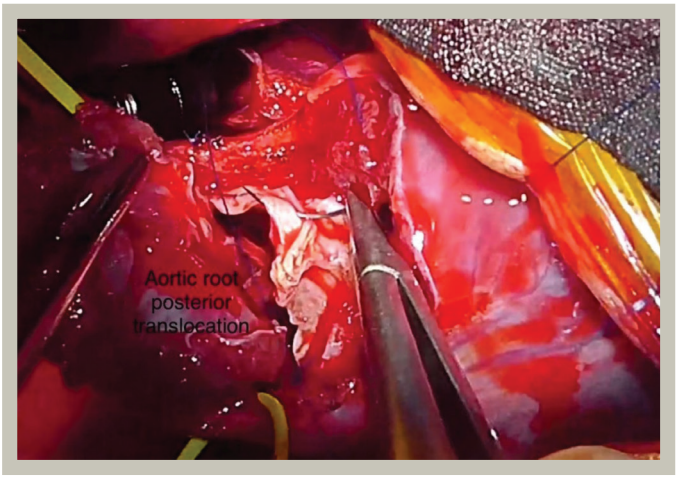

Figure 4. The posterior aspect of the aortic root is sutured to the pulmonary annulus in the beating heart

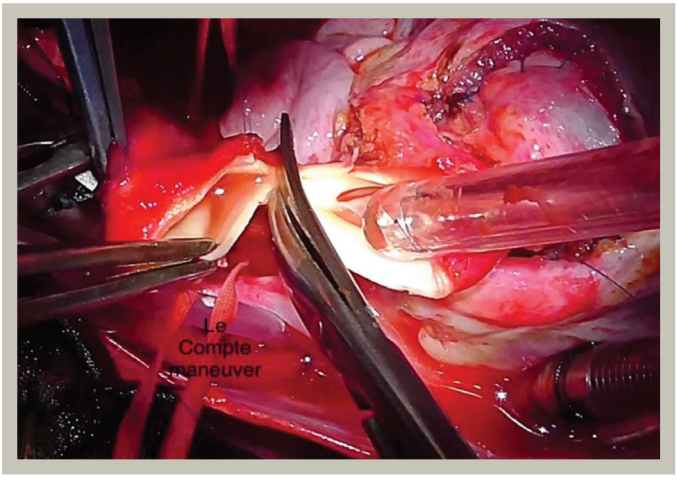

Figure 5. The aorta was transected for the Le Compte maneuver

The anterior aspect of the LVOT is subsequently repaired a running suture and a patch extending from the crest of the VSD to the aortic root (Figure 6). A segment of the ascending aorta of approximately 3-5 mm undergoes resectioning to avoid the posterior compression of the pulmonary arteries, and aortic anastomosis is performed, again with the application of a running suture. The anterior and posterior walls of the main PA are then reconstructed with autologous pericardium similar to the transannular patch approach used in cases of tetralogy of Fallot. RVOT reconstruction can be performed using an RV-PA conduit when a transannular patch is not suitable (Figure 7). When atrial septal defects are found to be present, they are closed via right atriotomy.The appearance at the end of the surgical procedure is shown in Figure 8.

Discussion

There is no consensus regarding the best surgical technique to be applied in cases of simultaneous TGA, PS, and VSD. Honjo et al. (7) defined the LVOT complexity score to standardize

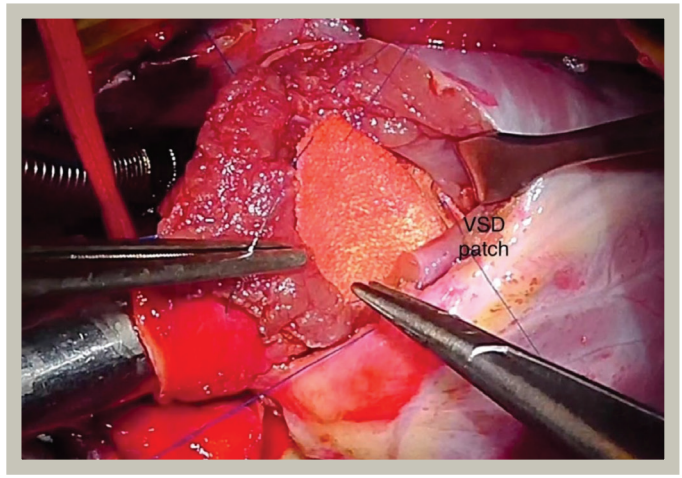

Figure 6. The anterior aspect of the LVOT is rebuilt with a patch that extends from the crest of the VSD up to the aortic root using running suture

