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REVIEW ARTICLE



# Clinical characteristics of confirmed COVID-19 in newborns: a systematic review

Meltem Karabay[a], Nursan Çınar[b], Özge Karakaya Suzan[b], Sinem Yalnızoğlu Çaka[b] and Oğuz Karabay[c]

[a]Department of Pedaitrics, Neonatology Unit, Faculty of Medicine, Sakarya University, Sakarya, Turkey; [b]Department of Pediatric Nursing, Faculty of Health Sciences, Sakarya University, Sakarya, Turkey; [c]Department of Infectious Diseases, Faculty of Medicine, Sakarya University, Sakarya, Turkey

**ABSTRACT**

**Objective:** Aim of this systematic review is to investigate the available evidence describing neonatal outcomes in newborns who have SARS-CoV-2 infection in order to guide prevention of COVID-19 in newborns.

**Methods:** This is the study protocol for a systematic review. MEDLINE, Web of Science, PubMed, Science Direct, CINAHL, Scopus, Cochrane, TUBİTAK databases, and key words of "Newborn" (neonatal OR clinical characteristics newborn OR infants less than 1 month OR infants less than 28 weeks OR Neonate) AND "clinical presentation" (epidemiology OR symptoms OR clinical course OR features) AND "COVID-19" (Coronavirus OR COVID-19 OR Sars-Cov2 OR coronavirus disease 2019 OR Novel Coronavirus OR 2019-nCoV) were searched for this systematic review. Randomized controlled trial, cross-sectional, case-control, and case reports, case reports examining neonatal outcomes in newborns who have SARS-CoV-2 infection were included. Studies were selected according to criteria around the population, intervention, comparator, outcome(s) of interest, and study design (PICOS framework). All citations and full-text articles were searched by independent five authors. The population that newborns with COVID-19 that confirmed within 28 d of birth are included. The interventions included in COVID-19 infection diagnosed *via* reverse transcription-polymerase chain reaction (RT-PCR) or serological. The primary outcomes were Neonatal clinical outcomes. The methodological quality of the studies was appraised using appropriate tools. Strength of the body of evidence was assessed according to the quality assessment tool for quantitative studies (QATQS).

**Results:** The electronic search identified 1051 records that were examined, after evaluating 35 of them were included in the study. Seven studies were research articles and twenty-eight were case reports. Methodological quality was medium. Most of the clinical characteristics of newborns were respiratory difficulty and secondly fever. Some newborns gastrointestinal (GIS) symptoms in the form of diarrhea and feeding intolerance and abdominal distension were present in 50%. The fatality case did not exist in any newborn due to COVID-19. Death occurred in one case due to prematurity.

**Conclusıons:** The most common symptoms in patients with COVID-19 infection in the neonatal period are respiratory tract symptoms and fever. It has been observed that the COVID-19 infection detected in the neonatal period is not fatal. However, data including more cases are needed.

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COVID-19; newborn outcome; clinical characteristics of newborns; confirmed COVID-19 infected neonate; SARS-CoV-2

## Introduction

COVID-19 began with an outbreak in Wuhan, China, in December 2019. The World Health Organization (WHO) has declared this disease a pandemic and by October 2020 the number of cases has exceeded 40 million worldwide [1]. Today, COVID-19 dramatically spread in many other countries worldwide [2].

When the literature is examined, there is no specific finding for newborns in the clinic. Infection in newborns may progress with insidious or nonspecific findings. Considering the clinical features that can be seen, in addition to high fever, respiratory symptoms such as tachypnea, groaning, cough, and tachycardia, lethargy, vomiting, diarrhea, and abdominal distention can be seen [3–6]. During previous pandemics, cases of newborns suffering from respiratory infections were frequently reported. The limited data available on COVID-19-positive infants indicate that these patients

CONTACT Özge Karakaya Suzan ozgekarakayasuzan@sakarya.edu.tr Sakarya University, Institutes of Health Sciences, Esentepe Campüs, Sakarya 54187, Turkey

Due to the urgent and developing nature of the topic, this paper was accepted after an expedited peer review process. For more information about the process, please refer to the Instructions for Authors.

have benign infections [8], although concerns about preterm delivery and low birth weight [7]. Available data for SARS-CoV-2-positive preterm newborns suggest that infected neonates (even if extremely preterm) may not be susceptible to serious disease with clinically significant or major morbidity [8].

A limited number of infant infections related to COVID-19 have been reported to date. It is known that COVID-19 has been defined as a mild disease in newborns. However, there are certain concerns about this issue especially among pediatricians and parents. More data are needed on the effects of the infection on newborns, both in terms of efficacy and appropriate care. There are many unclear issues regarding newborns. This systematic review aims to investigate the available evidence describing neonatal outcomes in newborns who have SARS-CoV-2 infection in order to guide prevention of COVID-19 in newborns. Moreover, what are the clinical characteristics of confirmed COVID-19 in newborns? To answer their questions and to present them in accordance with the evidence systematically by reviewing the current literature is aimed.

## Materials and methods

Prior to undertaking the review, we registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020204737; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=204737). The Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) checklist was applied as a writing and reporting guideline. Prism flow diagram has been created [9]. The scanning of the related publications was carried out retrospectively in the form of electronic search in databases. The studies conducted after 1 December 2019 investigating clinical characteristics of confirmed COVID-19 in newborns were examined between 20 August and 23 September 2020.

This section describes the design of the study, inclusion/exclusion criteria, screening strategy, evaluation, and reporting stages.

### *Formulation of the questions*

The question formulated for this systematic review:

Has COVID-19 death been reported in newborns? Are there any different characteristics in newborns than adults?

Information on all these topics is limited. More information is needed on all these issues.

### *Design of the study*

The study examining clinical characteristics of confirmed COVID-19 in newborns is a kind of systematic review.

### *Eligibility criteria*

Studies were selected according to criteria around the population, intervention, comparator, outcome(s) of interest, and study design (PICOS framework) [10]. These are detailed as follows:

### *Type of population*

Newborns with COVID-19 that confirmed within 28 days of birth are included.

