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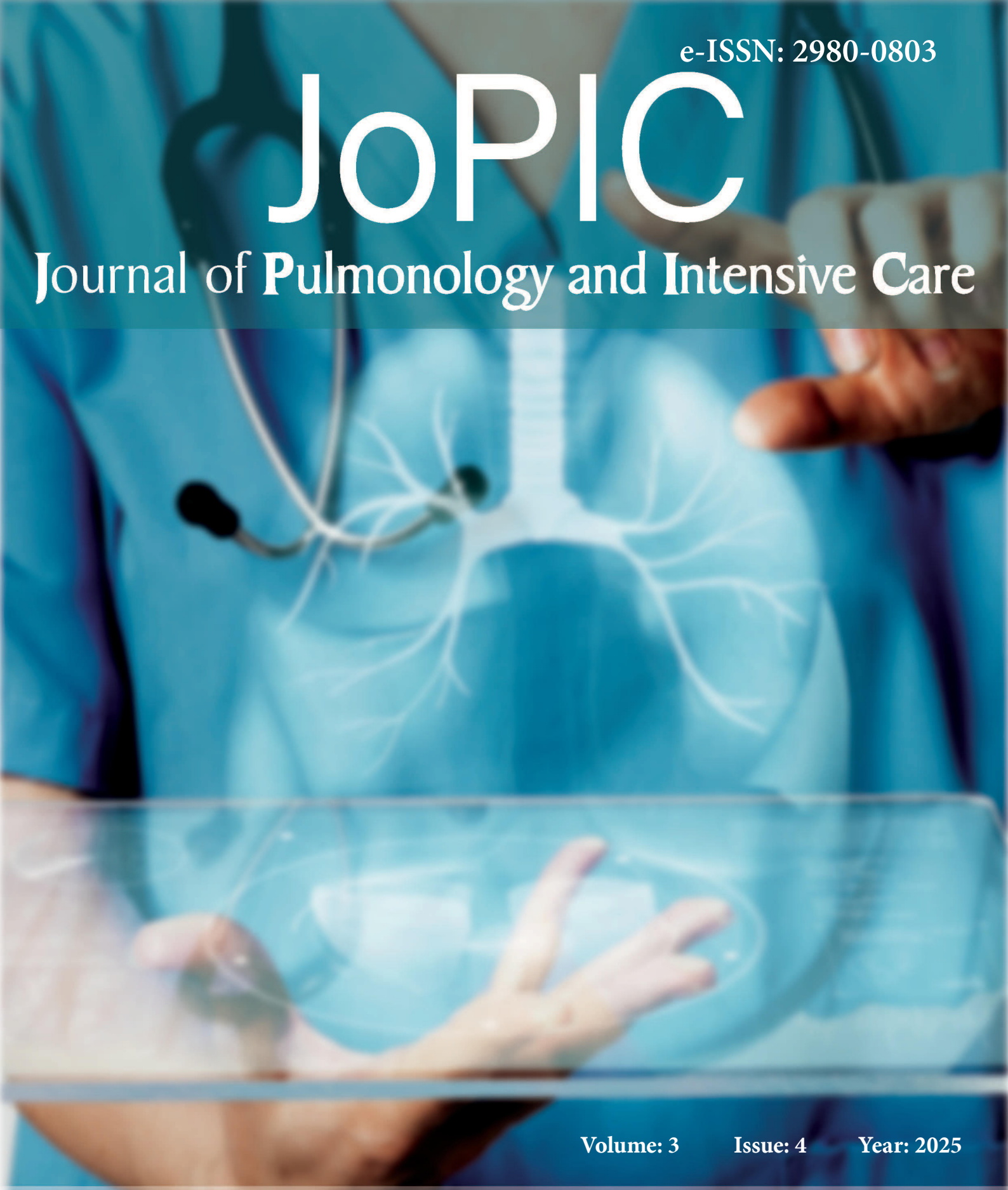

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Original Article

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Effect of tocilizumab or anakinra use on prognosis in patients admission to intensive care due to COVID-19

Havva Kubat[1], Elif Karabacak[2], Esra Aybal[3], Özlem Erçen Diken[4]

[1]Department of Pharmacology, Adana City Training and Research Hospital, Adana, Turkiye
[2]Department of Pharmacology, Faculty of Pharmacy, Düzce University, Düzce, Turkiye
[3]Department of General Intensive Care, Adana City Training and Research Hospital, Adana, Turkiye
[4]Department of Chest Diseases, Adana Faculty of Medicine, University of Health Sciences, Adana, Turkiye

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Corresponding Author: Elif Karabacak, elifkarabacak2010@hotmail.com

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ABSTRACT

Aims: Anticytokine treatments may be beneficial in patients who do not benefit from glucocorticoid treatment, which is the first choice in systemic hyperinflammation cases caused by SARS-COV-2. Interleukin 6 receptor blocker tocilizumab and interleukin-1 receptor antagonist anakinra are anticytokines that have been granted off-label use permits by the Ministry of Health of the Republic of Turkiye. In this study, the effects of these two drugs on laboratory parameters used to evaluate mortality and clinical severity of the disease were investigated.

Methods: The files of patients who received tocilizumab (n:38) and anakinra (n:36) for the treatment of coronavirus disease-2019 between 01.07.2020-31.03.2022 in the Chest Diseases Intensive Care Unit of Adana City Training and Research Hospital were retrospectively reviewed.

Results: Mortality and mechanical ventilation requirement were found to be significantly lower in the tocilizumab group compared to the anakinra group (p=0.005, 0.01, respectively). In both groups, CRP pro BNP and fibrinogen values decreased, while WBC, D-dimer and neutrophil values increased. Unlike anakinra, tocilizumab decreased ferritin values and increased lymphocyte, platelet, INR, urea and aspartate transaminase, total bilirubin, red blood cell values (p=0.004, 0.035, 0.032, 0.09, p<0.001, p=0.002, p=0.006, p=0.008, respectively).

Conclusion: Tocilizumab was associated with significantly lower rates of mortality and mechanical ventilation compared to anakinra.

