J Surg Med. 2022;6(4):440-444.
DOI: 10.28982/josam.961334

Research article

Journal of Surgery and Medicine
e-ISSN = 2602-2079

A comparison of the features of RT-PCR positive and negative COVID-19 pneumonia patients in the intensive care unit

Semiha Orhan [1], Nese Demirtürk [2], Bilge Banu Tasdemir Mecit [1], Erhan Bozkurt [3], Elif Dizen Kazan [3], Tunzala Yavuz [4], Cansu Koseoglu [5], İbrahim Etem Dural [6], Alper Sari [3], Ibrahim Guven Cosgun [7], Kemal Yetiş Gulsoy [8], Sinan Kazan [9]

[1] Intensive Care Unit, Afyonkarahisar Health Sciences University, Turkey
[2] Department of Infectious Diaseases, Afyonkarahisar Health Sciences University, Turkey
[3] Department of internal medicine , Afyonkarahisar Health Sciences University, Turkey
[4] Intensive Care Unit, Izmir University of Health Sciences Tepecik education and research hospital, Turkey
[5] Department of neurology, Afyonkarahisar Health Sciences University , Turkey
[6] Department of cardiology, Afyonkarahisar Health Sciences University, Turkey
[7] Department of chest diaseases, Afyonkarahisar Health Sciences University , Turkey
[8] Intensive Care Unit, Burdur Public hospital, Turkey
[9] Department of Nephrology, Afyonkarahisar Health Sciences University, Turkey

ORCID ID of the author(s)

SO: 0000-0003-2617-6197
ND: 0000-0002-6186-2494
BBTM: 0000-0002-7994-7816
EB: 0000-0002-1853-7098
EDK: 0000-0003-3550-0964
TY: 0000-0002-6750-2967
CK: 0000-0002-9224-9203
IED: 0000-0003-4005-4858
AS: 0000-0002-4327-8032
IGC: 0000-0001-7365-8098
KYG: 0000-0002-3496-7004
SK: 0000-0001-7290-4680

Corresponding Author
Semiha Orhan
Afyonkarahisar Health Sciences University, Department of Intensive Care Unit Afyonkarahisar, Turkey
E-mail: smhorhan@gmail.com

Ethics Committee Approval
Approval for the study was granted by the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University (decision no:187, dated:2021). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2022 April 10

Abstract

Background/Aim: COVID-19 is a serious disease, primarily affecting the respiratory system. The disease spreads from person to person and has become a global health problem of great concern worldwide. The aim of this study was to compare the clinical and laboratory characteristics and the mortality rates of suspected and confirmed COVID-19 cases admitted to the intensive care unit with severe pneumonia.
Methods: A retrospective case-control study examination was made of 397 patients diagnosed with suspected or confirmed COVID-19 who were followed up in the intensive care unit (ICU) of Afyonkarahisar Health Sciences University Medical Faculty Hospital between 20 March 2020 and 31 December 2020. The cases were compared in respect of demographic, clinical and laboratory characteristics, prognosis, and mortality rates.
Results: 397 patients comprised of 37 (9.3%) with suspected COVID-19 and 360 (90.7%) confirmed COVID-19. No difference was determined between the suspected and confirmed cases in respect of age, gender, and comorbidities ($P < 0.05$). Malignancy was determined in 14 (37.8%) and in 33 (9.2%) of the suspected and confirmed COVID-19 cases, respectively. PaO_2 and PaO_2/FiO_2 values of the confirmed COVID-19 patients were found to be significantly lower than those of suspected COVID-19 cases ($P = 0.027$ and $P = 0.018$, respectively). No statistically significant difference was determined between the mortality rates of suspected and confirmed COVID-19 patients (59.5% and 56.1%, respectively, $P = 0.731$).
Conclusion: When the blood analyses of 397 patients who were hospitalized in ICU with an initial diagnosis of severe COVID-19 pneumonia, regardless of COVID-19 RT-PCR test results, were compared, the LDH and CK values were determined to be significantly high, whereas PaO2 and PaO2/FiO2 values were significantly low. Since the sensitivity of RT-PCR test is low especially in cancer patients, it leads to false negative tests in a significant proportion of patients in acute phase of the disease. Therefore, the majority of patients with COVID-19 are not detected by this test, and clinical symptoms, as well as CT scans, are important to identify patients with COVID-19. Since COVID-19 infection has similar initial symptoms to other pneumonias, it is recommended to study other respiratory viral agents in patients with a negative RT-PCR test.

