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Research Article / Araştırma

Causes of COVID-19's Mortality and Prognostic Effect of Neutrophile-Lymphocyte Ratio

COVID-19 Mortalitesinin Nedenleri ve Nötrofil-Lenfosit Oranının Prognostik Etkisi

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ABSTRACT

Objectives: In this study, we aimed to investigate the prognostic value of the neutrophile-lymphocyte ratio and the effects of age, gender, and comorbidities on mortality.

Methods: In our study, 100 patients who had a ground-glass opacification on computed thorax tomography and who had a positive polymerase chain reaction test were included in our study. Demographic data, laboratory data and comorbidities of the patients were recorded.

Results: Sixty-five (65%) of the patients participating in the study were male. The mean age of the patients was 66 (21.5). The mortality rate was found to be 27% (n=27) High neutrophile-lymphocyte ratio, low lymphocyte count, high urea, and creatin levels were significant in terms of mortality. In addition, advanced age, diabetes mellitus, and hypertension are other factors that have an impact on mortality.

Conclusion: The neutrophile-lymphocyte ratio can solely be used as a prognostic marker because it is simple and economical.

Keywords: COVID-19, mortality, neutrophile-lymphocyte ratio

ÖZ

Amaç: Bu çalışmada nötrofil-lenfosit oranının prognostik değerini ve yaş, cinsiyet ve komorbiditelerin mortalite üzerine etkisini araştırmayı amaçladık.

Yöntem: Çalışmamıza bilgisayarlı toraks tomografisinde buzlu cam opasifikasyonu olan ve Polimeraz Zincir Reaksiyonu (PCR) testi pozitif olan 100 hasta dahil edildi. Hastaların demografik verileri, laboratuvar verileri ve komorbiditeleri kaydedildi.

Bulgular: Çalışmaya katılan hastaların 65'i (%65) erkekti. Hastaların yaş ortalaması 66 (21,5) idi. Mortalite oranı %27 olarak bulundu (n=27) Yüksek nötrofil-lenfosit oranı, düşük lenfosit sayısı, yüksek üre ve kreatin seviyeleri mortalite açısından anlamlıydı. Ayrıca ileri yaş, diabetes mellitus ve hipertansiyon da mortaliteyi etkileyen diğer faktörlerdir.

Sonuç: Nötrofil-lenfosit oranı basit ve ekonomik olduğu için yalnızca bir prognostik belirteç olarak kullanılabilir.

Anahtar sözcükler: Covid-19, mortalite, nötrofil-lenfosit oranı

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Introduction

The COVID-19 pandemic has caused millions of people to get sick and die worldwide. The COVID-19 virus progresses as asymptomatic or mild upper respiratory tract infection in most patients. In some of the patients, it causes severe clinical conditions or even death. Although there are some theories about which patients monitored in the intensive care unit died from the COVID-19 infection, information on this subject is limited. Determining the causes affecting mortality and planning the treatments correctly will contribute to reducing mortality and long-term disability and confinement to bed. In addition, it will enable effective usage of hospitals' intensive care unit bed capacities that are insufficient due to the pandemic.

Many methods are used to determine mortality and the course of the disease for patients monitored in intensive care unit. The neutrophil to lymphocyte ratio (NLR) also stands out as one of the methods used to predict the intensive care prognosis. NLR is basically an indicator of the immune system response and is used as a prognostic criterion for many diseases such as cancers, Behcet's disease, and coronary artery diseases.[1-3] Its use is increasing because it can be calculated easily and does not require additional costs. Although there are studies on the role of NLR in the mortality prediction of COVID-19 in the literature, their number is insufficient.

In our study, we aimed to investigate the relationship of lymphocytopenia and the NLR with mortality and the factors affecting mortality in COVID-19, which is a viral infection.

Methods

This study, which was planned to be retrospective, randomized and cross-sectional, was initiated in accordance with the Helsinki Declaration and the Strobe checklist after obtaining the informed consent of the local ethics committee, dated 22.04.2021 and numbered 2021/10. 100 patients over 18 years of age who were monitored in Malatya Training and Research Hospital with the diagnosis of COVID-19 between January 1, 2020, and December 31, 2020, were included in the study. Patients that had ground-glass opacification on computed thorax tomography during the study and positive polymerase chain reaction test results were included in the study. The sample size of the study was calculated as 100 patients with an alpha error of 0.05 and a beta error of 0.2 with reference to similar studies. Pediatric patients, pregnant women, patients who did not agree to participate in the study by themselves or their relatives, and patients diagnosed with COVID-19 after hospitalization were not included in the study. The demographic data (age, sex) of the patients, comorbidities and mortality status within 28 days (4 weeks) were recorded. In addition, the hemogram parameters (neutrophil, lymphocyte, thrombocyte, NLR, etc.), biochemical parameters (urea, creatinine, albumin, ferritin, creatine kinase (CK), taken on the day of hospitalization, Aspartate aminotransferase (AST), Alanine Aminotransferase (ALT), etc.), and coagulation parameters (D-dimer, fibrinogen, INR) were measured and recorded. References for this study were searched using indexes such as Pubmed, Google scholar, TRDizin.