Keywords: Anakinra, COVID-19, intensive care, tocilizumab

INTRODUCTION

SARS-CoV-2 (COVID-19) can cause pneumonia, acute respiratory distress syndrome (ARDS), cardiovascular changes, and multiple organ failure.[1] Approximately 20% of patients experience severe pulmonary dysfunction. This disease, which affects the whole world, can be asymptomatic or severe. It is possible that SARS-CoV-2 infects cell types such as endothelial vessels, alveolar walls, or macrophages in the lung. The onset of local inflammation caused by SARS-CoV-2 infection activates macrophages in that area. In severe cases, local inflammation cannot be alleviated within the lung and systemic hyperinflammation called mastoid activation syndrome (MAS) may develop. A series of inflammatory pathways are triggered by cytokine release, including interleukin-6 (IL-6) and interleukin-1 (IL-1). Not only hypercytokinemia, but also increased serum levels of ferritin, C-reactive protein (CRP), and D-dimer indicate the development of inflammation and fibrinolysis in COVID-19 patients.[2] There is no specific treatment for this condition, which is described as a cytokine storm, and anticytokine treatments are being investigated.[3] It is difficult to alleviate severe MAS symptoms, and steroids and immunosuppressive drugs are used in treatment. Cytokine-targeted MAS therapy has been studied by various research groups. The IL-1 receptor antagonist anakinra and the IL-6 receptor blocker tocilizumab have been suggested to be effective in alleviating clinical symptoms.[2,4] In the COVID-19 treatment guideline prepared by the Ministry of Health of the Republic of Turkiye, the use of tocilizumab or anakinra with an off-label drug request was recommended in patients with MAS symptoms who did not respond to glucocorticoid treatment.[5] In this study, we aimed to examine the effects of anakinra and tocilizumab treatment on mortality and laboratory parameters in cytokine storm caused by severe COVID-19, for which there is no definitive treatment protocol. The results

may contribute to the development of complex COVID-19 treatment protocols.

METHODS

This study has been approved by the Clinical Researches Ethics Committee of Adana City Training and Research Hospital (Date: 01.07.2021, Decision No:1482). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The files of patients with positive COVID-19 PCR tests who did not improve with favipravir, enoxaparin, levofloxacin, pulse glucocorticoid therapy and tocilizumab (Actemra®) or anakinra (Kineret®) were retrospectively reviewed through the hospital information system between 01.07.2020 and 31.03.2022 in the Chest Diseases Intensive Care Unit of Adana City Training and Research Hospital.

With off-label use approval from the Turkish Medicines and Medical Devices Agency of the Ministry of Health, tocilizumab (8 mg/kg intravenous infusion within 1 hour, 2nd dose 400 mg or 200 mg within 24 hours) or anakinra (2-10 mg/kg subcutaneously twice a day for 4 days) were used. Patients diagnosed with acquired human deficiency syndrome, tuberculosis, and active hepatitis were excluded from the study. Patients' age, gender, comorbid disease, number of days of intensive care, need for mechanical ventilation (MV), mortality or survival status, Acute Physiology and Chronic Health Evaluation (APACHE) II scores procalcitonin, troponin, glucose, urea, creatinine, glomerular filtration rate (GFR), albumin, ferritin, CRP, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, lactate dehydrogenase (LDH), pro B type natriuretic peptide (proBNP), D-dimer, white blood count (WBC), red blood count (RBC), platelet, neutrophil, lymphocyte, monocyte, international normalized ratio (INR), and fibrinogen values were recorded. Laboratory values immediately before administration of tocilizumab or anakinra (day 0) and on day 5 of treatment were compared.

Statistical Analysis

The data analyses were performed by SPSS 27 software (SPSS Inc, Chicago, IL, USA). Demographic differences between groups analyzed using Chi-square test for categorical variables and the Independent sample t-test for numaric variables, Fischer's exact test was used for the calculation of gender differences. Normality analysis was performed with the Shapiro-Wilk test. Independent Student's t-test and Mann-Whitney U test were used to analyze the differences between the tocilizumab and anakinra groups. Mortality rates and MV requirements were compared between the groups using the Pearson Chi-square test. Wilcoxon signed-rank test and Paired sample t-test were used to calculate differences in hematological and biochemical parameters, as repeated measures from day 0 to day 5 for the tocilizumab and anakinra groups. Significant p value was considered as $p<0.05$.

Limitations

The lack of a control group that did not use anticytokine treatment and the lack of comparison of laboratory values after the 5th day are the limitations of our study.

RESULTS

The study included 36 patients treated with anakinra (14 female, 28 male), 38 with tocilizumab (10 female, 28 male). The mean age of the anakinra group was 66.42±12 years, and the tocilizumab group was 58.03±13.4 years. There were 63.9% (23/38) comorbidities in the anakinra group and 57.9% (22/36) in the tocilizumab group. Both groups were different in terms of gender and mean age, and similar in terms of comorbid disease rates (p=0.048, p=0.006, p=0.598, respectively). Tocilizumab was administered on the 3.61±2.3rd day of the patient's admission to the intensive care unit, and similarly to anakinra on the 4.14±2.5th day (p=0.318). Mortality rates in the anakinra group (69.4% 25/36) were found to be significantly higher than in the tocilizumab group (36.8% 14/38) (p=0.005). The need for MV in the anakinra group (66.7% 24/36) was higher than in the tocilizumab group (36.8% 14/38) (p=0.01). There was no difference in the number of days of hospitalization after anakinra and tocilizumab treatment in surviving patients (16.97±9, 13.08±7.8, respectively) (p=0.064). The values of laboratory parameters on day 0 without tocilizumab and anakinra are given in **Table 1**.

On the 5th day of anakinra treatment, troponin, albumin, WBC, neutrophil, D dimer values increased, CRP, proBNP, fibrinogen values decreased. On the 5th day of tocilizumab treatment, procalcitonin, urea, AST, total bilirubin, D-dimer, WBC, RBC, platelet, neutrophil, lymphocyte, INR values increased significantly, ferritin, CRP, proBNP, fibrinogen values decreased (**Table 2**).

