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Covid-19 Yoğun Bakım Hastalarını Ayırt Etmek İçin Kullanılabilecek Laboratuvar Testleri

Laboratory Tests to Distinguish COVID-19 Intensive Care Patients

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ÖZ

Amaç: COVID-19 pandemisinde yoğun bakım ihtiyacı artmıştır ve bu süreçte laboratuvar parametreleri önem kazanmıştır. RT-PCR(+) 60 servis ve 26 yoğun bakım COVID-19 hastasının başvuru semptomlarını, eşlik eden hastalıklarını, yaş ortalamasını ve laboratuvar verilerini retrospektif olarak değerlendirip, hastaların klinik ve laboratuvar özelliklerini ortaya koymayı prognoz hakkında bize yardımcı olacak parametreleri belirlemeyi amaçladık.

Yöntem: RT-PCR (+) COVID-19 hastalarının verileri hastane ve laboratuvar bilgi sistemlerinden geriye dönük olarak toplandı. Hastanemizde tedavi gören toplam 86 COVID-19 hastası, yatan hastalar ve yoğun bakım hastaları olarak gruplandırıldı. Hastaneye başvuru semptomları, komorbid hastalıkları ve laboratuvar verileri istatistiksel olarak değerlendirildi.

Bulgular: Çalışma popülasyonunun ortalama yaşları yoğun bakım ve servis hastalarında sırasıyla 64 ve 58 idi. Yoğun bakım hastalarının %73'ünde, servis hastalarının %51,6'sında komorbid hastalık saptandı. Her iki grupta da hipertansiyon (43%) ve diabetes mellitus (22%) en sık eşlik eden hastalıklardı. Yoğun bakım hastalarında nötrofil [(6.11(1.18-19.7) ile 3.83(1.51-12.07) 109 /L, p=0.007], nötrofil/lenfosit oranı [5.74 (1.34-28.86) ile 2.11 (0.64-9.14), p<0.001], D-dimer [482 (52-2522) ile 249 (59-3561) µg/L, p=0.001], CRP [91.8 (0.49-331.7) ile 14 (0-161) mg/L, p< 0.001] ve prokalsitonin [0.19 (0-6.94) ile 0.04 (0-0.86) µg/L, p< 0.001] değerleri anlamlı olarak daha yüksek, lenfosit [(1.12±0.54) ile (1.81±0.90) 109 /L, p<0.001] değerleri daha düşük olarak bulundu.

Sonuç: COVID-19 virüsü insanları etkilemeye devam etmekte ve bazı hastalarda yoğun bakım ihtiyacı görülmektedir. Yoğun bakım hastalarında lenfopeni ve nötrofil, N/L oranı, D-dimer, CRP, prokalsitonin düzeylerindeki artış dikkat çekicidir.

Anahtar Kelimeler: COVID-19, Lenfopeni, D-dimer, CRP, Prokalsitonin.

ABSTRACT

Objective: The need for intensive care units has increased in the COVID-19 pandemic, and in this process, laboratory parameters are important. We aimed to evaluate the admission symptoms retrospectively, comorbid diseases, mean age, and laboratory data of RT-PCR(+) 60 service and 26 intensive care COVID-19 patients, to reveal the clinical and laboratory characteristics of the patients and to define the parameters that will help us about the prognosis..

Methods: We divided 86 COVID-19 RT-PCR (+) patients treated in our hospital into two groups as inpatients and intensive care patients. We compared symptom, comorbid disease and laboratory data in these patient groups and compared laboratory data statistically.

Results: In our study, while the mean age of intensive care patients was 64, it was 58 in service patients. Comorbid diseases were found in 73% of intensive care patients and 51.6% in service patients. Hypertension (43%) and diabetes mellitus (22%) are the most common comorbid diseases in both groups. In addition, while neutrophil [(6.11(1.18-19.7) vs. 3.83(1.51-12.07) 109 /L, p=0.007], N/L ratio [5.74 (1.34-28.86) vs. 2.11 (0.64-9.14), p<0.001], D-dimer [482 (52-2522) vs. 249 (59-3561) µg/L, p=0.001], CRP [91.8 (0.49-331.7) vs. 14 (0-161) mg/L, p< 0.001], and procalcitonin [0.19 (0-6.94) vs. 0.04 (0-0.86) µg/L, p<

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0.001] values were found to be significantly higher in intensive care patients, lymphocyte values [(1.12±0.54) vs. (1.81±0.90) 109 /L, p<0.001] were found to be significantly lower.