### *Type of interventions*

COVID-19 infection was diagnosed *via* reverse transcription-polymerase chain reaction (RT-PCR) or serological.

### *Type of comparators*

There will be no restrictions on the type of comparator.

### *Type of outcome measurements*

Neonatal clinical outcomes (NICU admission, fatality, infection, fever, mechanical ventilation, birth weight, gender, gestation week, Apgar Score, where the test sample was taken, how many days later diagnosis realized, pneumonia, resuscitation, and symptoms (fever, vomits, GIS symptoms, respiratory difficulty, tachypnea, cough, neurologic symptoms, and cyanosis), laboratory finding). Answer to be given for the question "What are the important clinical characteristics of confirmed COVID-19 specific to newborns?"

### *Study design*

The selection criteria have been summarized in Table 1.

## Research strategy

MeSH for keywords English (Medical Subjects Headings) and Turkey Science Terms to create the Turkish equivalent of the English keywords (TBT) were used for the content. Review has been made according to the keywords specified for scans using MEDLINE, Web of Science, PubMed, Scopus, and key words of "Newborn" (neonatal OR clinical characteristics newborn OR infants less than 1 month OR infants less than 28 weeks OR Neonate) AND "clinical

**Table 1.** Inclusion criteria and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Studies with 0–28 d age infants whose were confirmed COVID-19 | Newborns upper 28 d of age |
| Newborns whose confirmed COVID-19 infection who are taken care home or hospital or newborn care units | Newborns whose non-confirmed COVID-19 infection in intensive care unit |
| Randomized controlled studies cross-sectional studies, cohort, case–control, case reports, and case series | Expert opinions |
| | Qualitative studies |
| | Unpublished theses |
| | Summary studies |
| | Systematic Reviews, rapid review |
| The studies published in Turkish and English | The studies published out of Turkish and English |
| Published after 1 December 2019. | Meconium aspiration in newborn |

presentation" (epidemiology OR symptoms OR clinical course OR features) AND "COVID-19" (Coronavirus OR COVID-19 OR Sars-Cov2 OR coronavirus disease 2019 OR Novel Coronavirus OR 2019-nCoV). The search was performed independently by two authors, and disagreements were resolved through discussion with the third author. No constraints were placed on language, year of publication, and participant characteristics to ensure a comprehensive search and identify the maximum number of potential articles. Authors of specific articles were contacted to obtain additional information if necessary.

## Study selection

The study selection process was based on the PRISMA flow diagram. Existing studies for systematic review were screened by the authors (Ö.K.S, S.Y.Ç, N.Ç, O.K, and M.K). We identified a high number of case reports and case series. Appropriate or potentially appropriate articles were independently taken by the authors (Ö.K.S, S.Y.Ç, N.Ç, O.K, and M.K) for abstract and full-text review. Disputes at every stage of the screening process were resolved through discussion and consensus. The studies that meet the inclusion criteria from the summaries were recorded with the program EndNote (EndNote X9) and their full texts were reached. The scanning process was reported in a PRISMA flow diagram (Figure 1).

### *Data extraction and management*

The approach of populations, interventions, comparators, and outcomes (PICO's) were used. The authors (Ö.K.S, S.Y.Ç, and N.Ç) independently extracted data on trial features, methodology, participant features, intervention features, outcome measures, and outcome data. Any dispute was resolved with the help of discussion or other authors. The data were extracted as include: authors, publication year, country, definition of participants, research methods, neonatal age, symptoms at admission, laboratory and radiological findings, neonatal outcomes, sample collection (neonatal nasal, pharyngeal, rectal swab or endotracheal aspirate, or bronchoalveolar lavage), and results. Neonatal clinical presentations were evaluated. Articles following the diagnostic criteria for COVID-19 based on the "COVID − 19 Laboratory Testing/CDC Guidelines by CDC" and "Neonatal and Perinatal approaches to neonatal infants with COVID-19 (Sars-CoV2) infection or suspected (v2) issued by Turkısh Neonatologıcal Socıety" were considered [11,12]. PCR tests were used for the CDC to confirm infection [11]. The above-mentioned diagnostic criteria of COVID-19 include; positive in RT-PCR tests for SARS-CoV-2 in respiratory or blood sample. Viral tests are recommended to confirmed infection [12].

Moreover, considering the risk of false-negative results of laboratory tests (possibly related to low virus titers, inappropriate swabbing sites, or variability on laboratory test performance), positive results from all tests was decided (ex. 24 h, 72 h, 96 h, etc.) [13].

## Coding method

The coding table of the studies we have included in the systematic review include study type, design/sample size, aim of the study, data collection tool, study results, and recommendations.

## Assessment of risk of bias compilations

Quality assessments for each study were carried out by two independent researchers. The quality assessment tool for quantitative studies (QATQS) was used for quantitative studies. QATQS was used to evaluate the selection bias of the studies, study design, confounders, blinding, data collection method, and exclusion/abandonment. Furthermore, this provides an opportunity of assessment on the integrity and analysis of the studies examined. The validity and reliability studies of the original scale were conducted by Thomas et al. [14]. Validity and reliability of the tool's Turkish version (T-QATQS) were made by Ergin and