DISCUSSION

Previous studies have reported that anakinra or tocilizumab are beneficial or ineffective in COVID-19 disease.[6] Salama et al.[7] found that tocilizumab reduced the likelihood of progression to MV in patients with COVID-19 pneumonia who did not require MV, but did not affect survival. Dahms et al.[8] suggested that anakinra had no effect compared to standard care in terms of mortality and clinical improvement. Khani et al.[4] suggested that anakinra may be more beneficial in the early stages of the disease when high cytokine levels are not yet observed, thus preventing progression to severe disease and MV. When studies comparing the use of anakinra and tocilizumab were reviewed, no clear conclusion could be reached regarding the superiority of these two drugs in terms of survival and clinical improvement. There are studies in the literature that found anakinra use superior to tocilizumab[9,10] and reported that anakinra or tocilizumab provided clinical improvement without any difference.[11,12] There are studies reporting that tocilizumab is superior to anakinra, which supports our study.[13,14]

In addition, it has been shown that anakinra did not have a beneficial effect in patients who did not respond positively to tocilizumab treatment, which supports the superiority of tocilizumab treatment.[15]

During the course of COVID-19 disease, CRP, ferritin, and lymphocyte levels may provide insight into the viral load.[16] Continuing increases in CRP, ferritin, and D-dimer elevations, lymphopenia, thrombocytopenia, deterioration

Table 1. Values and comparison of laboratory parameters on day 0 in the anakinra and tocilizumab groups

Laboratory parameters	Reference range (unit)	Anakinra group (n=36)	Tocilizumab group (n=38)	p value
Procalsitonin	0-0.065(µg/L)	0.24±0.22	0.18±0.218	0.213
Troponin	0-16(ng/L)	83.58±326	19.13±24.73	0.147
Glukoz	74-106(mg/dl)	197.25±66.9	190.78±78.5	0.386
Ure	17-43(mg/dl)	64.89±23.85	43.87±16.5	<0.001
Serum creatine	0.67-1.17(mg/dl)	0.85±0.28	0.76±0.27	0.082
GFR	>90 ml/dk/1.7	83.92±22.43	98.89±21.02	0.003
Albumin	35-55(g/L)	28.45±3.36	29.76±3.7	0.116
Ferritin	23.9-336 (µg/L)	767±573	851.5±609	0.492
CRP	0-5 (mg/L)	95.47±57.2	101±82.2	0.825
ALT	5-50 (U/L)	38.86±24.8	70.92±64.76	0.028
AST	5-50 (U-L)	49.25±42.4	60.1±39.2	0.124
Total bilirubin	0.3-1.2 (mg/dl)	0.62±0.26	0.59±0.29	0.727
Lactate dehydrogenase	5-248 (U/L)	624±215	528±201.5	0.037
ProBNP	0-133 (µg/L)	2087±3459	864±1125	0.03
D-dimer	170-550 (µg/L)	2025±2359	1475±1438	0.439
WBC	3.8-11.8 (x10^3/µL)	11.1±3.78	9.98±4.39	0.255
RBC	3.63-4.92 (x10^6/ µL)	4.55±0.445	4.55±0.63	0.987
PLT	179-408 (x10^3/µL)	255±104	283±89	0.214
Neutrophil	1.9-8.2 (x10^3/µL)	10±3.65	8.97±4.27	0.171
Lymphocyte	1.1-3.1 (x10^3/µL)	0.47±0.29	0.54±0.43	0.772
Monocyte	0.2-0.9 (x10^3/µL)	0.522±0.4	0.413±0.25	0.382
INR	0.8-1.2	1.05±0.95	1.09±0.16	0.566
Fibrinogen	180-350 (mg/dl)	592±137.6	592±157	0.85
Interleukin 6	5.3-7.5 (pg/ml)	111±150.6	122.2±236.8	0.238
APACHE-II score		33.39±8.77	33.24±8.60	0.940

GFR: Estimate glomerular filtration rate, CRP: C-reactive protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ProBNP: pro-B-type natriuretic peptide, WBC: White blood cell, RBC: Red blood cell, PLT: Platelet, INR: International normalized ratio

Table 2. Laboratory parameter values and comparison of anakinra and tocilizumab groups on days 0 and 5

	Anakinra group (n=36)			Tosilizumab group (n=38)		
	0. day	5. day	p value	0. day	5. day	p value
Prokalsitonin	0.24±0.22	1.39±4.23	p=0.673	0.18±0.218	0.819±4.52	p<0.001
Troponin	83.58±326	104.1±261	p=0.06	19.13±24.73	34.39±85.3	p=0.238
Glukoz	197.25±66.9	206.6±81.7	p=0.367	190.78±78.5	188.3±85.6	p=0.824
Ure	64.89±23.85	81.43±41.6	p=0.056	43.87±16.5	62.5±51.15	p<0.001
Serum creatine	0.85±0.28	0.95±0.67	p=0.851	0.76±0.27	0.95±0.96	p=0.267
GFR	83.92±22.43	83.4±29.5	p=0.712	98.89±21.02	95.45±27.15	p=0.267
Albumin	28.45±3.36	28.85±17.7	p=0.009	29.76±3.7	30.65±4.25	p=0.129
Ferritin	767±573	674±408.6	p=0.326	851.5±609	770.84±1537	p=0.004
CRP	95.47±57.2	61.33±88.1	p=0.015	101±82.2	10.06±18.33	p<0.001
ALT	38.86±24.8	48.34±30.35	p=0.091	70.92±64.76	111.8±250.3	p=0.523
AST	49.25±42.4	40.14±20.7	p=0.176	60.1±39.2	79.82±253.8	p=0.002
Total bilirubin	0.62±0.26	0.748±0.394	p=0.169	0.59±0.29	0.758±0.318	p=0.006
LDH	624±215	632.6±320.8	p=0.174	528±201.5	662.6±656	p=0.592
Pro BNP	2087±3459	567.5±648	p=0.008	864±1125	617.3±1146	p=0.035
D-dimer	2025±2359	4030±4376	p=0.053	1475±1438	3106±4114	p=0.094
WBC	11.1±3.78	13.78±5.29	p=0.005	9.98±4.39	14.96±6.18	p<0.001
RBC	4.55±0.445	4.37±0.717	p=0.215	4.55±0.63	4.73±0.79	p=0.008
PLT	255±104	255±139.5	p=0.933	283±89	321.1±125.8	p=0.032
Neutrophil	10±3.65	12.97±5.3	p=0.003	8.97±4.27	13.14±6.42	p<0.001
Lymphocyte	0.47±0.29	0.44±0.37	p=0.403	0.54±0.43	0.726±0.39	p=0.035
Monocyte	0.522±0.4	0.466±0.39	p=0.403	0.413±0.25	0.558±0.49	p=0.208
INR	1.05±0.95	1.05±0.163	p=0.408	1.09±0.16	1.036±0.193	p=0.009
Fibrinogen	592±137.6	393.8±154.9	p<0.001	592±157	243.4±101	p<0.001