For statistical analysis and calculations, IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used. Number (n) and percentage (%) were used to show the distribution of demographic data. The Chi-square test and laboratory data were used in the analysis of categorical variables, and the T-Test or Mann-Whitney U test was used in the analysis of numerical data considering the distribution of the data. In all statistical calculations, $p<0.05$ was considered statistically significant.

Results

Sixty-five (65%) of the patients participating in the study were male. The mean age of the patients was 66 (21.5). The mortality rate was found to be 27% (n=27). The mortality rate increased as the age advanced ($p<0.001$). Considering the presence of comorbid diseases, diabetes mellitus (DM) ($p=0.004$) and hypertension (HT) ($p=0.008$) were the diseases that significantly increased mortality. Demographic data and comorbidities are given in Table 1.

When hemogram parameters are examined, it is seen that low lymphocyte ($p=0.006$) and increase in the NLR ($p=0.001$) are associated with mortality. The effect of other parameters (eosinophil, thrombocyte, mean platelet volume, etc.) on mortality was not significant ($p>0.05$). In the analysis of biochemical parameters, mortality was higher in patients with high urea ($p=0.012$) and high creatinine ($p=0.018$). In addition, high fibrinogen levels among hemostasis parameters were found to increase mortality ($p=0.018$). There was no significant correlation between other biochemical parameters (albumin, ferritin, CK, AST, ALT, etc.) and mortality ($p>0.05$). Laboratory parameters are given in Table 2.

Discussion

One of the most important health problems of the current century is undoubtedly the COVID-19 pandemic. More than 110 million people were affected and about 2.5 million people, unfortunately, lost their lives. Therefore, prognosis and mortality prediction is very important for planning treatment and ensuring the qualified use of health facilities. The NLR has been used increasingly in recent years

Table 1. Analysis of age and laboratory data

	Discharge (Median+IQR)	Exitus (Median+IQR)	Total (Median+IQR)	p
Age	64 (23.5)	77 (18.5)	66 (21.5) (iq)	**0.000**
RCB	4.3 (1)	4.2 (0.9)	4.3 (0.9)	0.138
Neutrophils	6.8 (5.1)	9 (7.8)	7.1 (5.7)	**0.031**
Lymphocytes	0.9 (0.8)	0.6 (0.7)	0.8 (0.7)	**0.006**
NLR	7.7 (9.8)	15.5 (22.2)	8.9 (12.6)	**0.001**
Eosinophiles	0.01 (0.09)	0.00 (0.01)	0.00 (0.05)	**0.014**
MCV	85.1 (6.2)	84.9 (6.7)	85 (6.5)	0.861
MCH	28.4 (2.8)	27.9 (3.6)	28.4 (2.9)	0.923
MHCH	33 (2.7)	33.5 (1.7)	33.4 (2.2)	0.426
RDW (%)	13.6 (1.6)	13.7 (2.3)	13.6 (1.7)	0.883
Hemoglobin	13 (2.5)	12.6 (2.8)	12.9 (2.5)	0.579
Hematocrit	38.8 (6.6)	37.1 (6.9)	38.5 (6.6)	0.537
Platelets	227000 (106250)	206000 (138500)	220000 (115500)	0.287
PDW	11.3 (3)	11.9 (1.7)	11.5 (2.4)	0.765
MPV	10.3 (1.2)	10.4 (1.3)	10.3 (1.2)	0.697
LDH	431 (267.8)	532 (263)	441 (287.3)	0.132
Ferritin	463 (679.7)	581.8 (596)	472.5 (664.2)	0.196
Fibrinogen	457.3 (367.7)	653.2 (302.3)	500.6 (366.3)	**0.018**
D-Dimer	0.9 (1.9)	0.8 (0.8)	0.8 (1.6)	0.442
INR	1.2 (0.2)	1.2 (0.1)	1.2 (0.2)	0.792
Urea	46 (35.8)	63 (61.8)	48 (39)	**0.012**
Creatinine	0.8 (0.3)	1 (0.7)	0.9 (0.4)	**0.015**
AST	39 (36.5)	48 (28)	40.5 (34.3)	0.163
ALT	29 (27.5)	32 (27.5)	29 (29.3)	0.273
Creatine Kinase	72 (117.8)	85.3 (260.8)	77.6 (156.6)	0.404
Albumin	3 (0.8)	3 (0.6)	3 (0.7)	0.317