Keywords: COVID-19 pneumonia, Intensive care unit, mortality, RT-PCR

How to cite: Orhan S, Demirtürk N, Mecit BBT, Bozkurt E, Kazan ED, Yavuz T, Koseoglu C, Dural İE, Sari A, Cosgun IG, Gulsoy KY, Kazan S. A comparison of the features of RT-PCR positive and negative COVID-19 pneumonia patients in the intensive care unit. J Surg Med. 2022;6(4):440-444.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, in December 2019, and the disease was defined as an infectious disease affecting the human respiratory system [1]. From January 2020, the disease spread rapidly across the globe, was reported as a severe threat to human life, and was declared a global pandemic by the World Health Organisation in March 2020 [2].

SARS-CoV-2 infection can be asymptomatic, cause mild upper respiratory tract infection or severe viral pneumonia that can result in respiratory failure or death [3]. Although the disease is basically characterised by lung inflammation, it may also cause damage to the gastrointestinal system, the liver, and the nervous system [4-5].

In the diagnosis of COVID-19, the reverse-transcriptase polymerase chain reaction (RT-PCR) method is often used, based on the amplification of the virus in nasal and oropharyngeal smears taken from infected individuals. However, there are views that the sensitivity of the RT-PCR test is insufficient in the diagnosis of COVID-19 as some infected patients can have at least one false-negative result [6].

As the PCR test does not provide sufficiently rapid results and sensitivity falls to 50%-70% especially in samples with a low viral load, non-contrast computed tomography (CT) of the lungs is frequently used at the diagnosis stage. In a study in China, CT examination was found to be 88% diagnostic and was positive in 97% of PCR-positive patients [7]. Therefore, clinical, laboratory, and thorax CT findings of the patient should be evaluated together for the diagnosis of the disease [8, 9].

The aim of this study was to compare the clinical and laboratory characteristics and the mortality rates of suspected COVID-19 cases and confirmed RT-PCR COVID-19 cases who were treated in the Intensive Care Unit because of severe pneumonia.

Materials and methods

This retrospective study was conducted in the COVID-19 Intensive Care Unit of Afyonkarahisar Health Sciences University Medical Faculty Hospital between 20 March 2020 and 31 December 2020. The study was conducted following the Declaration of Helsinki, and patients gave their written consent.

Two groups of patients were included in the study. The first group included patients defined as suspected COVID-19 cases according to the COVID-19 diagnosis, treatment, and follow-up guidelines of the Turkish Republic Ministry of Health, who had severe pneumonia but SARS-CoV-2 could not be determined with the RT-PCR test. The second group was defined as confirmed COVID-19 cases with severe pneumonia and SARS-CoV-2 positivity determined with the RT-PCR test in nasopharyngeal or respiratory samples [10].

All patients were evaluated in respect of demographic data, comorbidities, clinical and laboratory findings, prognosis, and mortality rates. The data were retrieved from the hospital's electronic patient records system. At the end of the study, the evaluated data were compared between the suspected and confirmed COVID-19 patient groups.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn. 26.0 software (IBM Corpn, Armonk, NY, USA). The patients were separated into two groups as suspected and confirmed COVID-19 cases (according to the RT-PCR test result as positive and negative). In the comparison of categorical variables between the groups, Chi-square test was used. Conformity of continuous variables to normal distribution was assessed visually with histograms and with the analytical method of the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Continuous variables showing normal distribution were stated as mean (standard deviation) values, and those not showing normal distribution, as median and interquartile range values. In the comparison of continuous variables between the groups, the Independent Samples t-test and the Mann Whitney U-test were used as appropriate to the parametric assumptions. A two-tailed *P*-value of < 0.05 was accepted as statistically significant.

Results

Evaluation was made of a total of 397 patients 37 (9.3%) comprised of COVID-19 cases and 360 (90.7%) confirmed cases. No difference was determined between the suspected and confirmed cases in respect of age, gender and comorbidities (hypertension, diabetes, heart failure, coronary artery disease, asthma, COPD, chronic liver disease, chronic renal failure) ($P < 0.05$). Malignancy was determined in 14 (37.8%) suspected and in 33 (9.2%) confirmed COVID-19 cases. The frequency of malignancy was determined to be statistically significantly higher in suspected cases ($P < 0.001$). The comparison of the comorbidities between groups is shown in Table 1.