GFR: Estimate glomerular filtration rate, CRP: C-reactive protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: Laktat dehidrogenaz, ProBNP: pro-B-type natriuretic peptide, WBC: White blood cell, RBC: Red blood cell, PLT: Platelet, INR: International normalized ratio

in liver function tests, and hypofibrinogenemia suggest that the course of the disease is worsening.[17] Ozdemir et al.[18] reported that the lymphocyte count and percentage increased on the third day of tocilizumab treatment, similar to our results. Increased D-dimer levels in COVID-19-associated MAS are a result of pulmonary infiltration and inflammatory response to damage.[19] High D-dimer levels may be a sign of developing MAS.[16] In this study, D-dimer levels increased by 300-400% and it was observed that tocilizumab and anakinra could not stop the increase in D-dimer levels on the 5th day, and the increase continued. Vural et al.[20] reported that serum CRP levels can effectively assess disease severity in COVID-19 disease. Since it does not directly inhibit CRP synthesis like tocilizumab, CRP can be used as a safe test to monitor the acute phase response in patients receiving anakinra treatment.[5] In this study, CRP levels decreased in both the anakinra and tocilizumab groups. Similar to our results, Aljuhani et al.[21] found that mortality decreased with tocilizumab treatment, and D-dimer peak levels did not change. Saruhan et al.[22] found that tocilizumab treatment decreased CRP and ferritin levels and increased urea, AST, D-dimer, and procalcitonin levels, supporting our study results. In our results, the decrease in fibrinogen levels and the increase in D-dimer levels in both groups indicate that laboratory indicators evaluated as MAS continued on day 5. Unlike anakinra, tocilizumab decreased ferritin levels on day 5 and increased lymphocyte, monocyte, platelet, and INR levels. These results suggest that tocilizumab is more beneficial than anakinra in correcting the deteriorated laboratory values in MAS. However, the increase in total bilirubin, AST, procalsitonin and urea are undesirable negative results in the tocilizumab group. An increase in procalcitonin may indicate secondary infection. Therefore, monitoring procalcitonin levels after treatment and obtaining blood and other tissue culture samples is recommended.[5] Liver and kidney function should also be monitored. In the anakinra group, no improvement was achieved in laboratory values different from tocilizumab, Increased troponin values in both groups may be a direct result of coronary thrombotic events, sepsis-related myocardial injury, or the inflammatory surge.[23]

Wang et al.[24] reported that there is no confirmed antiviral drug with a specific effect against SARS-CoV-2, and IL-6 targeted treatments can be used in pandemics where the virus is present. Hyperinflammation associated with COVID-19 is found in only a fraction of all patients, but no specific treatment has been reported for this population.[20] Langer et al.[25] emphasized that the timing of anticytokine treatment is more important than the choice of anticytokine. Clinical trials are ongoing for tocilizumab and anakinra.[26] Further studies are needed to clarify the indications and timing of drug administration.

Limitations

The lack of a control group without anticytokine treatment and the retrospective, single-center design with a limited sample size are the factors limiting our study.

CONCLUSION

As a result, tocilizumab was associated with significantly lower rates of mortality and MV and improvement of laboratory parameters compared to anakinra. In COVID-19 disease developing MAS, but liver and kidney functions should be monitored after tocilizumab treatment. However, the risk of developing secondary infection appears to be higher after use of tocilizumab. Anakinra may be preferred in patients who develop secondary infection or myocarditis.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Clinical Researches Ethics Committee of Adana City Training and Research Hospital (Date: 01.07.2021, Decision No:1482).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

REFERENCES

1. Zu ZY, Jiang MD, Xu PP, et al. Coronavirus Disease 2019 (COVID-19): a perspective from china. *Radiology.* 2020;296:(2):E16-25. doi:10.1148/radiol.2020200490
2. Otsuka R, Seino KI. Macrophage activation syndrome and COVID-19. *Inflamm Regener.* 2020;40:(19):2-6. doi:10.1186/s41232-020-00131-w
3. Hirano T, Murakami M. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. *Immunity.* 2020;52(5):731-733. doi:10.1016/j.immuni.2020.04.003
4. Khani E, Shahrabi M, Rezaei H, Pourkarim F, Afsharirad H, Solduzian M. Current evidence on the use of anakinra in COVID-19. *Int Immunopharmacol.* 022;111:109075. doi:10.1016/j.intimp.2022.109075
5. 5. Antisitokin-Antiinflamatuar Tedaviler, Koagülopati Yönetimi, 07 Kasım 2020. Available from: https://covid19.saglik.gov.tr/TR-66341
6. 6. Zanza C, Romenskaya T, Manetti AC, et al. Cytokine storm in COVID-19: immunopathogenesis and therapy. *Medicina.* 2022;58(2):144. doi:10.3390/medicina58020144
7. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *Engl J Med.* 2021;384(1):20-30. doi:10.1056/NEJMoa2030340
8. Dahms K, Mikolajewska A, Ansems K, Metzendorf MI, Benstoem C, Stegemann M. Anakinra for the treatment of COVID-19 patients: a systematic review and meta-analysis. *Eur J Med Res.* 2023;28(1):100. doi:10.1186/s40001-023-01072-z
9. Küçükşahin O, Erden A, Karakaş Ö, et al. Comparison of anakinra and tocilizumab in management of severe COVID-19: a retrospective cohort study. *Turkish J Med Sci.* 2022;52(5):1486-1494. doi:10.55730/1300-0144.5487
10. Akın A, Safi Y, Yılmaz TS. COVID-19'a bağlı sitokin fırtınasında anakinra ve tosilizumab tedavilerinin karşılaştırılması. *Sağlık Bil Değer.* 2023;13(1):73-79. doi:10.33631/sabd.1119769