Conclusion: COVID-19 is still affecting our world, and patients need intensive care. Lymphopenia, increase in neutrophil level, N/L ratio, D-dimer, CRP and procalcitonin levels are remarkable in intensive care patients.

Key words: COVID-19, Lymphopenia, D-dimer, CRP, Procalcitonin.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first observed at the end of 2019 and then spread worldwide to become a pandemic, seriously affecting our country and the world. For the first time, on December 29, 2019, four patients were reported in connection with the Huanan seafood market in Wuhan, China (1).

Coronaviruses are enveloped RNA viruses common among mammals, birds, and humans that cause acute respiratory infections and hepatic, neurological, and enteric diseases (2). A coronavirus caused severe acute respiratory syndrome (SARS) in 2002–2003 and Middle East respiratory syndrome (MERS) in 2011. The causative agents in both cases (SARS-CoV and MERS-CoV) were coronaviruses of animal origin in the newly identified beta coronavirus genus. At the end of 2019, another coronavirus caused a new epidemic, called COVID-19 (3, 4). Although the main transmission route is respiratory droplets, COVID-19 can also be transmitted through physical contact (5).

The clinical presentation of the disease ranges from asymptomatic to respiratory failure, sepsis, septic shock, and multi-organ failure. COVID-19 causes acute respiratory failure syndrome in some patients, and these patients require intensive care units with mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) is used for critically ill patients, although most patients still die from COVID-19 (6, 7).

In the months following the onset of COVID-19, many academic centers have published observational studies based on clinical features, computed tomography (CT) imaging features, and laboratory results (8-10). In some patients, radiological ground-glass opacity, normal or below reference lymphocyte and platelet counts, hypoxemia, and impaired liver and kidney function have been reported (11). Currently (1/06/2023), the number of confirmed cases is 657 977 736, and the number of confirmed deaths is 6 681 433 (12).

Laboratory parameters are important in distinguishing patients in intensive care and monitoring treatment. In our study, we aimed to reveal the clinical and laboratory characteristics of COVID-19 patients and to define laboratory parameters that will help us to determine prognoses.

2. METHOD

Study Design, Patient Groups and Laboratory Findings

Eighty-six COVID-19 RT-PCR (+) patients were hospitalized at the Izmir Katip Celebi University Atatürk Training and Research Hospital and retrospectively analyzed between March 15 and June 30, 2020. In total, 114 patients diagnosed with COVID-19 and treated in the service (87 patients) or intensive care unit (27 patients) were examined in our study. Diagnostic criteria published by the Ministry of Health were used for the diagnosis of COVID-19. Twenty-seven patients were excluded from the study so that the ages of the two groups were

equalized. Patients treated at home or outpatients diagnosed with COVID-19 were also excluded from the study.

Patient symptoms (including fever, cough, shortness of breath, and headache), laboratory findings (including biochemistry, hemogram, and coagulation), comorbid diseases (including hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and coronary artery disease), and length of hospitalization were searched using the hospital information system. Comorbid diseases were defined through the ICD (International Statistical Classification of Diseases and Related Health Problems) diagnosis and code list published by the Ministry of Health. For this study, the necessary permissions were obtained from the İKCU Non-Invasive Clinical Research Ethics Committee (Decision No: 1000, Date: 10/22/2020) and the T.C. Ministry of Health, General Directorate of Health Services (Leyla Demir-2020-06-04T10_05_06).

Complete blood cell count was measured by Sysmex XN 1000 (Sysmex, Kobe, Japan) with fluorescence flow cytometry and hydrodynamically focussed impedance methods. CRP was measured by Abbott Architect c16000 (Abbott Diagnostics, Abbott Park, IL, USA) with Immunoturbidimetric method. Procalcitonin was measured by ADVIA Centaur Immunoassay Systems (Siemens, USA). D-dimer was measured by ACL TOP 700 instrument (Instrumentation Laboratory Company, Werfen, Bedford, MA, USA) with turbidimetric immunoassay.

