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The Effect of Anesthesia and Surgery on Post-Operative Lymphocyte Count, Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratio in Covid-19 Patients

Covid-19 Hastalarında Anestezi ve Cerrahinin Postoperatif Lenfosit Sayısı, Nötrofil-Lenfosit ve Platelet-Lenfosit Oranına Etkisi

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ABSTRACT

Objectives: Anesthesia applications and surgery can cause not only immediate immune dysfunction, but also an early systemic inflammatory response. Therefore, they can adversely affect the course of coronavirus disease 2019 (COVID-19). In our study, we aimed to retrospectively evaluate the effect of anesthesia and surgical procedures on lymphocyte count, neutrophil- and platelet-lymphocyte ratios (PLR), and post-operative prognosis in COVID-19 patients undergoing emergency surgery.

Methods: The demographic, clinical, and laboratory data of 14 patients with pulmonary involvement suggestive of COVID-19 in computed tomography performed preoperatively and who were taken to emergency surgery were examined. Pre- and post-operative total leukocyte, neutrophil, lymphocyte counts, neutrophil-lymphocyte ratio (NLR) and PLR, C-reactive protein, lactate dehydrogenase, ferritin, liver enzymes and kidney function test results, post-operative complications, intensive care (ICU) admission, and presence of mortality were examined.

Results: In the pre-operative period, 28.6% patients were symptomatic and 75% of these patients had fever. There was a significant decrease in lymphocyte counts in the first 24 h postoperatively compared to the pre-operative period ($p<0.028$). There was no significant change in NLR, PLR, and other parameters. In these patients, post-operative complications were 35.5%, pulmonary complications were 21.4% (acute respiratory distress syndrome 7.1%, pneumonia 14.3%), ICU admission was 50%, and mortality was 24%.

Conclusion: In the early post-operative period after anesthesia and surgery in COVID-19 patients with pulmonary involvement who undergo emergency surgery, lymphocyte count is affected more severely compared to NLR and PLR and decreases significantly. In these patients with impaired immune response, anesthesia and emergency surgical interventions may increase the risk of post-operative pulmonary complications and mortality.

Keywords: Anesthesia COVID-19; lymphocytes; neutrophils; pneumonia.

ÖZET

Amaç: Anestezi uygulamaları ve cerrahi sadece ani immün disfonksiyona neden olmakla kalmayıp, aynı zamanda erken bir sistemik inflamatuar yanıta da neden olabilmektedir. Bu nedenle coronavirus hastalığı 2019'un (COVID-19) seyrini olumsuz etkileyebilirler. Çalışmamızda acil cerrahi uygulanan COVID-19 hastalarında anestezi ve cerrahi işlemlerin lenfosit sayısı, nötrofil-lenfosit ve trombosit-lenfosit oranları ve postoperatif prognoz üzerine etkisini retrospektif olarak değerlendirmeyi amaçladık.

Yöntem: Preoperatif olarak yapılan bilgisayarlı tomografide COVID-19'u düşündüren akciğer tutulumu olan ve acil cerrahiye alınan 14 hastanın demografik, klinik ve laboratuvar verileri incelendi. Ameliyat öncesi ve postoperatif dönemdeki toplam lökosit, nötrofil, lenfosit sayıları, nötrofil-lenfosit oranı (NLR) ve trombosit -lenfosit oranı (PLR), C-reaktif protein (CRP), laktat dehidrojenaz, ferritin, karaciğer enzimleri ve böbrek fonksiyon testi sonuçları, postoperatif komplikasyonlar, yoğun bakıma (YBÜ) yatış ve mortalite varlığı incelendi.

Bulgular: Preoperatif dönemde hastaların %28.6'sı semptomatikti ve bu hastaların %75'inde ateş vardı. Ameliyat sonrası ilk 24 saatte lenfosit sayısında ameliyat öncesi döneme göre anlamlı düşüş vardı (p <0,028). NLR, PLR ve diğer parametrelerde anlamlı bir değişiklik yoktu. Bu hastalarda postoperatif komplikasyonlar %35.5, pulmoner komplikasyonlar %21.4 (akut solunum sıkıntısı sendromu %7.1, pnömoni %14.3), YBÜ yatışı %50 ve mortalite %24 idi.