11. Zantah M, Castillo ED, Gangemi AJ, et al. Anakinra and intravenous IgG versus tocilizumab in the treatment of COVID-19 pneumonia. *MedRxiv*. 2020:9. doi:10.1101/2020.09.11.20192401
12. Arcani R, Correard F, Suchon P, et al. Tocilizumab versus anakinra in COVID-19: results from propensity score matching. *Front Immunol*. 2023;26(14):1185716. doi:10.3389/fimmu.2023.1185716
13. Acat M, Çavdar Ö, Tezce A, Acat BP. Comparison of tocilizumab and anakinra in the treatment of COVID-19: a single-center experience. *Duzce Med J*. 2022;24(2):116-120. doi:10.18678/dtfd.1084026
14. Ozkan F, Sari S. Comparison of anakinra and tocilizumab in anticytokine therapy in the treatment of coronavirus disease-2019. *Indian J Crit Care Med*. 2022;26(10):1091-1098. doi:10.5005/jp-journals-10071-24320
15. De la Calle C, Lopez-Medrano F, Pablos JL, et al. Effectiveness of anakinra for tocilizumab-refractory severe COVID-19. A single centre retrospective comparative study. *Int J Infect Dis*. 2021;105:319-325. doi: 10.1016/j.ijid.2021.02.041
16. Yao XH, Li TY, He ZC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Chinese J Pathol*. 2020;49(5):411-417. doi:10.3760/cma.j.cn112151-20200312-00193
17. Jamilloux Y, Henry T, Belot A, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmunity Reviews*. 2020;19(7):102567. doi:10.1016/j.autrev.2020.102567
18. Özdemir L, Özdemir B, Çelik MM, Urfalı S, Akgündüz B, Gegin S. COVID-19 pnömonisi nedeni ile tosilizumab uygulanan hastaların özellikleri. *İzmir Göğüs Hastanesi Dergisi*. 2024;38(1):95-107.
19. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420-422. doi:10.1016/S2213-2600(20)30076-X
20. Vural DG, Usta B, Emre Daştan MS, et al. COVID-19 tanılı hastalarda interlökin-6, C-reaktif protein ve prokalsitonin düzeylerinin hastalığın prognozuna etkisinin değerlendirilmesi. *Turk J Immunol*. 2022;10(3):149-154. doi:10.4274/tji.galenos.2022.70298
21. Aljuhani O, Al Sulaiman K, Korayem GB, et al. The association between tocilizumab therapy and the development of thrombosis in critically ill patients with COVID-19: a multicenter, cohort study. *Sci Rep*. 2024;14(1):3037. doi:10.1038/s41598-024-53087-z
22. Saruhan R, Uzundere O. Efficacy of tocilizumab in critically ill COVID-19 patients followed in the intensive care unit. *Turk J of Intensive Care*. 2024;22(3):197-206. doi:10.4274/tybd.galenos.2023.28199
23. Majure DT, Gruberg L, Saba SG, et al. Usefulness of elevated troponin to predict death in patients with COVID-19 and myocardial injury. *Am J Cardiol*. 2021;138:100-106. doi:10.1016/j. amjcard.2020.09.060
24. Wang X, Tang G, Liu Y, et al. The role of IL-6 in coronavirus, especially in COVID-19. *Front Pharmacol*. 2022;13:1033674. doi:10.3389/fphar.2022.1033674
25. Langer-Gould A, Smith JB, Gonzales EG, et al. Early identification of COVID-19 cytokine storm and treatment with anakinra or tocilizumab. *Int J Infect Dis*. 2020;99:291-297. doi:10.1016/j.ijid.2020.07.081
26. Available from: https://clinicaltrials.gov. 06.26.2025

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The lethal dance of COVID-19 with sepsis: predicting mortality using C-reactive protein, red cell distribution width, albumin and their ratios

Nazan Has Selmi[1], Necmiye Şengel[2], Özlem Balkız Soyal[3], Erol Toy[3], Seval İzdeş[3], Nevzat Mehmet Mutlu[3], Semih Aydemir[1]

[1]Department of Critical Care, Yenimahalle Training and Research Hospital, Ankara, Turkiye
[2]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Gazi University, Ankara, Turkiye
[3]Department of Anesthesiology and Reanimation, Ankara Bilkent City Hospital, Ankara, Turkiye

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Corresponding Author: Semih Aydemir, drsemihaydemir@gmail.com

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ABSTRACT

Aims: This study aimed to assess the impact of sepsis or secondary infection on mortality among COVID-19 patients admitted to the intensive care unit (ICU), and to evaluate the prognostic utility of C-reactive protein (CRP), red cell distribution width (RDW), albumin levels, and their derived ratios—CRP/albumin (CAR), RDW/albumin (RAR), and CRP×RDW/albumin (CRAR).

Methods: A retrospective cohort of 471 patients aged 18–75 years, treated between January and May 2021 at Ankara Bilkent City Hospital, was analyzed. Patients were classified into three groups: isolated COVID-19, COVID-19 with sepsis, and COVID-19 with secondary non-sepsis infection. Demographic and clinical characteristics, as well as ICU mortality rates, were compared between survivors and non-survivors. The predictive value of CAR, RAR, and CRAR ratios was statistically evaluated.

Results: Sepsis was associated with significantly higher mortality, age, APACHE II scores, lactate, and procalcitonin levels. Deceased patients had lower albumin levels and higher RDW and RAR values. ROC analysis revealed that RDW and RAR were significant predictors of mortality in the isolated COVID-19 group, while albumin and RAR were significant in the secondary infection group. Although univariate analysis highlighted associations between RAR and CRAR with mortality, multivariate analysis identified age, lactate, and sepsis status as independent predictors; notably, sepsis increased mortality by approximately 2.8-fold.