Table 1: Comparison of the groups according to gender and comorbidities

	Possible COVID-19	Definitive COVID-19	*P*-value
Female sex (n-%)	11-29.7	114-31.7	0.809*
Median age (interval)	69 (31-92)	68 (27-95)	0.639**
Hypertension (n-%)	17-45.9	168-46.7	0.933*
Diyabetes mellitus (n-%)	9-24.3	118-32.8	0.357*
Congestive heart failure (n-%)	11-29.7	94-26.1	0.696*
Coronary artery disease (n-%)	5-13.5	94-26.1	0.111*
Asthma- Chronic obstructive lung disease (n-%)	10-27	69-19.2	0.279
Liver disease (n-%)	0	7-1.9	0.392*
Cerebrovascular disease (n-%)	0	15-4.2	0.379*
Chronic kidney failure (n-%)	2-5.4	30-8.3	0.755*
Malignancy (n-%)	14-37.8	33-9.2	< 0.001*

Fisher'sexact test, ** Mann-Whitney U test

In comparison of two groups mentioned, in respect of initial symptoms and physical examination findings, PaO_2 and PaO_2/FiO_2 values of the suspected COVID-19 patients were found to be significantly higher than values of confirmed COVID-19 cases ($P = 0.027$ and $P = 0.018$, respectively). No significant difference was determined between the groups in respect of the other findings evaluated. The initial symptoms and physical examination findings of the suspected and confirmed COVID-19 patients are shown in Table 2.

In the comparison of the laboratory values of the patients, D-dimer, procalcitonin and troponin levels were determined to be statistically significantly higher in suspected COVID-19 cases ($P < 0.05$). In the same group, LDH, creatinine kinase, potassium, magnesium, albumin, and fibrinogen levels were found to be significantly lower ($P < 0.05$). The comparison of the laboratory values of the groups is shown in Table 3. Bacterial growth was determined in the blood and tracheal

aspirate cultures of 10 (27%) suspected COVID-19 cases, divided in 6 tracheal aspirate and 4 blood cultures.

Table 1: Comparison of the groups according to clinical symptoms and physical examination findings

	Possible COVID-19	Definitive COVID-19	*P*-value
Fever (n-%)	6-16.2	34-9.4	0.244*
Shortness of breath (n-%)	37-100	358-99.4	1*
Dry cough (n-%)	27-73	213-59.2	0.114*
Fatigue (n-%)	6-16.2	83-23.1	0.412*
Myalgia (n-%)	1-2.7	26-7.2	0.494*
Headache (n-%)	1-2.7	19-5.3	1*
Systolic pressure(mmHg)	130 (90-145)	130 (110-210)	0.881
Diastolic pressure (mmHg)	78 (50-89)	74.5 (90-157)	0.086
Heart rate (/min)	89 (69-116)	87 (62-174)	0.397
Breath rate(/min)	26 (20-32)	26 (18-45)	0.408
SpO_2 (%)	87 (55-93)	87 (56-98)	0.451
PaO_2 (%)	64.5 (50-120)	61.2 (25-120)	0.027
PaO_2/FiO_2	120 (80-240)	110 (58-1120)	0.018
SOFA	5 (1-9)	4 (1-9)	0.115
GKS	13 (3-15)	12 (3-15)	0.958

SOFA: Sequential Organ Failure Assessment, GKS: Glasgow coma scale

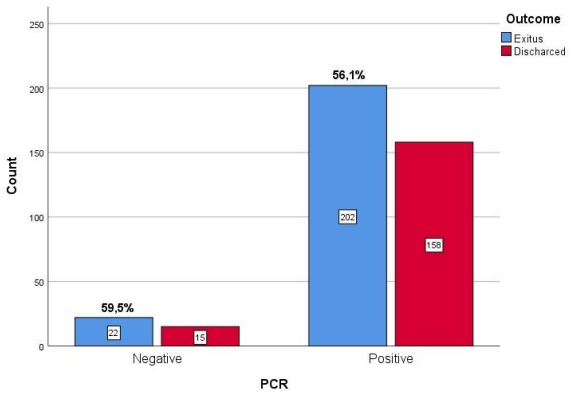
Table 3: Comparisons of the laboratory values of the patients