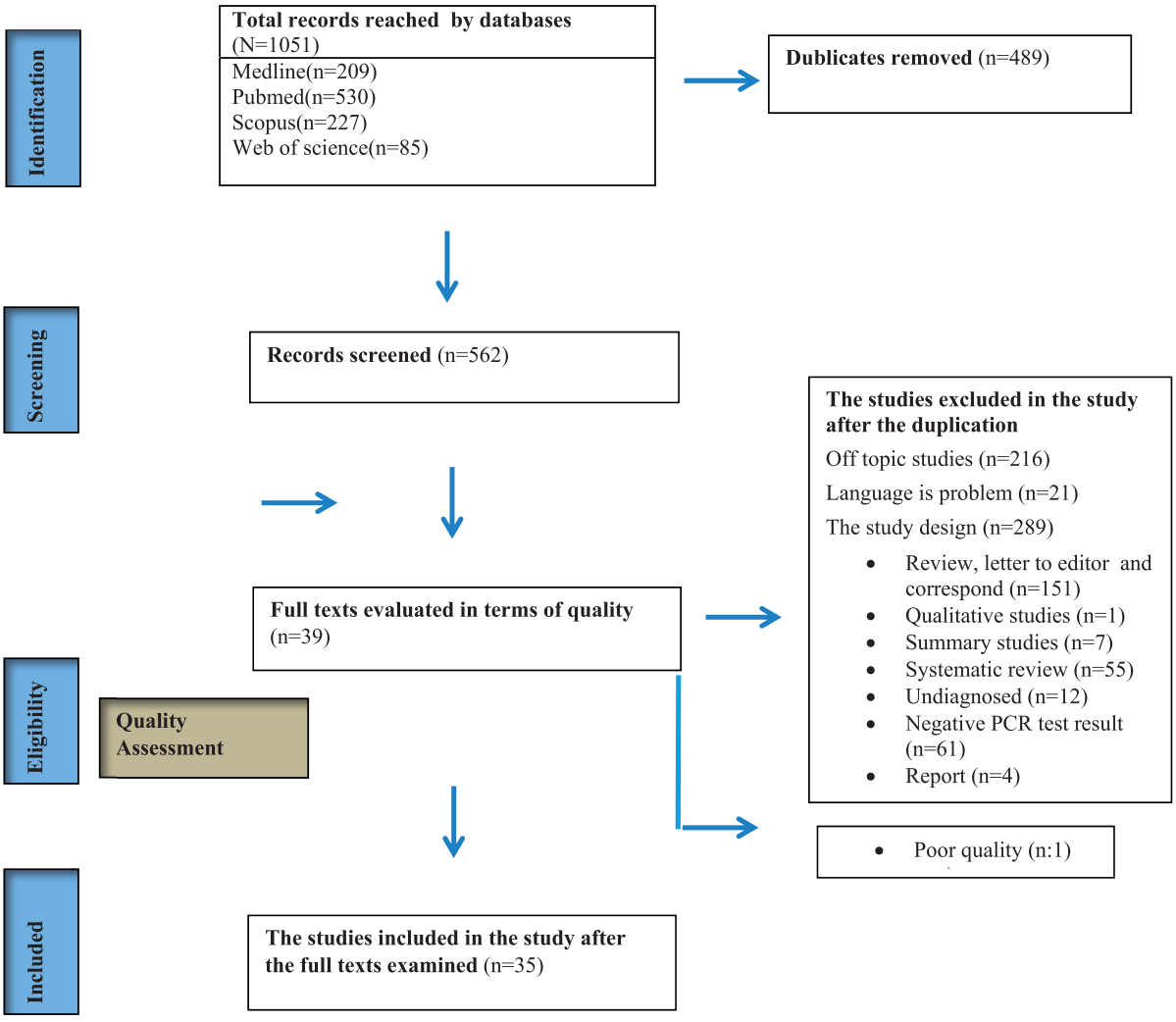


Figure 1. The flow chart (Flow diagram) in the selection of the studies.

Akın (2018) [15]. With this tool, the methodological quality of the studies can be classified as "weak," "medium," and "strong." Evaluation if there is no weak score after scoring each field (selection bias of studies, study design, confounders, blinding, data collection method, and exclusion/abandonment) in line with the scale legend, the study is "strong" in terms of methodology; "medium" if there is one weak score; if there are two or more weak points, it is considered as "weak." As a result of the evaluation, the studies with "medium" and "strong" scores are included in the systematic review. The measurement tool we used in quality assessment was developed by the public health group. This measurement tool focuses on external validity in the selection bias category and is actively used in field studies. In many studies that evaluated when evaluating quality with this measurement tool, it has been determined that the population selection does not comply with the external validity condition since it is made in a clinical setting. For this reason, after the selection bias was ignored in the studies where the quality assessment was made in order to prevent data loss due to the selection bias category, the studies with medium and strong quality levels were included in the systematic review. The quality assessment of the studies was done by two experienced independent researchers. Researchers evaluating the quality of the research also realized the coding simultaneously.

## Statistical analysis

Statistical analysis was performed using Microsoft Excel (Microsoft Corporation, 2018). Categorical variables were expressed as the number of cases (N) and percentages (%). Continuous variables were expressed as the mean with standard deviation (SD).