Conclusion: Sepsis dramatically increases mortality risk in COVID-19 ICU patients. RDW, albumin, and their corresponding ratios offer practical value for risk stratification, but must be interpreted within the context of established risk factors such as age and lactate. These biomarkers can aid prognostication, yet should be validated across larger and multicentric cohorts for wider clinical application.

Keywords: Ratio of C-reactive protein to albumin (CAR), ratio of red cell distribution width to albumin (RAR), COVID-19, sepsis, mortality, secondary infection

INTRODUCTION

Since its initial emergence in Wuhan, China in December 2019, COVID-19 has manifested with symptoms ranging from mild fatigue and myalgia to severe pneumonia and respiratory distress, with ICU mortality rates reaching as high as 40%.[1-3] Many patients admitted to intensive care present with symptoms directly related to COVID-19, but the co-occurrence of secondary infections or sepsis is common and frequently accompanied by multi-organ failure, further worsening prognosis.[4-6]

Inflammatory mechanisms are fundamental in organ dysfunction and mortality in COVID-19, notably through cytokine-driven lymphopenia and hyperinflammation.[7,8] COVID-19 patients typically show elevations in inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate, and lactate dehydrogenase.[9] CRP, an acute phase protein primarily synthesized by the liver, rises rapidly in plasma following tissue injury or infection, often within 48 hours, and high CRP levels are consistently associated with poor prognosis and increased mortality in critically ill patients.[10,11]

Similarly, albumin is produced by hepatocytes; its synthesis is suppressed by proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, making hypoalbuminemia a marker of severe inflammatory

response.[12] The CRP/albumin ratio (CAR) has been introduced in several studies as a valuable prognostic marker for disease severity in COVID-19.[13,14]

Red cell distribution width (RDW), calculated as the standard deviation of red blood cell volume divided by the mean corpuscular volume, is a cost-effective index of erythrocyte size variability and is widely used in hematological diagnostics.[15] Elevated RDW serves as a predictor of ICU mortality and is strongly correlated with disease severity and poor outcomes in COVID-19.[16-18] Furthermore, RDW elevation at hospital admission independently predicts mortality and advanced support needs, while high RDW/albumin ratios (RAR) also reflect systemic inflammation and nutritional impairment, indicating higher risk for ICU admission and mortality.[19]

Studies have established the prognostic value of CRP, CAR, RDW, and RAR in COVID-19.[11,19] The unique aspect of this study is stratifying ICU-admitted COVID-19 patients into isolated COVID-19 (COV), COVID-19 with sepsis (COV-S), and COVID-19 with non-sepsis secondary infection (COV-SE) subgroups. The hypothesis is that CRP, RDW, albumin, CAR, RAR, and CRP×RDW/albumin (CRAR) ratios yield improved prediction of mortality in patients with secondary infection or sepsis.

The aim of this study is to evaluate the predictive value of CRP, RDW, albumin, CAR, RAR, and CRAR for mortality in COVID-19 patients with or without secondary infection or sepsis.

METHODS

This study has been approved by the Ethics Committee of Clinical Researches No. 1 at Ankara Bilkent City Hospital (Date: 23.03.2022, Decision No: E1-22-2487). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patient data were obtained from hospital electronic medical records and files, retrospectively. Between January 1 and May 31, 2021, COVID-19 ICU patients aged 18-75 years were included; cases with missing data were excluded, yielding 471 evaluated patients. Patients were classified into three groups: COV, COV-S, and COV-SE. COV-SE were defined as microbiologically or clinically confirmed infections that did not meet Sepsis-3 criteria (i.e., no SOFA score increase ≥2 attributable to infection). This group included conditions such as hospital-acquired or ventilator-associated pneumonia, urinary tract infections, catheter-related bloodstream infections, and soft-tissue infections. The timing of infection onset, clinical findings, laboratory results, and culture data were reviewed to classify patients accurately. Sepsis diagnosis was based on 2021 SSC guidelines, procalcitonin levels, and blood culture positivity.[20] Sepsis diagnosis was made in accordance with the 2021 Surviving Sepsis Campaign (SSC) guidelines and fully aligned with the sepsis-3 definition. An acute increase of ≥2 points in the SOFA score was required for diagnosing sepsis. SOFA scores were available for all patients and were systematically evaluated at ICU admission. Elevated procalcitonin levels and blood culture positivity were used as supportive findings to differentiate sepsis from non-sepsis secondary infections, but SOFA ≥2 remained the essential diagnostic criterion.

Demographic data (age, sex), comorbidities (hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease (CKD), asthma, chronic obstructive pulmonary disease, heart failure, prior stroke, malignancy), pregnancy status, presence of sepsis or secondary infection at ICU admission, ICU and hospital length of stay, laboratory values at admission (CRP, RDW, albumin, procalcitonin, WBC, urea, creatinine, lymphocyte, lactate), APACHE II score, and clinical outcomes (survival, death) were recorded. APACHE II scores were recorded at ICU admission for all patients. The variability in APACHE II values reflects the heterogeneity in clinical severity at presentation. Some patients were admitted while receiving non-invasive respiratory support such as CPAP or high-flow nasal oxygen, whereas others had already been intubated before ICU transfer. Because patients entered the ICU at different stages of respiratory failure and organ dysfunction, baseline APACHE II scores naturally showed wide variation.

Statistical Analysis

The data analyses were performed using SPSS version 27.0 with a 95% confidence level. The distribution of numerical variables was assessed using Shapiro–Wilk and Kolmogorov–Smirnov tests. Normally distributed variables were analyzed with independent samples t-test or one-way ANOVA, while non-normally distributed variables were evaluated with Mann–Whitney U or Kruskal–Wallis tests. Categorical data were compared using Chi-square tests.

Correlations between numerical variables were examined using Pearson or Spearman methods based on normality. Logistic regression analysis was applied first in a univariate model to identify variables potentially associated with mortality. Variables with $p<0.10$ in univariate analysis were included in the multivariate logistic regression model.