Sonuç: Acil cerrahi uygulanan akciğer tutulumu olan COVID-19 hastalarında anestezi ve ameliyat sonrası erken postoperatif dönemde lenfosit sayısı NLR ve PLR'ye göre daha şiddetli etkilenmekte ve anlamlı olarak azalmaktadır. Bozulmuş immün yanıtı olan bu hastalarda anestezi ve acil cerrahi müdahaleler, postoperatif pulmoner komplikasyon ve mortalite riskinin artmasına neden olabilir.

Anahtar sözcükler: Anestezi COVID-19; lenfosit; nötrofil; pnömoni.

In December 2019, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly all over the world after it emerged in Wuhan, China. COVID-19 often includes signs of fever, dry cough, dyspnea, myalgia, fatigue, lymphopenia, and radiographic pneumonia. In the advanced stages of the disease, acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute cardiac damage, secondary infections, acute kidney damage, and death in severe cases may occur.[1] Lymphopenia, increased leukocyte and neutrophil count, increased C-reactive protein (CRP) and cytokine levels in these patients are among the laboratory abnormalities encountered and are associated with the severity of the disease.[1,2]

Surgery and anesthesia not only cause immediate immune dysfunction but also induce an early systemic inflammatory response.[3] Therefore, anesthesia and surgical interventions can adversely affect the course of COVID-19. COVID-19 can also increase macrophage and neutrophil infiltration and proinflammatory cytokine levels in the infected lung. Studies have reported that surgeries performed in the incubation period or in the presence of mild disease worsen the clinical symptoms and prognosis.[1,4] Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are simple markers that can be measured in the peripheral blood to evaluate the inflammatory response and physiological stress. It has been shown that high NLR levels are associated with the severity and prognosis of the disease in COVID-19 cases.[5,6]

In the present study, we aimed to retrospectively evaluate the effect of anesthesia and surgical procedures on total leukocyte, lymphocyte count, NLR, and PLR in the COVID-19 patients who underwent emergency surgery. We further assessed the post-operative prognosis in these patients.

Methods

This single-center study was conducted after approval was obtained from the Ministry of Health and from the local ethics committee (FSM EAH-KAEK 2021/12). The data of 22 adult patients who had lung involvement suggestive of COVID-19 in computed tomography (CT) examination during pre-operative evaluation (multifocal and peripheral ground glass pattern), whose polymerase chain reaction (PCR) test was positive or negative, and who were taken to emergency surgery with general anesthesia between 01 April, 2020, and 31 December, 2020, were retrospectively analyzed. Since post-operative follow-up data of eight patients were not available, 14 patients (who were treated as COVID-19 infection) were included in the study. Demographic data (age, gender, body weight, the American Society of Anesthesiologists (ASA) scores, current comorbid diseases, thoracic CT reports pertaining to the pre-operative period, type of surgery and anesthesia performed, duration of operation and anesthesia) and clinical data (presence of pre-operative COVID-19 symptoms, post-operative respiratory complications, presence of post-operative secondary infection, durations of post-operative intensive care and hospital stay, post-operative 30-day mortality) of the 14 patients were recorded. Fever (measurement from the forehead region, values of 38°C and above), dry cough and desaturation (peripheral oxygen saturation below 93) were accepted as clinical symptoms of COVID-19. Total leukocyte (WBC), neutrophil and lymphocyte counts, and NLR, and PLR were analyzed from blood samples taken preoperatively and post-operative 4^{th} and post-operative 24^{th} h in the biochemistry laboratory of our hospital with standard methods (Mindray BC 6800 blood count device, 2017, China). CRP, aspartate amino-

transferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen, creatinine and ferritin values were recorded during the same time period. Since the blood samples of the patients are evaluated in the 4^{th} and 24^{th} h postoperatively in routine practice, these test results were assessed in our study pre- and post-operative laboratory data were statistically compared.

As a routine practice in our clinic, a combination of PCR test, non-contrast thoracic tomography and laboratory data were used in the pre-operative period to evaluate the COVID-19 status in emergency or elective cases. Nasal and pharyngeal swabs were used for COVID-19 screening by PCR. Due to the emergency nature of the cases, the patients were taken for surgery after evaluating the thoracic CT and laboratory data without waiting for the PCR results. The patients with unknown PCR results but with involvement suggestive of COVID-19 in their thoracic CT were considered COVID-19-infected and were taken to the operating room with the necessary isolation measures. The PCR results of these patients were followed up, and test was repeated at the post-operative 24^{th} h in patients whose first result was negative. Appropriate antibiotic therapy according to the type of surgery and antiviral therapy for COVID-19 treatment were initiated in all patients in the early post-operative period.