Values are median and IQR. P<0.05 was considered statistically significant. IQR: Interquartile range; RCB: Red blood cells; NRL: Neutrophil to lymphocyte ratio; MCV: Mean corpuscular volume; MCH: Mean concentration hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell volume distribition width; PDW: Platelet distribution width; MPV: Mean platelets volume; LDH: Lactate dehydrogenase; INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

due to its ease of use and simplicity. Lagunas-Rangel stated in his meta-analysis study on 828 patients that NLR would be a signal of poor prognosis.[4] As a result of our study, we found that NLR was a reliable indicator for predicting prognosis and mortality in COVID-19 disease.

Many diseases, especially infection, cause immune system activation. NLR is also an important indicator of this systemic activation[5,6] Just like any other infection, COVID-19 viral infection activates the immune system and develops leukocytosis. In COVID-19 cases with a mild clinical course, lymphocyte levels are usually normal or increased. In cases, such as acute respiratory distress, where the clinical course is aggravated, lymphocytopenia occurs and NLR increases. [7,8] Forget et al. [9] reported in their study on 413 patients that the normal value of NLR was 0.78 and 3.53. Lymphopenia is rather observed on $CD4^+$ T and $CD8^+$ T cells. On B-type lymphocytes and natural killer cells, lymphopenia is not observed, on the contrary, there is an increase.[10] Bone marrow examinations also support this reduction.[11] The reason for this decrease is thought to be caused by increased cytokine levels (IL6, IL10. IL2 and IFN etc) and lymphocytes accelerating apoptosis. This increase in cytokines also causes an increase in lung damage caused by an increase in neutrophils. [10,12] In severe cases, the increased immune response causes cytokine storms, causing systemic inflammatory response syndrome. The use of arginine increases. Arginine is the basic building block for nitric oxide, which has an antiviral effect.[13] Increasing consumption decreases arginine level and decreases nitric oxide production.[14] Although nitric oxide is used in the treatment in severe cases, there are not enough studies on its effectiveness. During the course of COVID-19, secondary infection is frequently seen, especially in severe cases. Due to secondary infections, the increase in neutrophile and even more increased cytokines contribute to lung damage and a decrease in lymphocyte levels. In our study, lymphocytopenia and an increase in NLR were associated with mortality in accordance with the literature.

Table 2. Statistical analysis of gender and comorbid diseases

Parameter	Discharge (n)	Exitus (n)	Total (n)	p	Odds ratio
Gender					
Male	44	21	65	0.103	0.4 (0.2-1.2)
Female	29	6	35	-	-
Malignancy					
None	73	27	99	-	-
CKD					
None	71	25	96	0.120	5.7 (0.5-65.4)
Yes	1	2	3	-	-
Alzheimer					
None	72	26	98	0.459	2.8 (0.2-45.9)
Yes	1	1	2	-	-
CVD					
None	72	27	99	0.541	-
Yes	1	0	1	-	-
DM					
None	59	14	73	**0.004**	3.9 (1.5-10.2)
Yes	14	13	27	-	-
COPD					
None	60	24	84	0.417	0.6 (0.2-2.2)
Yes	13	3	16	-	-
HT					
None	46	9	55	**0.008**	3.4 (1.3-8.6)
Yes	27	18	45	-	-
CHF					
None	67	24	91	0.654	1.4 (0.3-6.0)
Yes	6	3	9	-	-
IHD					
None	62	20	82	0.210	2.0 (0.7-5.8)
Yes	11	7	18	-	-
Arrhythmia					
None	71	27	98	0.385	0.7 (0.6-0.8)
Yes	2	0	2	-	-

P<0.05 was considered statistically significant. CKD: Chronic renal failure; CVD: Cerebrovascular disease; IHD: ischemic heart disease; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; HT: Hypertension; CHF: Congestive heart failure.