Due to high multicollinearity between RDW, RAR, and CRAR, RDW was excluded from the multivariate model to avoid model instability and overfitting. Receiver operating characteristic (ROC) curves were used to assess the discriminatory power of CRP, albumin, RDW, CAR, RAR, and CRAR. ROC AUC values were interpreted as follows: 0.5–0.6 (poor), 0.6–0.7 (fair), 0.7–0.8 (acceptable), 0.8–0.9 (excellent), and >0.9 (outstanding). Cut-off values were selected using Youden's index. Interpretation of ROC findings was performed clinically as well as statisticall.

RESULTS

Of the 471 patients, 71.3% were in the COV group, 17.2% in COV-S, and 11.5% in COV-SE. The male proportion was 58.4%. Hypertension (48.4%), diabetes mellitus (33.3%), and coronary artery disease (19.3%) were the most common comorbidities. Overall mortality was 47.1% (**Table 1**).Comparing group characteristics, comorbidity count (p=0.014), CKD (p=0.000), prior stroke (p=0.001), malignancy (p=0.038), and mortality (p=0.000) differed significantly; COV-SE had higher comorbidity (%31.5) and stroke rates(%13.0), while the COV-S group showed higher

CKD (%27.2), malignancy (%17.3), and mortality rates (74.1) (**Table 1**).

Among deceased patients, comorbidity count (p=0.004), CKD (p=0.001), and heart failure (p=0.023) were significantly higher (**Table 1**).

The mean age was 65.29±16.15 years, with significant differences between groups (p=0.002); COV-S had the highest mean age, significantly more than COV (p=0.008). Mean APACHE II score was 18.1±13.77, lowest in COV (16.41±13.6) and higher in COV-S (22.95±12.92) and COV-SE (21.33±13.99) (**Table 2**).

Table 1. Comparison of patients' demographic and clinical characteristics in terms of diagnosis and mortality

		COV[a]	COV-S[b]	COV-SE[c]	Total	p	p[a-b]	p[a-c]	p[b-c]	Alive	Deceased	p
		(n=336)	(n=81)	(n=54)	(n=471)					(n=249)	(n=222)	
Gender	Male	198 (58.9)	53 (65.4)	24 (44.4)	275 (58.4)	0.051				141 (56.6)	134 (60.4)	0.412
	Female	138 (41.1)	28 (34.6)	30 (55.6)	196 (41.6)					108 (43.4)	88 (39.6)	
Number of comorbidities	None	69 (20.5)	6 (7.4)	8 (14.8)	83 (17.6)					57 (22.9)	26 (11.7)	
	1	62 (18.5)	22 (27.2)	8 (14.8)	92 (19.5)					46 (18.5)	46 (20.7)	
	2	88 (26.2)	17 (21)	10 (18.5)	115 (24.4)	0.014*	0.012*	0.08	0.349	65 (26.1)	50 (22.5)	0.004*
	3	63 (18.8)	15 (18.5)	11 (20.4)	89 (18.9)					44 (17.7)	45 (20.3)	
	≥4	54 (16.1)	21 (25.9)	17 (31.5)	92 (19.5)					37 (14.9)	55 (24.8)	
Comorbidity	HT	158 (47)	43 (53.1)	27 (50)	228 (48.4)	0,6				119 (47.8)	109 (49.1)	0.777
	DM	112 (33.3)	25 (30.9)	20 (37)	157 (33.3)	0.759				81 (32.5)	76 (34.2)	0.695
	CAD	62 (18.5)	16 (19.8)	13 (24.1)	91 (19.3)	0.633				42 (16.9)	49 (22.1)	0.153
	CKD	31 (9.2)	22 (27.2)	10 (18.5)	63 (13.4)	0.000**	0.000**	0.068	0.342	21 (8.4)	42 (18.9)	0.001*
	Asthma	24 (7.1)	4 (4.9)	3 (5.6)	31 (6.6)	0.872				15 (6)	16 (7.2)	0.741
	COPD	30 (8.9)	5 (6.2)	4 (7.4)	39 (8.3)	0.802				17 (6.8)	22 (9.9)	0.296
	History of stroke	11 (3.3)	10 (12.3)	7 (13)	28 (5.9)	0.001*	0.003*	0.006*	0.999	11 (4.4)	17 (7.7)	0.197
	Malignancy	26 (7.7)	14 (17.3)	7 (13)	47 (10)	0.038*	0.016*	0.194	0.663	20 (8)	27 (12.2)	0.181
	HF	20 (6)	9 (11.1)	7 (13)	36 (7.6)	0.069				12 (4.8)	24 (10.8)	0.023*
Pregnancy	No	331 (98.5)	80 (98.8)	54 (100)	465 (98.7)	0.999				244 (98)	221 (99.5)	0.22
	Yes	5 (1.5)	1 (1.2)	0 (0)	6 (1.3)					5 (2)	1 (0.5)	
Exitus	No	201 (59.8)	21 (25.9)	27 (50)	249 (52.9)	0.000**	0.000**	0.226	0.007*			
	Yes	135 (40.2)	60 (74.1)	27 (50)	222 (47.1)							

COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, HF: Heart failure
**p<0.001 *p<0.05 statistically significant relationship, p>0.05 not significant; Pearson Chi-square test

Table 2. Comparison of patients' clinical, demographic, and laboratory measurements in terms of diagnosis and mortality