Statistical Analysis

Conformity of the data to normal distribution was examined by Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation and median (minimum–maximum) for quantitative data. Qualitative data were presented as frequency and percentage. The Wilcoxon signed rank test was used to compare dependent samples. The level of significance was determined as $\alpha = 0.05$. Statistical analysis was performed using IBM SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) statistical package program.

Results

The data of the 14 patients were examined in our study. The pre-operative PCR test positivity rate was 28.6%. In the pre-operative period, 28.6% of the patients were symptomatic, and among the symptomatic patients, 75% had fever. Fever and cough were present in one patient, fever was present in two patients and cough was present in one patient. Desaturation was not observed in any patient. In a symptomatic (fever) patient, the pre-operative PCR test was (+). At least one comorbid disease history was observed in 78.6% of the patients. The rate of two or more comorbid diseases was 28.6% (Table 1).

The post-operative complication rate was 35.5%. Post-operative pulmonary complication rate was 21.3% (Table 2).

The characteristics of three patients who developed respiratory complications between post-operative days 3 and 10 are given in Table 3.

Table 1. Demographic data, presence of pre-operative symptoms, PCR results, anesthesia type, surgery type and duration

Parameters	Mean±SD (n=14)
Age (Years)	59.64±19.31
Gender (F/M) n (%)	8 (57.1)/6 (42.9)
ASA Score: n (%)	
1 and 2	3 (21.4)
3	8 (57.1)
4	3 (21.4)
Duration of Operation (min)	129.29±81.37
Anesthesia Duration (min)	153.21±89.37
PCR (±) n (%)	4 (28.6)/10 (71.4)
Pre-operative Symptom: n (%)	
Asymptomatic	10 (71.4)
Symptomatic (Fever, Cough)	4 (28.6)
Presence of Comorbid Disease: n (%)	11 (78.6)
Diabetes Mellitus	4 (28.6)
Hypertension	8 (57.1)
Coronary Artery Disease	3 (21.4)
Other (COPD, SVO, Akc. Ca)	3 (21.4)
Surgery Type: n (%)	
Intracranial	5 (35.7)
Abdominal	4 (28.6)
Other (Urological, Head and Neck, Orthopedics)	5 (35.7)

Values are presented as mean±SD or frequency and percentage. PCR: Polymerase chain reaction; ASA: American Society of Anesthesiologists.

Table 2. Post-operative complications

Post-operative complication	
ARDS n (%)	1 (7.1)
Secondary bacterial pneumonia n (%)	2 (14.3)
Surgical site infections n (%)	2 (14.3)
Post-operative ICU admission n (%)	7 (50)
Post-operative ICU stay (Day) Mean±SD	2.78±6.37
Length of hospital stay (Day) Mean±SD	10.21±7.78
Post-operative 30-day mortality n (%)	3 (21.4)

Values are presented as mean±SD or frequency and percentage. ARDS: Acute respiratory distress syndrome; ICU: Intensive care.

Table 3. Characteristics of patients with post-operative respiratory complications

Operation Type	Operation Time	Age/Gender	ASA	Comorbid Disease	PCR	Pre-operative Symptom	Post-operative Complication	Mortality
Intracranial bleeding/craniectomy	170 Min	67 M	3	SVO	+	Fever	Post-operative 3rd Day ARDS ICU admission	+
Intracranial mass/craniectomy	155 Min	53 M	3	Lung Cancer Remission	–	No symptoms	Post-operative 3rd Day Respiratory Distress/Viral+ Bacterial Pneumonia ICU Admission	+
Ileus/bowel resection	150 Min	65 F	3	HT	+	No symptoms	Post-operative 10th Day Respiratory Distress/ Secondary Bacterial Pneumonia ICU Admission	+

GA: General Anesthesia; M: Male; F: Female; SVO: Cerebrovascular occlusion; HT: Hypertension; MV: Mechanical ventilation; ICU: Intensive Care Unit. ASA: American Society of Anesthesiologists scores; PCR: Polymerase chain reaction; ARDS: Acute respiratory distress syndrome; Min: Minutes.