VSD: Ventricular septal defect, LVOT: Left ventricular outflow tract

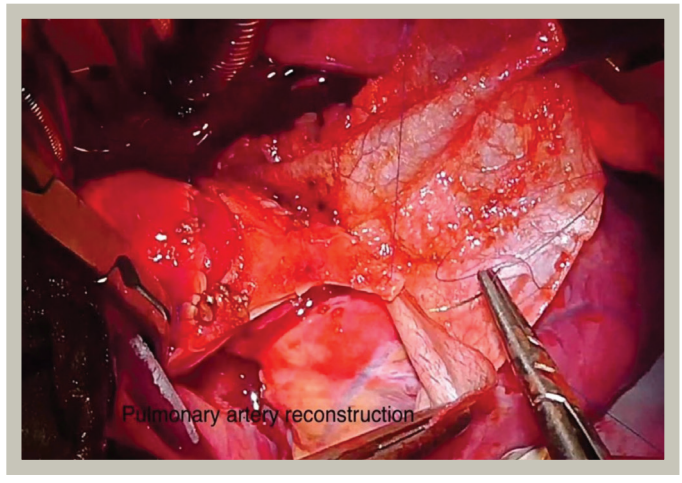

Figure 7. Pulmonary artery reconstruction with transannular patch

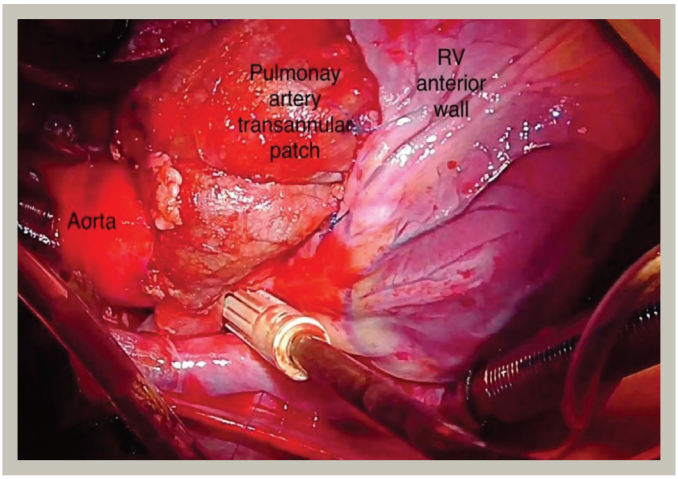

Figure 8. Appearance at the end of the surgical procedure

RV: Right ventricle

patient selection. With this scoring system, surgical decisions are made on the basis of echocardiography results and depending on the anatomical characteristics of the case. The absence of a double-outlet right ventricle, pulmonary valve dysplasia/hypoplasia, posterior infundibular septal deviations and degree of left ventricular infundibular fold obstruction, fibromuscular ridges, presence of septal hypertrophy, and atrioventricular valve overriding/straddling were all carefully evaluated. The Z-scores of the pulmonary valve and LVOT and the peak gradients are also considered. Each component is scored considering the extent of its contribution to the LVOT obstruction. Accordingly, it has been reported that the Nikaidoh procedure is probably a better choice for patients with LVOT complexity scores of >3 (7). In our clinic, we decide on surgical interventions by considering the patient's age, echocardiographic findings, aorta-PA relationship, structure of the VSD, and the expected anatomy after the formation of the intracardiac conduit.

Although the Nikaidoh procedure was first described in 1984, it had been performed for only 100 patients as of 2011 (8). One of the reasons why this surgical procedure is performed less commonly is its complexity. As their main theoretical advantages, the Nikaidoh procedure and its modified versions allow for the achievement of a more natural intracardiac geometry and RVOT reconstruction. An appropriate LVOT configuration reduces the risk of LVOT obstruction. Regardless of the VSD location and morphology, the Nikaidoh procedure can also be performed for patients with additional intracardiac malformations who have contraindications to the Rastelli procedure.

Furthermore, it is obvious that the Nikaidoh technique is superior in cases with smaller right ventricles. In the event of right ventricular hypoplasia, it may be possible to achieve a 1.5 ventricular repair by performing the Nikaidoh procedure in conjunction with the placement of a bidirectional Glenn shunt. If the aorta is seen to be remote from the left ventricle, the Rastelli procedure would necessitate a long intracardiac conduit but the Nikaidoh procedure would not. However, if the VSD is seen to be remote from the left ventricle or it is non-committed or insignificant, the Rastelli procedure becomes impossible, but biventricular repair can be performed using the Nikaidoh procedure (3). The Nikaidoh procedure can also be performed in cases of straddling mitral valves or straddling tricuspid valves (9).

In 2020, Agarwal and Vaidyanathan (10) described the prerequisites for performing the Nikaidoh procedure. The size of the pulmonary annulus and the translocation distance of the aorta are directly related to each other. Therefore, pulmonary atresia is a contraindication to the Nikaidoh procedure. Generally, the Nikaidoh procedure should be performed for patients with a pulmonary annulus diameter of 5 mm and above (10).