	Suspected COVID-19	Confirmed COVID-19	*P*-value
WBC (10^3/uL)	10140 (1400-24550)	9005 (1290-12980)	0.430*
Lymphocyte (10^3/uL)	570 (90-1670)	690 (74-1310)	0.116*
Hemoglobin (g/dL)	11.6 (6.6-19.6)	12.75 (6.4-16.2)	0.008*
Platelet (10^3/uL)	223 (6-611)	209 (16-883)	0.702*
C-reactive protein, (mg/dL)	13.78 (10.7)	13.16 (8.9)	0.877**
Procalcitonin (ng/mL)	3,15 (7.5)	2.33 (11.9)	0.026**
Lactate (mg/dL)	16 (7-45)	18 (6-120)	0.370*
d-Dimer (µg/mL)	6.59 (14.7)	3.61 (9.3)	<0.001**
Ferritin (ng/mL)	453 (6-9600)	733 (28-4021)	0.093*
Lactate dehydrogenase (LDH) (U/L)	326 (65-1430)	470 (17-1910)	<0.001*
Creatinine kinase (CK) (IU/L)	68 (32-757)	106.5 (12-9345)	0.001*
Aspartate aminotransferase (AST) (U/L)	32 (11-945)	43 (11-707)	0.054*
Alanine aminotransferase (ALT) (U/L)	24 (3-489)	25 (6-321)	0.136*
Gamma glutamyl transpeptidase (GGT) (U/L)	50 (8-581)	45.5 (4-718)	0.459*
Alkaline phosphatase (ALP) (U/L)	86 (36-813)	71.5 (23-416)	0.031*
Creatinine (mg/dL)	1.87 (3.1)	1.39 (1.6)	0.953**
Glomerular filtration rate (eGFR) (mL/dk/1.73 m²)	68.16 (31.7)	69.44 (28.1)	0.667**
Sodium (mmol/L)	137.7 (6.6)	137.2 (7.1)	0.261**
Potassium (mmol/L)	4.28 (0.7)	4.51 (0.7)	0.05**
Magnesium (mg/dL)	2.05 (0.36)	2.21 (0.47)	0.032**
Phosphorus (mg/dL)	3.33 (0.6)	3.46 (0.8)	0.107**
Albumin (g/dL)	3.01 (0.5)	3.14 (0.5)	0.035**
Fibrinogen (mg/dL)	461.2 (155.2)	523.5 (150.4)	0.018**
Sedimentasyon (mm/h)	54 (5-103)	65 (2-124)	0.097*
Troponin (ng/mL)	0.125(0.3)	0.056 (0.2)	0.001**

*Mann-Whitney U test, ** t test

When the prognoses of the two groups were evaluated, the mortality rate was determined to be 59.5% in suspected and 56.1% in confirmed cases. The mortality rates were found to be similar (P = 0.731). The mortality rates of two groups are shown in Figure 1.

Figure 1: Mortality rates of the suspected and confirmed COVID-19 patient groups



Discussion

Although PCR tests are mostly accurate for the diagnosis of SARS-CoV-2 infection, they are suboptimal for upper respiratory tract samples [11]. Previous studies have reported that COVID-19 basically involves the lower respiratory tract and rates of nucleic acid determination with nasopharyngeal smear are low (30%-50%) [12]. Lei et al. [13] stated that infected patients can be overlooked when only nucleic acid tests are used. In some studies that have evaluated antibody response in COVID-19 patients using serological tests, it is stated to be useful for the diagnosis of patients with negative RT-PCR results [14, 15]. Serological tests have been developed using spike (S) and nucleocapsid (N) high antigenic structure proteins as the target. In most people, measured antibodies develop within days or weeks of the onset of symptoms [16], and therefore serological tests are limited to the early stage of infection [17].

Song et al. [18] recommended thorax CT as a tool that can be used for screening suspected COVID-19 patients. In a study of 205 COVID-19 patients by Wang et al. [19], 1070 samples were collected and the rates of positive determination in those samples were as follows; the highest positivity rate was in bronchoalveolar lavage fluid samples (14/15, 93%), followed by sputum (72/104, 72%), nasal smears (5/8, 63%), and pharyngeal smears (126/398, 32%). According to the results from that study, it was stated that more accurate results could be obtained with the use of thorax CT together with RT-PCR testing.