Statistical Analysis

Patients were grouped according to intensive care and inpatients, and 27 patients were excluded from the study to equalize their ages. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 22.0 (IBM Corp., Armonk, NY, USA). To compare the groups, their distribution was checked using the Kolmogorov–Smirnov test. Those with normal distribution were compared parametrically with the independent samples t-test, and the values are presented as mean ± standard deviation. Parameters that did not fit the normal distribution were compared using the Mann–Whitney U test, and the values are presented as the median (min–max). Statistical significance was set at $P < 0.05$.

3. RESULTS

Of the 86 patients, 42 (48.8%) were female and 44 (51.2%) were male. The mean age of the total patient group was 60 years, and the age range was 32–87 years. Sixty (69.8%) patients were treated in the service unit, while 26 (30.2%) patients were treated in the intensive care unit. The age distribution and comorbidities of the intensive care patients and inpatients are shown in Table 1. Fifty (58.1%) patients presented with comorbidities, 37 (43%) with hypertension, 19 (22%) with diabetes mellitus, 6 (7.0%) with chronic obstructive pulmonary disease, 5 (5.8%) with asthma, and 5 (5.8%) with coronary artery disease. The comorbidities of intensive care patients and inpatients are shown in Table 2. The mean hospital stay of the patients was 16 days (range, 5–63 days). Twelve (46.2%) of the 26 intensive care patients and one of the 60 inpatients (1.7%) died during this period. The mean age of patients with ex was 63. Of the 13 patients with ex, 8 (61.5%) were male, and 5 (38.4%) were female.

Table 1. Demographic and Clinical Characteristics of The Patients

	Total Number of Patients (N=86)	**Intensive Care Patients (N=26)**	**Inpatients (N=60)**
Mean age (range)	60 (32-87)	64 (32-87)	58 (37-86)
Sex (%)			
Female	42 (48.8%)	9 (34.6%)	29 (50%)
Male	44 (51.16%)	17 (65.3%)	29 (50%)
Comorbid diseases (%)	50 (58.1%)	19 (73%)	31 (51.6%)
Hypertension	37 (43%)	15 (57.7%)	22 (6.6%)
Diabetes	19 (22%)	8 (30.8%)	11 (18.3%)
Chronic obstructive pulmonary disease	6 (7.0%)	4 (15.4%)	2 (3.3%)
Asthma	5 (5.8%)	3 (11.5%)	2 (3.3%)
CoronaryArtery Disease	5 (5.8%)	2 (7.4%)	3 (5%)

Table 2. Signs and Symptoms

Initial Symptoms	**Total Number of Patients (N=86)**	**Intensive Care Patients (N=26)**	**Inpatients (N=60)**
Cough	37	7	30
Dyspnoea	22	14	8
No obvious symptoms	18	0	18
Fever	15	4	11
Headache	5	3	2

The laboratory parameters of the COVID-19 patients hospitalized in service and intensive care units are shown in Table 3. While there were no significant differences in the leukocyte, thrombocyte, and erythrocyte counts of the patients, lymphocyte counts were found to be significantly lower in intensive care patients (1.12±0.54 × 109/L) than in inpatients (1.81±0.90 × 109/L; $p < 0.001$). The neutrophil-lymphocyte ratio was significantly higher in intensive care patients (5.74 [1.34–28.86]) than in inpatients (2.11 [0.64–9.14]; $p< 0.001$). Neutrophil counts were found to be significantly higher in intensive care patients than in inpatients (6.11 [1.18–19.70] × 109/L vs. 3.83 [1.51–12.07] × 109/L, respectively; $p = 0.007$). D-dimer levels were significantly higher in intensive care patients (482 [52–2522] µg/L) than in inpatients (249 [59–3561] µg/L; $p = 0.001$). C-reactive protein (CRP), an infection marker, was significantly higher ($p < 0.001$) in intensive care patients than in inpatients (91.8 [0.49–331.7] vs. 14 [0–161] mg/L, respectively). Pro-calcitonin was significantly higher ($p < 0.001$) in intensive care patients than in inpatients (0.19 [0–6.94) vs. 0.04 (0–0.86) µg/L, respectively).