**Table 2.** Demographic characteristics of the ıncluded studies.

| Study | Types of studies/sample* | Birth weight (g) | Gender | Average gestation (range), GW/Apgar score 1–5 min | Where the test sample was taken | How many days later diagnosis realized | Mechanical ventilation | NICU | Pneumonia | Resuscitation | Discharge/ Fatality | Studies quality assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [16] | Retrospective/*n*:3 | NR | NR | Preterm (*n*: 3)/NR | NR | NR | Yes, 1 d (*n*:1) | Yes | NR | NR | Yes/no | Medium |
| [17] | Cohort study/*n*:1 | NR | NR | NR/2,4 | NR | NR | Yes, 2 d | Yes | NR | NR | Yes/no | Medium |
| [18] | Cohort Study/*n*:2 | NR | NR | NR | Naso-oropharyngeal swab | NR | No | Yes | No | No | Yes/Non | Medium |
| [19] | Cohort Study/*n*:1 | NR | NR | NR | NR | NR | NR | NR | No | No | Yes/no | High |
| [20] | Retrospective study/*n* = 2 | *N*1:3.360 *N*2: 3.570 | N1and *N*2: Female | *N*1:40 + 4/9 *N*2:39 + 1/10 | Throat swabs, anal swabs | NR | NR | *n*1: yes, 14 d *n*2: yes,16 d | NR | NR | NR/NR | Medium |
| [21] | Retrospective study *n* = 3 | NR | NR | NR | Pharyngeal swab | NR | NR | NR | NR | NR | NR/NR | Medium |
| [22] | Cohort study/*n*:1 | NR | NR | NR | Nasopharyngeal swab | 8 d | NR | NR | NR | NR | Yes/no | Medium |
| Case reports (individual patient analysis) | | | | | | | | | | | | |
| [4] | Case reports/*n*:18 | 900–3500 (median 2.250) | Female:7 Male:10 | 36W/9–10 (median) | Nasopharyngeal swab | 7 d | Yes (*n*:5) | Yes | Yes (*n*:1) | Yes (*n*:1) | Yes/no | NR |
| [23] | Case reports/*n*: 1 | 3.390 | NR | 38 + 3/9–10 | Nasopharyngeal swab | 15 d | No | No | No | No | Yes/no | NR |
| [24] | Case reports/*n*:1 | 2.970 | Male | 33 + 4/6–8 | Nasopharyngeal swab | 16 h after delivery | Yes | Yes | NR | NR | Yes/no | NR |
| [25] | Case reports/*n*:1 | 3.250 | Male | 40/8–9 | Oropharyngeal swab | 36 h after delivery | No | No | No | No | Yes/no | NR |
| 26] | Case reports/*n*:1 | 3550 | Male | 39 + 6/NR | Nasopharyngeal swab | 6 d | No | NR | No | No | Yes/no | NR |
| [5] | Case reports/*n*:4 | NR | *n*1: Female *n*2: Female *n*3: Male *n*4: Male | *n*1:11 d/NR *n*2: 11 d/NR *n*3: 27 d/NR *n*4: 26 d/NR | Nasopharyngeal swab | 1 d | No | No | NR | NR | Yes/no | NR |
| [27] | Case reports/*n*:1 | 2540 | Male | 35 + 5/4–2 | Nasopharyngeal and rectal swabs | 1 h of life, 3 and 18 d of postnatal age: all positive | Yes | Yes | NR | Yes | Yes/no | NR |
| [6] | Case reports/*n*:3 | *n*1:3200 *n*2: 4230 *n*3: 2850 | *n*1: Male *n*2: Male *n*3: Female | *n*1:15 d/10 (1 min) *n*2: 12 d/10 (1 min) *n*3: 16 d//10 (1 min) | Nasal swab | 1 d | No | No | NR | NR | Yes/no | NR |
| [28] | Case reports/ *n*:2 | NR | *n*1: Male *n*2: Male | *n*1:17 d/NR *n*2: 27 d/NR | Nasopharyngeal swabs | *n*1:17 d *n*2: 27 d | No (3) | Yes (3) | NR | NR | Yes/no | NR |
| [29] | Case reports/*n*:1 | 3250 | Male | 40/8–9 | Throat swab | 24–36 h of life | No | No | No | No | Yes/no | NR |
| [30] | Case reports/*n*:1 | NR | Male | 28 d/NR | Nasopharyngeal swab | 1 d | No | No | No | NR | Yes/no | NR |
| [31] | Case reports/*n*:1 | 3205 | Male | 40/8–9 | Pharyngeal swab | 36 h after birth | No | No | No | No | Yes/no | NR |
| [32] | Case reports/*n*:1 | 960 | Female | 26 + 6/5–8 | Nasopharyngeal swab | 7 d | No (CPAP) | Yes | NR | NR | Yes/no | NR |
| [33] | Case reports/*n*:1 | 3280 | Female | 34/7–9 | Nasopharyngeal swab | 24 and 48 h of life | No ( nasal cannula) | Yes | NR | NR | Yes/no | NR |
| [34] | Case reports | NR | NR | 40 + 3/9–9 | Nasopharyngeal and rectal swaps | 54 h of life | No (CPAP) | Yes | NR | NR | Yes/no | NR |
| .[35] | Case reports/*n*:1 | 2930 | Male | 35 + 5/9–9 | Nasopharyngeal swab | Day of birth | No | Yes | NR | NR | Yes/no | NR |
| [36] | Case reports/*n*:1 | NR | Male | Term/9–10 | Nasopharyngeal swab | 2 d | No (nasal cannula) | Yes | Yes | NR | Yes/no | NR |
| [37] | Case reports/*n*:1 | NR | Male | 39/NRterm | Nasopharyngeal swab | 1 d | No (nasal cannula) | Yes | NR | NR | Yes/no | NR |
| [38] | Case reports/*n*:1 | 2840 | Male | 38/9–10 | Nasopharyngeal swab | 36 h of life | No (nasal cannula) | Yes | NR | NR | Yes/no | NR |
| [39] | Case reports/*n*:1 | NR | Female | NR | Nasopharyngeal swab | NR | NR | Yes | NR | NR | Yes/no | NR |
| [40] | Case reports/*n*:1 | 3250 g | NR | 39 + 6W/8–9 | Throat swab | 36 h | NR | Yes | NR | NR | Yes/no | NR |
| [41] | Case reports/*n*:2 | NR | NR | Preterm (*n*:1) | NR | NR | NR | Yes (*n*:2) | NR | NR | Yes (*n*:1)/ no (*n*:1)/yes (*n*:1) | NR |
| [42] | Case reports/*n*:1 | 2100 g | NR | 30 + 5/8–9 | Nasopharyngeal swab | 7 d | Yes | Yes | Yes | NR | Yes/no | NR |
| [43] | Case reports/*n*:1 | NR | Male | 39W/NR | Nasopharyngeal swab | 10 d | NR | Yes | NR | NR | Yes/no | NR |
| [44] | Case reports/*n*:1 | 3400 | Male | Term/NR | Nasopharyngeal swab | 11 d | NR | Yes | NR | NR | Yes/no | NR |
| [45] | Case reports/*n*:4 | NR | *n*1: male *n*2: male *n*3: male *n*4: female | *n*1: 39 + 6 *n*2: mature *n*3: mature *n*4: 40 + 1 | Nasopharyngeal swab | *n*1: 30 h *n*2: 17 d *n*3: 5 d *n*4: 5 d | No | No | NR | NR | Yes/no | NR |
| [46] | Case reports/*n*:1 | 3460 | Male | Term/NR | Pharyngeal swab | 15 d | NR | Yes | NR | NR | Yes/no | NR |
| [47] | Case reports/*n*:1 | NR | Male | NR/NR | Nasopharyngeal swab | 26 d | NR | NR | NR | NR | Yes/no | NR |