Shah et al. [20] reported that of a total of 316 patients, 31 other respiratory tract viruses were determined in 283 COVID-19-negative patients. In the current study, 9.3% of the cases had a negative RT-PCR test result for COVID-19. As there were not sufficient facilities available for COVID-19 antibody testing or for other respiratory tract viral agents in negative patients, these were not studied as a limitation of the study.

In this study, the confirmed COVID-19 patients who were in the Intensive Care Unit (ICU) with clinical findings of severe COVID-19 infection and thorax CT findings consistent with COVID-19 pneumonia, were compared with suspected COVID-19 patients in respect of age, gender, comorbidities, symptoms, blood tests, and mortality rates. No difference was determined between the groups in respect of age. When comorbidities were evaluated, only the frequency of malignancy was found to be significantly higher in the suspected COVID-19 patients. Assad et al. [21] reported that of 302 cancer patients who presented with suspected COVID-19, 247 (81.8%) were SARS-CoV-2 RT-PCR negative, and 55 (18.2%) were determined as positive. In cancer patients in particular, serological tests have low sensitivity [22]. Therefore, in the vast majority of cancer patients, COVID-19 cannot be determined with serological tests, and it is important to identify COVID-19 patients with both CT scans and clinical symptoms.

The most common symptoms of COVID-19 are fever, dry cough, shortness of breath, and listlessness [23]. The clinical symptoms of both groups in the current study were similar, with the most common symptoms of shortness of breath and cough. As these symptoms can be caused by other respiratory tract viruses, and acute respiratory tract infections are common, it is difficult to bring this pandemic under control.

In patients infected with COVID-19, acute phase reactants show pathological changes with hematological, biochemical, and coagulation tests. Of the hematological changes, lymphopenia, leukocytosis, leukopenia, and mild thrombocytopenia may be seen [24].

Although there was no difference between the current study groups in the lymphocyte values, they were reduced in both groups. This result demonstrates the similarity of COVID-19 to many other respiratory tract infections, triggering of the natural immune response by inflammation and the destruction of lymphocytes after infection [25, 26].

Previous studies have reported that an excessive immune response plays an important role in severe influenza or the pathogenesis of SARS [27]. Elevated CRP, which is an acute phase reactant, may be linked to an excessive immune response [28]. In the current study, elevated CRP levels were determined in both suspected and confirmed COVID-19 patients.

In the suspected COVID-19 cases of the current study, the leukocyte and procalcitonin levels were higher than those of the confirmed COVID-19 cases. The reason for this could be that the potential for bacterial infection could be high in the suspected COVID-19 group. There was determined to be nosocomial bacterial infection in the suspected COVID-19 patients in the current study. Prompt determination of bacterial infections is very important to be able to start antibiotic treatment in time during treatment.

Some studies have reported abnormalities of varying degrees in the liver function tests of COVID-19 patients [29, 30]. In a study that compared the level of markers related to liver functions in patients with and without COVID-19, it was reported that the liver function test levels were significantly higher in the COVID-19 patients, suggesting acute liver damage [31]. In the current study, the liver function test markers (ALT, AST, GGT) were observed to be significantly high in both groups.

LDH is an enzyme that contributes to energy production with the conversion of lactate to pyruvate, and present in almost all cells of the body, with highest in the heart, liver, lungs, muscles, kidneys and blood cells. LDH is a marker of acute and chronic tissue damage, and accepted as an inflammatory marker [32]. In a case series in literature, it was reported that LDH was high in cases with cardiac involvement, those with a severe clinical course, and mortal cases [33]. Shi et al. [34] reported that an elevated LDH level was an independent risk factor for exacerbation in mild COVID-19 patients. Poggiali et al. [35] reported that LDH could be a precursor marker in the evaluation of respiratory function (PaO_2 / FiO_2) and respiratory failure in COVID-19 patients.

Consistent with findings in literature, LDH and CK values of the confirmed COVID-19 patients in ICU were found to be statistically significantly high. Furthermore, the PaO_2 value and PaO_2 / FiO_2 ratio were found to be statistically significantly lower than those of suspected COVID-19 patients. In a study by Zheng et al. [36], the viral load of patients with severe COVID-19 was significantly higher than patients with mild COVID-19, and it was reported that high viral load could be a risk factor for severe disease.