Table 3. Laboratory Findings of Patients Infected with COVID-19

Laboratory Parameters	**Intensive Care Patients**	**Inpatients**	**p-value**
White blood cell count (10^9 /L)	8.81±5.11	6.80±2.73	0.068
Lymphocyte count (10^9 /L)	1.12±0.54	1.81±0.90	<0.001
Neutrophil count (10^9 /L)	6.11 (1.18-19.7)	3.83 (1.51-12.07)	0.007
Platelet count (10^9 /L)	235.9±97.9	242.2±90.6	0.770
Erythrocyte count (10^{12} /L)	4.34±0.89	4.68±0.49	0.073
N/L ratio	5.74 (1.34-28.86)	2.11 (0.64-9.14)	<0.001
D-dimer (µg/L)	482 (52-2522) (n=21)	249 (59-3561)	0.001
CRP (mg/L)	91.8 (0.49-331.7)	14 (0-161)	<0.001
Procalcitonin (µg/L)	0.19 (0-6.94)	0.04 (0-0.86)	<0.001 (n=37)

4. DISCUSSION

Our descriptive study was conducted by retrospectively evaluating the complaints, comorbid diseases, demographic data, and laboratory data of COVID-19 RT-PCR test-positive patients. CT was requested from the patients by evaluating their symptoms, such as fever and cough, and their contact with COVID-19 patients. The patients with CT findings compatible with COVID-19 were admitted to the COVİD-19 service unit.

The age range of the 86 patients included in the study was 32–87 years, and the mean age was 60. Evaluating the age range, we can say that COVID-19 affects not only the elderly population but also young people. The mean age of the intensive care patient group was 64 years, and the mean age of the inpatients was 58. The high mean age of intensive care patients suggests that comorbid diseases are more common in this patient group and that COVID-19 infection is more severe.

Of the 86 patients, 42 (48.8%) were female and 44 (51.2%) were male. Although the number of male patients was slightly higher, no significant difference was observed between the sexes. Examining the patients hospitalized in intensive care, we observed that 17 (65.3%) patients were male and 9 (34.6%) were female, and the high number of male patients was remarkable.

Of the 86 patients, 37 were admitted to the hospital with a cough, 22 with shortness of breath, and 15 with fever. As can be seen, the highest admission rate in patients was not due to fever. Fever, which is used as a diagnostic criterion for COVID-19 in the initial period of the disease, is insufficient on its own and does not initially occur in the majority of patients. In their study, Guan et al. showed that cough was the most common symptom, and fever symptoms were present in only half of the patients at the time of hospital admission (13).

Most patients in our study had chronic diseases. Fifty (58.1%) of the 86 patients presented with a comorbid disease: 37 (43%) had hypertension and 19 (22%) had diabetes mellitus, which were the most common comorbid diseases (Table 1). Recent evidence on COVID-19 has shown that comorbidities increase the risk of death in patients with COVID-19 (14,16). In their study, Qin et al. stated that 44% of the patients had at least one comorbid disease; among them, hypertension and cardiovascular disease were seen at a higher rate in severe cases, which showed that it mainly affects the elderly and men with comorbidities (15).

Patients with diabetes mellitus, hypertension, and severe obesity are more likely to be infected with COVID-19 and are at an increased risk of developing complications and death (14,18). According to a meta-analysis by Yang et al. (18), hypertension and diabetes were the most common comorbidities, followed by cardiovascular and respiratory diseases. In a meta-analysis by Parveen et al. (16), diabetes mellitus was less common in COVID-19 survivors than in those who died from COVID-19. However, no difference was found in diabetes mellitus comorbidity between the groups who required intensive care and those who did not (16,17, 18).

An increased leukocyte level suggests a bacterial infection, whereas a decreased lymphocyte ratio suggests a viral infection. One possible mechanism is that SARS-CoV-2 affects hematopoietic progenitor cells via CD13 or CD 66a or auto-antibodies and immunocomplexes. Another mechanism is that glucocorticoid use causes lymphopenia in some patients (19).

In our study, lymphocyte counts were significantly lower in intensive care patients (1.12±0.54 × 109/L) than in inpatients (1.81±0.90 × 109/L; p< 0.001). Qin et al. suggested that COVID-19 damages lymphocytes, especially T lymphocytes, and the immune system is impaired during this disease process (15). A significant elevation in leukocyte levels in patients with severe COVID-19 may indicate a poor clinical course and a risky situation. Survival in COVID-19 depends on the regenerative ability of the lymphocytes lysed by the virus. Therefore, lymphocyte counts, especially CD4 counts, may indicate disease severity and prognosis (20).