**n*: only those diagnosed with COVID-19 from PCR.
NR: Not reported

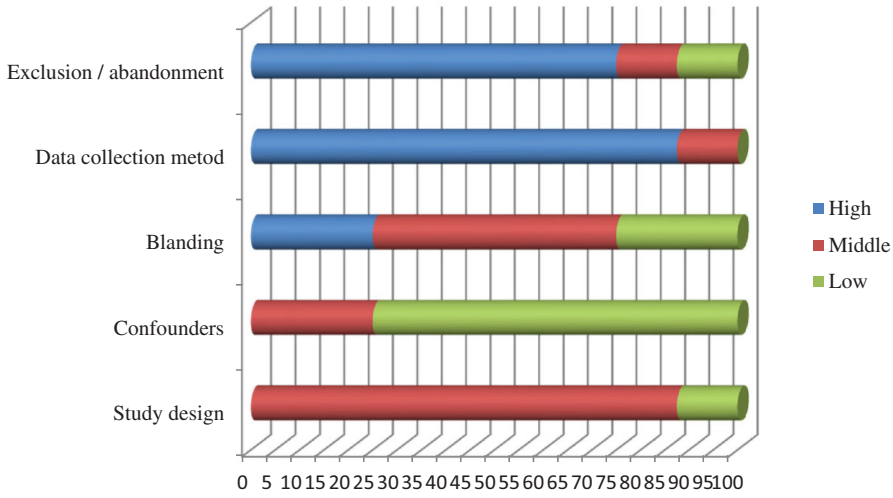


Figure 2. Graph showing the distribution of the scores received from each field according to the QATQS of all studies assessed in quality ($n = 8$).

## Ethical aspect of the research

In order to use the QATQS used in the study, written permission was obtained from Emine Ergin who was done validity and reliability in Turkish. No funding sources were used in this research.

## Result

### Search results

With the help of keywords, a total of 1051 studies were obtained in the scanning performed in four databases. Of 1051 studies, 489 were eliminated due to duplication. In the evaluation of the full texts by the researcher after the elimination of the duplications. A total of 526 studies were eliminated because it was irrelevant to the subject ($n = 216$), published in a language other than English and Turkish ($n = 21$) and was not suitable for the study design ($n = 289$). The full texts of the remaining 36 studies were examined by two independent researchers in terms of suitability and quality. In the evaluation, one study was eliminated because it received a weak score. Of the remaining 35 studies, 28 were case reports and were directly submitted to the study. The remaining seven studies were evaluated with the help of "Quality Assessment Tool for Quantitative Research." Six studies of medium score and one study of high quality and included in the systematic review. The flow chart (Flow diagram) in the selection of the studies is shown in Figure 1.

### Features of the studies

Seven of the thirty five studies included in this systematic review are research articles. Populations of evaluated studies consist of newborns with COVID-19 that confirmed within 28 d of birth are included. The number of samples varies between one and eighteen. Studies are cohort studies [8–14] and have been taken as case reports [15–42]. Detailed coding table showing the features and study results of the studies included in the systematic review is given in Table 2.

### Quality in studies (evidence quality)

The QATQS was used for quantitative studies. In the quality assessment conducted by two independent researchers, it was determined that all studies received poor scores from the selection bias category. Studies that received "medium" and "strong" scores from the assessment made by ignoring the selection bias category were included in the systematic review. The score distribution of the eight studies included in the systematic review according to the QATQS is shown in Figure 2. In case report studies concluding with laboratory findings were taken directly.

### Study findings evaluating the clinical characteristics of confirmed COVID-19 in newborns

#### Demographic characteristics of the newborns

The demographic characteristics of the included studies are summarized in Table 2. A total of 68 newborn with confirmed COVID-19 were identified. Among those patients, males were 34 and females were 16. Nine neonates were delivered prematurely. A nasopharyngeal swab was usually taken from the newborn for testing. For the test, the sample was taken at the earliest at the 16th hour and on the 27th at the latest.

Eight newborns received mechanical ventilation support. In the majority of the cases, 26 were admitted to the NICU. Pneumonia was recorded in three cases. Resuscitation was recorded in two cases. The fatality case did not exist in any newborn due to COVID-19. Death occurred in one case due to prematurity [41].

A newborn was excluded from the study because it had meconium aspiration [26].

### *Clinical characteristics of the newborns*

The coding table of the studies included reported symptoms are summarized in Table 3. A total of 12 cases of infants were asymptomatic and 56 were symptomatic. Most of the clinical characteristics of newborns were respiratory difficulty 74% (29 cases) and fever 63% (21 cases). It has been reported that 16 of 22 preterm babies have respiratory distress. While 8 of 16 babies received mechanical ventilation support, 14 of them had respiratory difficulty. Respiratory difficulty was observed in 16 out of 35 term babies, but it was determined that there were no term babies receiving mechanical ventilation support. Some newborns have gastrointestinal (GIS) symptoms in the form of diarrhea and feeding intolerance and abdominal distension were present in 50% (10 cases). Newborns neurologic manifestations symptoms in the form of irritability, hypertonia, lethargy, hyporeactivity, and hypotonia were present in 53% (9 cases). Other symptoms include a cough in 42% (8 cases) and a few cases with vomiting and cyanosis.

### *Laboratory findings of the newborns*

The laboratory findings of the included studies are summarized in Table 4. According to laboratory findings, full blood count showed the following: leucopenia and lymphopenia were present in 11% (one case) and 35% (nine cases), respectively. Monocytes concentrations were raised in 12.5% (one case) and D-dimer concentrations were raised in 67% (2 cases). Hemoglobin concentrations were normal. Aspartate transaminase (ALT) and aspartate transaminase (AST) concentrations were raised in 9% (one case) and 58% (seven cases), respectively. Procalcitonin (PCT) concentrations were raised in 10% (one case). White blood cell concentrations were decreased by 19% (3 cases). Raised C-reactive protein concentrations were present in 22% (five cases).