In a study by Ke et al. [37] that compared patients who were PCR(+) and had clinical symptoms with patients who were diagnosed from clinical symptoms despite a negative PCR test, the BUN and D-dimer levels were reported to be significantly higher in the clinically diagnosed group than in the PCR(+) group, and the hemoglobin level was lower. In the current study, the creatinine level was higher in the suspected COVID-19 group than in the confirmed COVID-19 patients, the D-dimer level was statistically significantly higher and the hemoglobin level was statistically significantly lower. In addition the potassium, magnesium, and albumin values were significantly low and the troponin level was significantly high in the suspected COVID-19 group compared to the confirmed COVID-19 group. These results were thought to be due to the greater number of patients with malignancy, COPD, and CRF in the suspected COVID-19 patient group.

The mortality rates were similar in both groups of this study. However, the higher mortality rate in the suspected COVID-19 group can be explained by the fact that there was a significantly higher number of patients with malignancy in that group.

Conclusions

When the blood analyses of the 397 patients hospitalized in ICU with an initial diagnosis of severe COVID-19 pneumonia were compared with positive and negative COVID-19 RT-PCR tests, LDH and CK values were determined to be significantly high and the PaO2, and PaO2/FiO2 values were significantly low in confirmed cases group. Since the sensitivity of RT PCR test is low especially in cancer patients, it leads to false negativity in a significant proportion of patients in the acute phase of the disease. Therefore, the majority of patients with COVID-19 are not detected by this test, and clinical symptoms, as well as CT scans, are important to identify patients with COVID-19. Since COVID-19 infection has similar initial symptoms to other infections, it is recommended to study other respiratory viral agents in patients with a negative RT-PCR test.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33. doi: 10.1056/NEJMoa2001017
2. Organization WH. Coronavirus Disease (COVID-19) Situation reports. https:// www.who.int/emergencies/diseases/novel-coronavirus-2019/situation- reports.
3. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):10592. doi: 10.1016/j.ijantimicag.2020.105924
4. Liu Y, Yang Y, Zhang C, Huang F, Wang F, et al., Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury, Sci. China Life Sci. 2020;63:364–74. doi: 10.1007/s11427020-1643-8.
5. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series, BMJ. 2020;368. doi: 10.1136/bmj.m606
6. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. New England Journal of Medicine. 2020;1177–9. doi: 10.1056/nejmc2001737.
7. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing in Coronovirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology Radiology. 2020 Aug;296(2):E32-E40. doi: 10.1148/radiol.2020200642.
8. Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020;92:1518–24. doi: 10.1002/jmv.25727.
9. Wikramaratna PS, Paton RS, Ghafari M, Lourenço J. Estimating the false-negative test probablity of SARS-CoV-2 by RT-PCR. Euro Surveill. 2020;25(50):2000568. doi: 10.2807/1560-7917.ES.2020.25.50.2000568.
10. https://COVID-19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf
11. Woloshin S, Patel N, Kesselheim AS. False negative tests for SARS-CoV-2 infection– challenges and implications. N Engl J Med. 2020;383:e38
12. Liu Q, Wang RS, Qu GQ, Wang YY, Liu P, Zhu YZ, et al. Gross examination report of a COVID-19 death autopsy. Fa Yi Xue Za Zhi. 2020;36:21–3. doi: 10.12116/j.issn.1004-5619.2020.01.005.
13. Lei P, Fan B, Mao J, Wang P. Comprehensive analysis for diagnosis of novel coronavirus disease (COVID-19) infection. J Infect. 2020.80;6. doi: 10.1016/j.jinf.2020.03.016.