Another important point to consider is whether these operations are more appropriate at younger ages or in later years. Cyanosis is most often moderate and the surgical operation can be delayed. If cyanosis needs to be treated, a modified Blalock shunt might be the best choice (11). In our study, we performed m-BT shunt operations for 50% of the patients before applying the Nikaidoh procedure due to desaturation and PA hypoplasia.

Aortic translocation is a high-tech operation, and its most important part of it is the stabilization of the aortic valve and coronary arteries. Based on experience from Toronto, it was recommended to apply the Rastelli procedure in the presence of coronary anomalies (7). In a study conducted in 2018, Olds et al. (12) reported that coronary anomalies are not contraindications but require special maneuvers. For patients with posterior looping, it was recommended to mobilize the coronary arteries more and anastomose them more medially than otherwise expected using the trap-door technique. For patients with anterior looping, kinking is expected to be more prominent during reimplantation and the arteries should be anastomosed more distally. Partial reimplantation and rotation of the aortic root have been presented as other options (12). Chernogrivov et al. (13) recommended aortic translocation following the complete mobilization of the coronary arteries and the aortic root. In the first years of our clinical experience, the classical Nikaidoh technique was used. As our experience increased over the years, we began to prefer to perform coronary artery exploration and aortic root posterior translocation on beating hearts. In this way,

posterior aortic anastomosis is performed in the beating heart, as well. This is intended to shorten the cross-clamp time and prevent coronary malpositioning. In this study, this technique was performed for 33.3% of patients. Cross-clamp times of these patients were significantly shorter than those of the others. None of them were found to have coronary malpositioning or aortic valve dysfunction. Although one of them had atrioventricular valve straddling, the technique could still be used successfully.

Early results of the Nikaidoh procedure are promising. It has a low early mortality rate that is reported to be 0%-5% (5,14). Its mortality rates in the late period were also found to be lower than those of the Rastelli or REV procedures. In the study by Kramer et al. (5), prolonged durations of aortic cross-clamping and cardiopulmonary bypass were reported to be associated with early mortality. The Rastelli procedure has been reported to be less risky for patients of advanced age with coronary anomalies, severe LV hypertrophy, and dysfunction (15).

In our study, one patient died in the early stage (16.6%). This patient was the one with the lowest body weight and the longest cross-clamp time in this study, weighing 8 kg and needing an RV-PA conduit. Hazelkamp et al. (1) reported that children weighing less than 10 kg are at higher surgical risk and that their reoperation rate is higher. Although this prevailing opinion in the literature is also dominant in our clinic, a surgical operation was planned due to desaturation and growth retardation for the patient who had a history of m-BT shunt operation. In our study, the cause of the higher mortality rate was thought to be associated with the small number of included patients.

It has been demonstrated in the literature that small PA diameters homografting, and body weight are critical determinants of the need for conduit replacement. If the standard deviation of the homograft from the Z-score is higher than 3, it is defined as excessively large, and placing an inappropriately large homograft increases the likelihood of duct bending and sternal compression (16). While this consideration is important for patients who have undergone anatomical repairs with Rastelli-type procedures, it is also relevant in the event of Bex-Nikaidoh procedures. Fiore et al. (16) indicated that the optimal Z-scores for pulmonary conduits in Rastelli-type/non-Ross operations range from +1 to +3. For some anatomical subtypes, the diameter of the implanted conduit is probably vital (17). According to another opinion, the use of an oversized conduit in the Nikaidoh procedure does not cause sternal decompression and can reduce the risk of reoperation (13). Raju et al. (17), in their study investigating the effect of the type of RVOT reconstruction, reported RV-PA conduit operations to be a risk factor for reoperation. In our study, the rate of reoperation was 20%. Reoperation was not required for any patient who underwent reconstruction with a transannular patch. One patient who underwent RV-PA conduit replacement needed reoperation 4 years later due to conduit degeneration. In our clinic, we think that the use of conduits should be avoided unless absolutely necessary.

Conclusion

The Nikaidoh procedure has been shown to be a good option in cases of complex TGA. It provides better anatomical correction. compared with the Rastelli and REV procedures, no difference was found in terms of early and mid-term mortality or reoperation. Coronary anomaly and AV valve straddling are not contraindications to the Nikaidoh procedure. Performing the aortic translocation procedure on a beating heart provides advantages both in terms of shortening the cross-clamp time and ensuring a proper configuration of the coronary arteries. These operations should preferably be performed with transannular patches for patients with body weights of more than 10 kg. RV-PA conduits are risk factors for reoperation.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Z.T.R., A.C.H., Concept: B.Z.T.R., A.C.H., Design: B.Z.T.R., A.C.H., Data Collection or Processing: B.Z.T.R., Analysis or Interpretation: B.Z.T.R., Literature Search: B.Z.T.R., Writing: B.Z.T.R.

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