## Discussion

Based on our results from this systematic review, COVID-19 is not as severe as to be fatal in the neonatal period. Also, according to the results we obtained from the systematic compilation findings, the most common findings in the neonatal period were listed as respiratory distress (73%), fever (63%), neurological (lethargy, irritability), and gastrointestinal symptoms (50%). The most common symptom in infants is associated with the respiratory tract, suggesting that the respiratory tract of this age group is not sufficiently developed and it can easily become symptomatic with inflammation in this area. Different age groups often also have different susceptibility to COVID-19 infection [48,49]. It is well known that people aged >70 years have higher mortality than younger people [50,51]. Similar findings have been found by different researchers. A study from Chicago showed that 90-d-old babies who are positive for COVID-19 tend to well with little to none respiratory involvement [52]. The second important symptom is fever. It is thought that the primary cause of fever in newborns is due to released cytokines (interleukin [IL]-1, IL-6, and IL-8). However, wider data are needed on this subject [53]. According to our findings, COVID-19 signs and symptoms are less severe in newborns compared to adults. It is the over-stimulating immune system that causes a fatal reaction in adults. Adults, their immune systems overreact to the virus, causing more damage to their bodies. However, as babies interact differently, they are less likely to occur in newborns. Moreover, angiotensin-converting enzyme II (ACE2) was defined as cell receptor COVID-19. It is known that that ACE2 receptors found in the children were less sensitive to virus because the in-maturity and function of ACE2 in babies might be fewer than that in older persons [54]. The usefulness of the data we fixed in laboratory findings in diagnosis is limited. In this study, the most common laboratory findings detected in patients were lymphocytopenia and neutropenia. Lymphocytopenia in nine of the cases was detected. Lymphocytopenia is a very common finding in many viral diseases [55]. lCytokines (such as IL-6, IL-8, IL-12) and chemokines released from macrophages and lymphocytes in the blood attack infected cells. Functional exhaustion of lymphocytes is very common finding for COVID-19 infection [56]. Also, pulmonary recruitment of immune cells from the blood and the infiltration of lymphocytes into the airways may explain the lymphopenia and increased neutrophil–-lymphocyte ratio seen in around 80% of patients with this infection. Besides lymphopenia, another laboratory data were AST elevation, one of the liver enzymes. These two findings may be due to viremia. A finding that was detected in the foreground in other

**Table 3.** Coding table of the studies included reported symptoms.

| | | | Symptoms | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Types of studies/Sample* | | Asymptomatic | Fever | Hypothermia | Vomits | GIS symptoms | Respiratory difficulty | Tachypnea | Cough | Neurologic symptoms | Cyanosis |
| [16] | Retrospective/*n:*3 | NR | NR | NR | NR | Yes (*n:*1) | Yes (*n:*1) | NR | NR | NR | NR |
| . [17] | Cohort study/*n:*1 | No | NR | Yes (*n:*1) | NR | NR | Yes (*n:*1) | NR | NR | NR | NR |
| [18] | Cohort study/*n:*2 | Yes (*n:*2) | No | No | No | No | No | No | No | No | No |
| [19] | Cohort study/*n:*1 | Yes | No | No | No | No | No | No | No | No | No |
| [20] | Retrospective study/*n* = 2 | No | *n*1:NR *n*2: 37.5 ˚c days 3 | NR | NR | NR | NR | NR | NR | NR | NR |
| [21] | Retrospective study/*n* = 3 | Yes -2 | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [22] | Cohort study/*n:*1 | No | NR | NR | Yes | NR | NR | Yes | NR | NR | NR |
| Case reports (individual patient analysis) | | | | | | | | | | | |
| [4] | Case reports/*n:*18 | Yes (*n:*2) | Yes (*n:*5)<br>Fever for 2 weeks:1 | NR | NR | Yes (*n:*4)<br>poor feding:1<br>abdominal distension*n:*1<br>Diarrhea:1 | Yes (*n:*11) | NR | Yes (n:3) | Yes (*n:*2) Hypotonia:2<br>Lethargy:1 | Yes (*n:*1) |
| [23] | Case reports/*n:*1 | Yes | No | NR | No | No | No | No | No | No | No |
| [24] | Case reports/*n:*1 | No | NR | NR | NR | NR | Yes | NR | Yes | NR | NR |
| [25] | Case reports/*n:*1 | Yes | No | NR | NR | No | No | NR | No | No | No |
| [26] | Case reports/:1 | Yes | No | NR | No | No | No | No | No | No | No |
| [5] | Case reports/*n:*4 | No | Yes (4) (*n*1:38.7 °C *n*2:38.7 °C, *n*3:38.4 °C, *n*4: 38.9 °C) | NR | NR | NR | Yes (1) hypoxia | Yes (1) | NR | NR | NR |
| [27] | Case reports/*n:*1 | No | NR | NR | NR | Yes<br>(feeding difficulty) | Yes | NR | NR | Yes (hypertonia) | NR |
| [6] | Case reports/*n:*3 | No | Yes (2) 37.3 °C, – 38.8 °C infrared electric body thermometer) | NR | NR | NR | NR | Yes (1) | Yes (1) | Yes (1) (hypotonia and lethargy) | NR |
| [28] | Case reports/<br>*n:*2 | No | Yes (2) | NR | NR | NR | Yes (2) | No | NR | NR | NR |
| [29] | Case reports/*n:*1 | Yes | No | NR | No | No | No | No | No | No | No |
| [30] | Case reports/*n:*1 | No | Yes (38.8 °C rectally) | NR | NR | Yes<br>(feeding difficulty) | No | No | No | Yes (irritability and lethargy) | NR |
| [31] | Case reports/*n:*1 | Yes | No | No | No | No | No | No | No | No | No |
| [32] | Case reports/*n:*1 | No | No | NR | No | No | Yes | NR | NR | NR | NR |
| [33] | Case reports/*n:*1 | No | Yes | NR | NR | NR | Yes | NR | NR | NR | NR |
| [34] | Case reports/*n:*1 | No | Yes (38.6 °C) | NR | NR | NR | Yes | NR | Yes | Yes (Lethargy) | NR |
| [35] | Case reports/*n:*1 | No | No | Yes (35.9 °C) | NR | NR | NR | NR | No | NR | NR |
| [36] | Case reports/*n:*1 | No | No | NR | NR | NR | Yes | NR | NR | NR | NR |
| [37] | Case reports/*n:*1 | No | Yes (38.0 °C rectally) | NR | NR | NR | Yes | NR | NR | NR | NR |
| [38] | Case reports/*n:*1 | No | No | NR | NR | Yes (feeding intolerance with abdominal distension) | Yes | NR | NR | Yes (hyporeactivity) | NR |
| [39] | Case reports/*n:*1 | No | NR | NR | NR | NR | Yes | NR | NR | NR | NR |
| [40] | Case reports/*n:*1 | No | NR | NR | NR | NR | Yes | NR | NR | NR | NR |
| [41] | Case reports/*n:*2 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [42] | Case reports/*n:*1 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [43] | Case reports/*n:*1 | No | NR | NR | NR | NR | Yes (SpO2:90%) | NR | NR | NR | NR |
| [44] | Case reports/*n:*1 | No | No (37.1) | NR | Yes | Yes | No | NR | No | Yes (*n:*1) Irritability sunken-eyes skin pinch went back slowly | NR |
| . [45] | Case reports/*n:*4 | No | Yes (*n:*2) | NR | NR | NR | Yes (*n:*1) | NR | Yes (*n:*2) | NR | NR |
| . [46] | Case reports/*n:*1 | No | Yes (38.2 axillaries) | NR | NR | No | Yes (*n:*1 SpO2: 93%) | Yes (solunum sayısı:66) | NR | NR | NR |
| [47] | Case reports/<br>*n:*1 | No | Yes (38.8) | NR | Yes | Yes (watery stool) | NR | NR | NR | Yes (*n:*1)<br>İrritability<br>upward rolling of the eyes<br>hypertonia | NR |
| Total | *N:* 68 | 19% (*N:*62)** | 63% (*N:*35)** | 40% (*N:*5)** | 27% (*N:*11)** | 50% (*N:*20)** | 74% (*N:*39)** | 31% (*N:*13)** | 42% (*N:*19)** | 53% (*N:*17)** | 11% (*N:*9)** |