SARS-CoV-2 causes alveolar damage and microvascular thrombi in the human body by targeting pneumocytes, immune cells, and vascular endothelial cells. In coagulopathies caused by COVID-19, D-dimer, vWF, and fibrinogen levels are found to increase, whereas PT, APTT, and platelet levels are relatively normal (21). Zhou et al. suggested that advanced age and D-dimer levels > 1 μg/mL are associated with the risk of death in hospitalized patients (22). Tang et al. found that abnormal coagulation tests and significantly increased levels of D-dimer and fibrin degradation products were associated with the risk of death in COVID-19 patients (23). Yao et al. concluded that significantly high D-dimer values in SARS-CoV-2 patients are predictive for the risk of death, especially in critically ill patients (24).

In this study, D-dimer levels were significantly higher in intensive care patients than in inpatients (p = 0.001). We conclude that regular follow-up of D-dimer levels in intensive care patients will be beneficial, both in the treatment process and in guiding prognosis.

CRP production is an acute phase response to inflammation, infection, and tissue damage. CRP alone is not diagnostic; hence, it should be evaluated with other clinical and pathological results (25). As a result of inflammatory stimulation, hepatocytes release CRP, facilitating complement activation by binding to eukaryotic and prokaryotic pathogens and initiating immunological processes such as immune activation and lymphocyte infiltration. Clinically, increased CRP levels may be an early indicator of nosocomial infections in COVID-19 patients (26).

In their study, Xiong et al. found that sedimentation rate, CRP, and lactate dehydrogenase (LDH) levels were significantly correlated with severe pneumonia detected during initial CT in COVID-19 patients (9). Guan et al. found that patients with severe COVID-19 had higher CRP and LDH levels than those in the mild group (13). Liu et al. showed that COVID-19 patients with CRP > 41.8 mg/L were more likely to be in the severe patient group (27). In our study, CRP values were found to be significantly higher at 91.8 (0.49–331.7) mg/L in intensive care patients than in inpatients with 14 (0–161) mg/L (p < 0.001). Monitoring serum CRP levels is an important criterion for the course and worsening of the disease.

Procalcitonin is synthesized in parafollicular thyroid cells and is a precursor of the hormone calcitonin; however, it is also synthesized by most non-thyroid tissues during bacterial infections. In their meta-analysis, Lippi et al. suggested that serial measurements of procalcitonin levels would help to demonstrate the development of more severe disease. Increased IL-1β, TNF-α, and IL-6 levels in bacterial infections increase the synthesis of procalcitonin and its release into the circulation outside the thyroid tissue. In viral infections, IFN-γ synthesis, which suppresses procalcitonin synthesis, increases (28, 29). Zhang et al. suggested that CRP, procalcitonin, D-dimer levels, and leukocyte counts were higher in the severely ill group. High procalcitonin and leukocyte levels resulted from secondary bacterial

infection (30). In our study, procalcitonin was found to be significantly higher in intensive care patients (0.19 [0–6.94] µg/L) than in inpatients (0.04 [0–0.86] µg/L) $p<0.001$.

In this process, 13 of 86 patients died, and the mean age of these patients was 63. Of the 13 patients with ex, 8 (61.5%) were male and 5 (38.4%) were female. The mean hospitalization period was 16 (5–63) days.

Our study had some limitations. First, this single-center study included only 86 RT-PCR (+) patients, and the total number of cases was relatively low. Second, as our study was retrospective, regular follow-up of laboratory parameters could not be achieved.

5. CONCLUSION

Consequently, COVID-19 remains a serious threat to global health. With normalization in our country, the number of patients is increasing, and there is a serious need for more intensive care units. In this process, laboratory parameters are important for identifying patients who need intensive care. In our study group, we observed that the mean age of intensive care patients was high, comorbid diseases were high in these patients, and the male sex was predominant. Comorbid diseases mainly consisted of hypertension and diabetes mellitus. Lymphopenia, increased neutrophil levels, neutrophil-to-lymphocyte ratios, D-dimer, CRP, and procalcitonin levels are remarkable in intensive care patients. More precise results can be obtained by planning prospective studies on these parameters in larger study groups.

Ethicial Considerations

For this study, the necessary permissions were obtained from the İKCU Non-Invasive Clinical Research Ethics Committee (Decision No: 1000, Date: 10/22/2020) and the T.C. Ministry of Health, General Directorate of Health Services (Leyla Demir-2020-06-04T10_05_06).

Conflict of Interest

The authors have no conflicts of interest to declare.

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