In general, age is an important cause of mortality for many diseases. COVID-19 is no exception. In our study, we identified age as a factor that increases mortality. The main reasons for this are the presence of comorbid diseases, decrease in T cell and B cells, and excessive cytokine production. Chen et al.[15] demonstrated that the risk of mortality started to increase in 65-year-old and older patients in China. Zhou et al.[16] similarly concluded in their study in Wuhan that mortality increased with age. Again, in a study conducted in Italy, it was concluded that age was an independent prognostic factor.[17] In the same study, the mortality rate in Italy was found to be 29.7%. According to the data of the Ministry of Health, the mortality rate in Turkey has been 1.02% as of March 14, 2021. The main reason for this low rate can be seen as the early initiation of treatment, sufficient number of hospital and intensive care beds, vaccination program, and a young population structure. The meta-analysis study conducted by Levin et al.[18] revealed that the middle age group was at risk for mortality. However, there may be differences between countries due to the development levels of the health system and the deficiencies in the recording.[19] Although it is not the subject of our study, it appears as an important factor in the spread of infection as it has an asymptomatic or mild course in pediatric patients.[20]

In our study, there was no significant relationship between gender and mortality. Similar to our study, Zhou et al.[16] did not find a significant relationship between gender and mortality. However, there are studies arguing that the disease is more severe in men and that the mortality rate is higher than in women. For example, the study of Jin et al.[21] revealed that the mortality rate in males was 2.4 times higher.The reason for this rate is that the COVID-19 virus damage Angiotensin-converting enzyme (ACE) receptors, and ACE inhibitors are more in men.

Comorbid diseases have an undeniable effect on the prognosis of COVID-19. In our study, we observed that DM and HT increased mortality. When the publications about DM on COVID-19 mortality are examined, it appears as a serious prognostic factor. This depends on the reasons such as the increase of ACE 2 receptors, storms of the pro-inflammatory cytokine, weakening of natural immunity and increased coagulation activity (fibrinogen, d-dimer, etc.). The role of ACE 2 is interesting here. ACE 2 has an antioxidant and anti-inflammatory effect. However, the ACE receptor provides an entry point for COVID-19 cells, especially pneumonocytes.[22] Therefore, ACE receptor inhibitors should be used with caution as they increase the expression of ACE. Ritesh Gupta and Anoop Misra stated in their article that ACE inhibitors decreased mortality.[22] In a meta-analysis conducted on 16,003 patients by Kumar et al.[23] it was concluded that mortality increased by two times in the case of DM.On the other hand, Huang et al.[24] claimed that there was a stronger relationship in young diabetic patients, and the reason for this was related to the high (ACE2) level. The common main idea of the studies and our study is the fact that DM patients require closer attention in terms of preventive medicine.

Another important factor that increased mortality found in our study was HT. It is one of the most common comorbid diseases in COVID-19 cases. Its direct effect on mortality is controversial. Gao et al.[25] said in their studies that the relative mortality rate increased by 2 times. The main prediction is that ACE inhibitors used increased viral infection and their cardiovascular complications such as heart fail-

ure.[26,27] The role of ACE inhibitors used in treatment was not understood. ACE expression caused by Ace inhibitors is known to accelerate virus entry. However, there have been publications stating that anti-inflammatory and antioxidant effects protect against lung and kidney damage in the inflammatory phase in literature.[28] The recommendation of the European Cardiology Association is also to continue the current antihypertensive treatment. Another factor is cardiac ischemia that may be caused by increased coagulation activity. It should be known that ACE inhibitors have positive effects on remodeling. Therefore, we are of the opinion that comprehensive studies should be conducted on the effect of ACE inhibitors on cardiac complications caused by COVID-19.

In the analysis of the data we obtained in our study, kidney dysfunction was also a prognostic factor. We found that mortality was significantly higher in patients with high urea creatinine levels. The results of the cohort studies with 701 patients conducted by Cheng et al.[29] supported our findings.Proteinuria is present in the majority of patients.[30] Causes such as COVID-induced right ventricular failure, endothelial damage, nephrotoxic drugs and steroids used in the treatment, hypoxia and storm of the kidney are factors that cause the impairment of renal functions. It is very important to protect kidney functions in these patients. Fluid replacement should be performed by monitoring urine without causing cardiac overload, and blood sugar regulation should be enabled.

Limitations

Since our study is a mono-center study, the data obtained are limited. Using larger data will increase the power of the results. Another factor is that ACE levels and lymphocyte subgroups cannot be determined in the laboratory of our hospital.

Conclusion

The data, we obtained, showed that the NLR is an indicator of the prognosis of COVID-19 patients followed in the intensive care unit. We think that it should be used in prognosis estimation as it is a simple and cost-free laboratory parameter. In addition, we found that age, DM and HT and kidney function disorders were among the factors affecting mortality.

Disclosures

Ethics Committee Approval: The study was approved by The Malatya Turgut Ozal University Clinical Research Ethics Committee (Date: 22/04/2021, No: 2021/10).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

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