**n:* Only those diagnosed with COVID-19 from PCR NR: Not Reported.
**Newborns whose symptoms are yes or no.

**Table 4.** Laboratory findings of neonate with COVID-19 reported in studies.

| | Laboratory findings | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Leukocytes (reference range) | Neutrophilia (reference range) | Lymphocyte (reference range) | Monocytes (reference range) | Hemoglobin (reference range) | D-dimer (reference range) | ALT (reference range) | AST (reference range) | PCT (reference range) | WBC (reference range) | CRP (reference range) |
| [16] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [17] | NR | NR | NR | NR | NR | 809 μg/L (0–230) | NR | NR | NR | NR | 1.5 mg/dL (increased) |
| [18] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [19] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [20] | NR | NR | *n*1: 2.61 $\times 10^9$/L (Normal) *n*2: 2.19 $\times 10^9$/L | NR | NR | NR | NR | NR | *n*2: 2.95 μg/L ($N < 0.5$) | *n*1: 19.23 $\times 10^9$/L *n*2: 14.27 $\times 10^9$/L (range not available) | *n*1:<0.75 *n*2: 11.4 mg/dL |
| [21] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| . [22] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Case report** | | | | | | | | | | | |
| [4] | NR | NR | Yes (*n:* 1) (Lymphopenia) | NR | NR | NR | NR | NR | NR | NR | NR |
| [23] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [24] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [25] | NR | 9.51 $\times 10^9$/L (3.9– 9.4) | 2.43 $\times 10^9$/L (2–17) | 1.16 $\times 10^9$/L (0.2–3.1) | 146 g/L (170–200) | NR | NR | NR | NR | 13.24 $\times 10^9$/L (5–20) | NR |
| .[26] | NR | NR | 3.7 $\times 10^9$/L (Normal) | NR | NR | 1891 μg/L (range not available) | NR | NR | 0.1 μg/L (Normal) | NR | <5 mg/dL |
| [5] | *n*1:11 $\times 10^9$/l *n*2: 5.11 $\times 10^9$/l *n*3: 10.04 $\times 10^9$/l *n*4: 8.5 $\times 10^9$/l Normal) | NR | *N*1:5.01 $\times 10^9$/L *N*2: 1.62 $\times 10^9$/L *N*3: 4.05 $\times 10^9$/L *N*4: 3.66 $\times 10^9$/L ($N > 2,2$) | NR | NR | NR | *n*1:13 U/L *n*2: 24 U/L *n*4: 29 U/L ($N < 33$) | *n*1:47 U/L *n*2: 59 U/L *n*4: 40 U/L ($N < 32$) | *n*1:0.14 *n*2: 0.41 *n*3: 0.13 *n*4: 0.16 ($N < 0.5$), | NR | *n*1:0.7 mg/dL *n*2: 1.9 mg/dL *n*3: 1.7 mg/dL *n*4: 1.3 mg/dL ($N < 5$) |
| [27] | NR | 3.97 $\times 10^9$/L (Normal) | 4.39 $\times 10^9$/L (Normal) | NR | 13.9 g/dL (Normal) | NR | 9 U/L (Normal) | 38 U/L (Normal) | 0.95 (Normal) | 10.32 $\times 10^9$/L (Normal) | <5 mg/dL (Normal) |
| [6] | NR | NR | *n*1: 5.92 $\times 10^9$/L *n*2:4.95 $\times 10^9$/L *n*3: 5.76 $\times 10^9$/ L (Normal) | *n*1: 5.0% *n*2:6.9% *n*3: 12.5% (Normal) | *n*1: 12.8 g/dL *n*2:11.5 g/dL *n*3: 9.8 g/dL (Normal) | NR | *n*1: 14 U/L *n*2:26 U/L *n*3: 25 U/L (Normal) | *n*1: 49 U/L *n*2:46 U/L *n*3:36 U/L (Normal) | NR | *n*1: 10.6 $\times 10^9$/L *n*2:13.7 $\times 10^9$/L (Normal) *n*3:13.2 $\times 10^9$/L (Normal) | *n*1: <5 mg/dL *n*2:<5 mg/dL *n*3:72.8 mg/dL (Pathologic value) |
| [28] | *n*1:4.86 $\times 10^9$/L *n*2: 9.06 $\times 10^9$/ L (Normal) | *n*1:920/μL *n*2: 1.170/μL (< 1,500) (Low) | *n*1:1.070/μL (lymphopenia) *n*2: 5.130/μL | *n*1:1.280/μL *n*2:1.720/μL (Normal) | NR | NR | Normal | Normal | *n*1:0.1 μg/L *n*2: 0.5 μg/L (Normal) | NR | *n*1:1.5 mg/dL (mildly elevated ) *n*2: 1.1 mg/dL |
| [29] | NR | 4.2 $\times 10^9$/L (Normal) | 7.4 $\times 10^9$/L (Normal) | NR | 16 g/dL (Normal) | NR | 14 U/L (Normal) | 52 U/L (Normal) | 0.1 μg/L (Normal) | 12.1 $\times 10^9$/L (Normal) | 0.1 mg/dL (Normal) |
| [30] | 7.49 $\times 10^9$/L (5–19.5) | 4.44 $\times 10^9$/L (1.0–9.0) | 1.62 $\times 10^9$/L (2.5–16.5) | NR | NR | NR | NR | NR | NR | NR | NR |
| [31] | NR | NR | 2.43 $\times 10^9$/L (3–8) | NR | NR | NR | NR | 143 U/L ($N \leq 41$) elevated liver enzymes | NR | NR | NR |
| [32] | NR | NR | 1.34 × 109/L (2.5–10.0) | NR | NR | NR | NR | NR | NR | 3.64 $\times 10^9$/L decreased (7.3–16.6) | 5.1 mg/dL (maximal) |
| [33] | NR | 75% (24–61) | 13% (30–53) | 6% (4–18) | 18.3 g/dL (14.5–22.5) | NR | 10 U/L (10–35) | 64 U/L (10–35) | NR | 1.146 × 103 per $mm^3$ (5–21) | NR |