When the total leukocyte, neutrophil, lymphocyte, NLR, PLR, and CRP values were compared, a significant decrease was observed in the lymphocyte count in the post-operative period compared to the pre-operative values. Pre- and post-operative AST, ALT, urea, creatinine, LDH and ferritin values of the patients were similar (Table 4).

Discussion

In the present study, while there was no significant change in NLR, PLR, and CRP in the first 24 h postoperatively, there was a significant decrease in lymphocyte counts in patients who underwent emergency surgery and were suspected to have COVID-19 in pre-operative evaluation. We observed that post-operative respiratory complications, intensive care (ICU) admission rates and mortality were high in these patients with pulmonary involvement suggestive of COVID-19 in CT performed during pre-operative evaluation (CT image in multifocal, bilateral, and peripheral ground glass pattern).

In our patients, the reasons for admission to the hospital were pathologies requiring emergency surgery, and 28.6% of them had symptoms compatible with COVID-19 during the initial evaluation. Similar to other studies in the literature, the most common symptom was fever, which was observed in 75% of the patients.[6,7] Furthermore, 78.6% of our patients

Table 4. Total leukocyte count, neutrophil, lymphocyte, NLR, PLR, and CRP Values, AST, ALT, urea, Creatinine, LDH and ferritin values

	Pre-operative Med (min–max)	Post-operative 4th h Med (min–max)	Post-operative 24th h Med (min–max)	P1	P2
WBC 10^3/uL	12 (6.4–21.2)	11.6 (5.6–18.3)	11.4 (6.1–19)	0.777	0.780
NEU 10^3/uL	9.6 (4.6–19.7)	9.8 (4.4–15.8)	9.3 (5.2–16.2)	0.683	0.484
LYM 10^3/uL	1.1 (0.4–3.55)	0.9 (0.3–3.2)	0.9 (0.5–2.2)	0.039 *	0.028 *
NLR	9 (1.5–49.2)	8.9 (3.4–50)	9.5 (4.6–26.2)	0.245	0.279
PLR	216 (71–643)	257 (52–630)	246 (96–523)	0.258	0.382
CRP mg/L	13.2 (0.1–30.1)	13.3 (0.5–28)	15 (0.87–34)	0.701	0.071
AST U/L	19.5 (11–37)	19 (12–43)	20 (13–56)	0.478	0.293
ALT U/L	15 (13–76)	18 (10–71)	20 (11–64)	0.220	0.609
Urea mg/dL	16 (7–51)	15.5 (4–54)	16 (3–64)	0.686	0.694
Creatinine mg/dL	0.8 (0.6–2.9)	0.7 (0.6–2.4)	0.7 (0.6–2.9)	0.510	0.363
LDH U/L	198 (151–315)	204 (129–300)	206 (117–298)	0.080	0.715
Ferritin ng/mL	190.43 (45.78–657)		186.95 (58.9–827)		0.091

*p<0.05. P1Comparison of pre- and post-operative 4th h values, P2Comparison of pre- and post-operative 24th h values. WBC: Total leukocyte count, NEU: Neutrophil, LYM: Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, CRP: C-reactive protein, AST: Aspartate amino transferase, ALT: Alanine amino transferase, LDH: Lactate dehydrogenase.

had at least one comorbid disease, and 28.6% had two or more comorbid diseases. Consistent with the literature, the most common comorbid disease was hypertension.[7]

NLR and PLR are parameters that demonstrate the degree of systemic inflammation and the severity of various diseases.[8-10] In a study involving healthy individuals, the basal values of NLR and PLR were reported to be 1.6 and 132.4, respectively, and in another study, the physiological value of NLR was reported to be 1.8–2.2 and the pathological value of NLR as <0.7 and >2.5.[11,12] There are studies showing that NLR is an important factor in determining the severity of the disease in COVID-19 patients.[6,10] It was reported that deep lymphopenia, increased NLR, PLR (threshold value NLR, PLR 3.3, 180), CRP and leukocytosis were observed in severe COVID-19 pneumonia cases when compared to mild-moderate cases, and NLR was a prognostic parameter in COVID-19 pneumonia.[6] In another study, it was reported that there was a significant increase in NLR, PLR, LDH and ferritin levels together with significant lymphopenia in COVID-19 (+) patients compared to COVID-19 (–) patients, and again, NLR was an important parameter in the diagnosis of the disease.[13] Consistent with the mild COVID-19 pneumonia cases reported in existing studies, in our study, the mean lymphocyte values were normal-low and total leukocyte, NLR and PLR levels were high in the pre-operative period. There was a slight increase in CRP, LDH and ferritin levels.