14. Jin Y, Wang M, Zuo Z, Fan C, Ye F, Cai Z, et al. Diagnostic value and dynamic variance of serum antibody in coronavirus disease 2019. Int J Infect Dis. 2020;94:49–52. doi: 10.1016/j.ijid.2020.03.065
15. Okba NMA, Muller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. Severe acute respiratory syndrome coronavirus 2specific antibody responses in coronavirus disease 2019 patients. Emerg Infect Dis. 2020;26:1478–88. doi: 10.3201/eid2607.200841
16. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465–9. doi: 10.1038/s41586-020-2196-x.
17. Xiang F, Wang X, He X, Peng Z, Yang B, Zhang J, et al. Antibody detection and dynamic characteristics in patients with coronavirus disease 2019. Clin Infect Dis. 2020;71(8):1930-34. doi: 10.1093/cid/ciaa461
18. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging coronavirus 2019-nCoV pneumonia. Radiology. 2020;295:210–7. doi: 10.1148/radiol.2020200274
19. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARSCoV-2 in Different Types of Clinical Specimens. JAMA 2020;323:1843-4. doi: 10.1001/jama.2020.3786
20. -Shah S J, Barish P N, Prasad P A, Kistler A, Neff N, Kamm J. Clinical features, diagnostics, and outcomes of patients presenting with acute respiratory illness: A retrospective cohort study of patients with and without COVID-19 E Clinical Medicine. 27 2020;100518. doi: 10.1016/j.eclinm.2020.100518
21. Assaad S, Avrillon V, Fournier ML, Mastroianni B, Russias B, Swalduz A. et al. High mortality rate in cancer patients with symptoms of COVID-19 with or without detectable SARS-COV-2 on RT-PCR. European Journal of Cancer. 2020;135:251-9. doi: 10.1016/j.ejca.2020.05.028
22. Solodky ML, Galvez C, Russias B, Detourbet P, N'GuyenBonin V, Herr AL, et al. Lower detection rates of SARS-COV2 antibodies in cancer patients vs healthcare workers after symptomatic COVID-19. Ann Oncol. 2020;31(8):1087-8. doi: 10.1016/j.annonc.2020.04.475
23. Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020 Feb;91:264–6. doi: 10.1016/j.ijid.2020.01.009.
24. Zhang ZL, Hou YL, Li DT, Li FZ. Laboratory findings of COVID-19: a systematic review and meta-analysis. Scand J Clin Lab Invest. 2020;80(6):441-7. doi: 10.1080/00365513.2020.1768587
25. Baskin CR, Bielefeldt-Ohmann H, Tumpey TM, Sabourin PJ, Long JP, García-Sastre A, et al. Early and sustained innate immune response defines pathology and death in nonhuman primates infected by highly pathogenic influenza virus. Proc Natl Acad Sci USA. 2009;106:3455–60.
26. Liu B, Zhang X, Deng W, Liu J, Li H, Wen M, et al. Severe influenza A(H1N1)pdm09 infection induces thymic atrophy through activating innate CD8(+)CD44(hi) T cells by upregulating IFN-γ. Cell Death Dis. 2014;5:e1440
27. Van den Brand JM, Haagmans BL, Van Riel D, Osterhaus AD, Kuiken T. The pathology and pathogenesis of experimental severe acute respiratory syndrome and influenza in animal models. J Comp Pathol. 2014;151:83–112.
28. Gao R, Wang L, Bai T, Zhang Y, Bo H, Shu Y. C-reactive protein mediating immunopathological lesions: a potential treatment option for severe influenza A diseases. E Bio Medicine. 2017;22:133–42. doi: 10.1016/j.ebiom.2017.07.010
29. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;10223:497-506. doi: 10.1016/S0140-6736(20)30183-5
30. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–13. doi: 10.1016/S0140-6736(20)30211-7.
31. Zhao D, Yao F, Wang L, Zheng L, Gao Y, Ye J, et al. A Comparative Study on the Clinical Features of Coronavirus 2019 (COVID-19) Pneumonia With Other Pneumonias Clinical Infectious Diseases. 2020;28:71(15):756-61. doi: 10.1093/cid/ciaa247.
32. Sepulveda J. Challenges in Routine Clinical Chemistry Analysis: Proteins and Enzymes. Editor(s): Dasgupta A, Sepulveda JL, Chapter 9, Accurate Results in the Clinical Laboratory, Elsevier, 2013:131-48.
33. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5
34. Shi J, Li Y, Zhou X, Zhang Q, Ye X, Wu Z, et al. Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study. BMC medicine. 2020;3;18(1):168. doi: 10.1186/s12916-020-01633-7
35. Poggiali E, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, et al. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. Clinica chimica acta; international journal of clinical chemistry. 2020;509:135-8. doi: 10.1016/j.cca.2020.06.012
36. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ. 2020;369:m1443. doi: 10.1136/bmj.m1443
37. Ke C, Yu C, Yue D, Zeng X, Hu Z, Yang C. Clinical characteristics of confirmed and clinically diagnosed patients with 2019 novel coronavirus pneumonia: a single-center, retrospective, case-control study Med Clin (Barc). 2020;155(8):327–34. doi: 10.1016/j.medcli.2020.06.055.

The National Library of Medicine (NLM) citation style guide has been used in this paper.