| [34] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [35] | NR | 0.3 $\times 10^9$/L (4–26) | 4.23 $\times 10^9$/L (2–7) | NR | 177 g/L (125–220) | NR | 26 U/L (15–54) | 99 U/L (13–37) | NR | 7.48 $\times 10^9$/L (8.4–34) | 0.4 mg/dL (Normal) |
| [36] | NR | 28% (Normal) | 5.6 $\times 10^9$/L (Normal) | NR | 17.2 g/dL (Normal) | NR | NR | NR | NR | 6.8 (Normal) | 0.1 mg/dL (Normal) |
| [37] | NR | 0.3 $\times 10^9$/L (neutropenia) | 5.0 $\times 10^9$/L (Normal) | 3.7 (monocytosis) | 17.7 g/dL (Normal) | NR | 40 U/L elevated liver enzymes | 64 U/L elevated liver enzymes | NR | 9.2 $\times 10^9$/L (Normal) | NR |
| [38] | 5.170/μL (9.000–30.000) leukopenia | NR | NR | NR | NR | NR | NR | NR | NR | NR | <5 mg/dL (Normal) |
| [39] | 10.220/μL (Normal) | NR | 6.310/μL (Normal) | NR | NR | 1.92 μg/L (0–0.5) | NR | NR | NR | NR | 0.11 mg/dL (0.01–1) |
| [40] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [41] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [42] | NR | NR | 26% (lymphopenia) | NR | NR | NR | NR | NR | NR | 8.9 × 109/L (Normal) | NR |
| [43] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [44] | NR | NR | NR | NR | NR | NR | NR | NR | NR | 13.000 per mm3 (Normal) | Negative |
| [45] | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| [46] | NR | NR | NR | NR | 14.4 g/dL (normal) | NR | NR | NR | NR | 6700/mL (normal) | 1 mg/dL (normal) |
| [47] | NR | NR | 2100/μL lower range | NR | NR | NR | NR | NR | NR | Normal | Negative |
| Total | *N:*9* | *N:*10 | *N:*26* | *N:*8* | *N:*11* | *N:*3* | *N:*11* | *N:*12* | *N:*10* | *N:*16* | *N:*23* |

AST: aspartate transaminase; ALT: alanine transaminase; PCT: procalcitonin; WBC: white blood cells; CRP: C-reactive protein; NR: not reported
*Number of newborns with laboratory results.

laboratory data could not be reached. This suggests that there is no laboratory data suggesting COVID-19 infection in routine laboratory tests. Therefore, it reveals the importance of tests such as PCR in diagnosis in cases with epidemiological compatibility. It has already been understood that almost all of the cases in this review are diagnosed in babies by PCR test using nasopharyngeal swaps. If there were more laboratory data, wider and stronger data could be obtained.

The weight of the children included in this systematic review ranged from 960 to 4230 g at different margins. Many babies given weight values were between 2.5 and 3.5 kg. A significant relationship between weight and frequency of infection was not observed.

## Conclusions

The most common symptoms in patients with COVID-19 infection in the neonatal period are respiratory tract symptoms and fever. It has been observed that the COVID-19 infection detected in the neonatal period is not fatal. However, data including more cases are needed.

## Limitation

In the studies reviewed within the scope of this systematic review, it is seen that joint pain and sore throat, which are among the symptoms of newborns diagnosed with COVID-19, are not evaluated in newborns. Although there are many scoring systems related to the assessment of pain in newborns, it is a limitation that pain was not evaluated in studies and we recommend that studies be conducted in this direction. Another limitation is that there is no complete information in some studies about where and how the fever is measured in newborns, how many degrees Celsius and how long it lasts. Another limitation of the study is that quality evaluations could not be made since there is no quality assessment tool with Turkish validity and reliability for case reports.

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## ORCID

Meltem Karabay http://orcid.org/0000-0001-7105-7176
Nursan Çınar http://orcid.org/0000-0003-3151-9975
Özge Karakaya Suzan http://orcid.org/0000-0003-4526-4619
Sinem Yalnızoğlu Çaka http://orcid.org/0000-0002-1572-7013
Oğuz Karabay http://orcid.org/0000-0003-1514-1685

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