Leukocyte, lymphocyte, NLR and other inflammatory parameters are influenced by the effects of anesthesia and surgery on the systemic inflammatory response.[13-15] The NLR can also be evaluated as an indicator of prognosis in critically ill patients after surgery and in intensive care.[8,16] In a meta-analysis, it was documented that increased NLR values in the pre-operative period were associated with increased post-operative complications and mortality.[17] In another study, it was shown that increased NLR (critical value NLR >5.5) rates in the post-operative period when compared to the pre-operative period in patients who underwent abdominal surgery were associated with increased complications and mortality in the 1st post-operative week.[15] We did not observe a significant change in the post-operative total leukocyte, NLR and PLR ratios in our patients compared to the pre-operative period. However, we observed a significant decrease in lymphocyte counts in the post-operative period. Although our findings are in this direction, comparative studies may be needed to determine the direct effect of surgery and anesthesia, since the decrease in lymphocyte count in COVID-19 is an expected finding.

Studies have reported that post-operative pulmonary complications are observed at a frequency of 8% and that mortality due to such complications is noted at a frequency of 2–3% in the normal population.[18,19] In a study involving COVID-19 patients, when compared to non-operated ones, elective and emergency surgical procedures were found to increase the risk of post-operative pulmonary complications (ARDS 32.4%), ICU admission (44.1%), and mortality rates (20.6%).[1] In another study, it was shown that 40% of the COVID-19 patients developed pneumonia and 14.3% developed ARDS after emergency surgery, and the post-operative 30-day mortality was 25.6%. In this study, it was reported that pulmonary complications and mortality rates were higher in patients with ASA score ≥3 who underwent elective or emergency surgery.[20] In the present study, we found that the rate of post-operative ICU admission was 50%, and the rate of post-operative respiratory complications was 21.4% (ARDS 7.1%, pneumonia 14.3%). All of our patients with post-operative pulmonary complications had an ASA score of 3, resulting in a poor prognosis. The post-operative 30-day mortality rate was 21.4%. Although our ARDS rates were lower than those in previous studies, ICU admission and mortality rates were comparable. We consider that our ARDS rates were lower since our patients were at the initial stage of COVID-19 pneumonia in the preoperative period and were mostly clinically asymptomatic.

We think that this study, in which we have shared our clinical experience, will be useful in the pre- and post-operative evaluations of similar cases during the on-going COVID-19 pandemic. Our study has some limitations. Since the patient group was specific, the number of cases was low. Elective surgeries were stopped in our centre during the pandemic, and the study sample only included patients with involvement suggestive of viral pneumonia on tomography and who underwent emergency surgery. We believe that this study will be a guide for our work with higher numbers. Another limitation was that the study was limited to the laboratory findings in the first 24 h postoperatively since some of our patients were discharged early. Laboratory data analysis covering a wider post-operative period would have been more useful in evaluating the prognosis. Another limitation was that the present symptoms and laboratory parameters of the patients were not evaluated according to the existing pathology that required emergency surgery.

Conclusion

In the early post-operative period after anesthesia and surgery in the COVID-19 patients with pulmonary involvement who undergo emergency surgery, the lymphocyte count is affected more severely than NLR and PLR and decreases significantly. It seems that the risk of post-operative pulmonary complications and mortality has increased in the COVID-19 patients undergoing emergency surgery and anesthesia, but since there are many unknowns about COVID-19, we believe this issue will be better understood with larger studies.

Disclosures

Ethics Committee Approval: Ethics committee approval was received from the Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (KAEK-2021/12).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – Ö.D., S.A.; Design – Ö.D., S.A.; Supervision – Ö.D., S.A.; Materials – Ö.D.; Data collection &/or processing – Ö.D.; Analysis and/or interpretation- Ö.D.,S.A.; Literature search – Ö.D.; Writing – Ö.D.,S.A.; Critical review – Ö.D., S.A.

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