	COV[a]	COV-S[b]	COV-SE[c]	Total	p	a-b p	a-c p	b-c p	Alive	Deceased	p
	(n=336)	(n=81)	(n=54)	(n=471)					(n=249)	(n=222)	
Age	63.65±16.29	69.6±15.42	68.96±14.78	65.29±16.15	0.002*	0.008*	0.072	0.999	61.07±15.69	70.01±15.36	0.000**
APACHE II	16.41±13.6	22.95±12.92	21.33±13.99	18.1±13.77	0.000**	0.000**	0.040*	0.999	11.86±8,45	25.11±15.16	0.000**
ICU stay	13.98±16.3	11.26±10.66	16.83±17.66	13.84±15.68	0.23				15.06±17.96	12.47±12.56	0.936
Hospital stay	21.24±21.01	17.36±15.82	28.06±32.96	21.36±22.08	0.114				26.39±26.06	15.71±14.63	0.000**
CRP	109.73±77.98	168.76±106.26	113±71.77	120.26±85.6	0.000**	0.000**	0.999	0.000**	116.04±87.68	124.99±83.15	0.136
Albumin	35.6±5.14	32.11±5.85	35.11±7.54	34.94±5.72	0.000**	0.000**	0.999	0.007*	35.73±5.35	34.06±6	0.002*
RDW	14.76±2.15	15.91±2.29	15.4±2	15.03±2.2	0.000**	0.000**	0.006*	0.174	14.6±1.98	15.52±2.33	0.000**
CAR	3.14±2.24	5.47±3.57	3.42±2.4	3.57±2.67 (3)	0.000**	0.000**	0.999	0.000**	3.36±2.67	3.82±2.67	0.06
RAR	0.43±0.1	0.51±0.12	0.46±0.13	0.44±0.12	0.000**	0.000**	0.084	0.026*	0.42±0.1	0.47±0.12	0.000**
CRAR	46.56±35.02	86.16±55.35	53.19±38.57	54.13±42.21	0.000**	0.000**	0.762	0.000**	49.26±40.48	59.59±43.60	0.008*
PRC	0.26±0.29	10.74±13.19	3.39±8.22	2.42±7.26	0.000**	0.000**	0.000**	0.000**	1.54±5.41	3.42±8.79	0.000**
WBC	10.1±4.84	12.55±7.17	9.98±4.83	10.5±5.38	0.012*	0.003*	0.819	0.044*	9.93±4.87	11.15±5.84	0.042*
Urea	61.49±44.74	110.42±64.97	76.74±46.87	71.65±52.24	0.000**	0.000**	0.002*	0.000**	57.74±41.48	87.27±58.39	0.000**
Lymphocyte	0.74±0.48	0.73±0.62	0.71±0.4	0.74±0.5	0.303				0.71±0.43	0.76±0.56	0.951
Lactate	2.08±1.54	3.12±3.25	2.19±1.49	2.27±1.97	0.032*	0.009*	0.487	0.203	1.76±0.76	2.85±2.64	0.000**

COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, CRP: C-reactive protein, RDW: Red cell distribution width, CAR: CRP/albumin, RAR: RDW/albumin, CRAR: CRP×RDW/albumin, WBC: White blood cell, **p<0.001 *p<0.05 indicates significant difference, p>0.05 indicates no significant difference

In COV-S, CRP, RDW, CAR, RAR, and CRAR values were highest; albumin was lowest. These biomarker values were significantly higher in COV-S than in both other groups (p<0.05), but not between COV and COV-SE. RDW was substantially higher in COV-S compared to COV (p=0.000), and in COV-SE compared to COV (p=0.006), (**Table 2**).

Procalcitonin, WBC, and lactate levels were highest in COV-S and lowest in COV; procalcitonin had significant differences across all groups (p=0.000), but WBC only differed between COV and COV-S. Lactate was significantly elevated in COV-S versus COV (p=0.009). Urea was lowest in COV (61.5±44.7) and highest in COV-S (110.4±65.0), (**Table 2**).

Deceased patients had significantly higher age (70.0±15.36), APACHE II (25.11±15.16), (p=0.000), and biomarker values (CRP, RDW, CAR, RAR, CRAR, PRC, WBC, urea, lymphocyte, lactate), whereas albumin was lower (**Table 2**).

ROC analysis demonstrated that, in the COV-SE group, albumin and RAR were significant predictors for survival (p<0.05); in the COV group, RDW and RAR were significant (p<0.05). Other biomarkers showed no significant predictive value (p>0.05) (**Table 3**). The cut-off values in COV-SE were 33.5 for albumin (**Figure 1**) and 0.4886 for RAR (**Figure 2**), with correct prediction rates for deceased patients of 0.593 and 0.519, and for survivors, 0.741 and 0.666. In the COV group, RDW and RAR cut-off values were 14.35 (**Figure 3**) and 0.4236 (**Figure 4**), with corresponding correct prediction rates for deceased patients of 0.637 and 0.504 and for survivors, 0.621 and 0.787 (**Table 4**).

Table 3. ROC analysis results

Measurement	Group (n)	ROC area	sh	p	%95 CI	
					Lower	Upper
CRP	COV (n=336)	0.537	0.032	0.251	0.474	0.599
	COV-S (n=81)	0.403	0.080	0.187	0.246	0.560
	COV-SE (n=54)	0.464	0.079	0.647	0.308	0.619
Albumin	COV (n=336)	0.549	0.032	0.131	0.485	0.612
	COV-S (n=81)	0.557	0.071	0.438	0.417	0.697
	COV-SE (n=54)	0.676	0.073	0.027*	0.532	0.820
RDW	COV (n=336)	0.630	0.031	0.000*	0.569	0.692
	COV-S (n=81)	0.547	0.068	0.525	0.414	0.680
	COV-SE (n=54)	0.582	0.079	0.303	0.427	0.736
CAR	COV (n=336)	0.542	0.032	0.187	0.480	0.605
	COV-S (n=81)	0.408	0.081	0.209	0.248	0.567
	COV-SE (n=54)	0.538	0.080	0.634	0.382	0.694
RAR	COV (n=336)	0.599	0.032	0.002*	0.537	0.661
	COV-S (n=81)	0.556	0.068	0.444	0.423	0.690
	COV-SE (n=54)	0.665	0.075	0.037*	0.518	0.812
CRAR	COV (n=336)	0.560	0.032	0.061	0.498	0.623
	COV-S (n=81)	0.418	0.081	0.265	0.258	0.578
	COV-SE (n=54)	0.549	0.080	0.539	0.392	0.705

ROC: Receiver operating characteristic, CI: Confidence interval, CRP: C-reactive protein, RDW: Red cell distribution width, CAR: CRP/albumin, RAR: RDW/albumin, CRAR: CRP×RDW/albumin, COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, *p<0.05

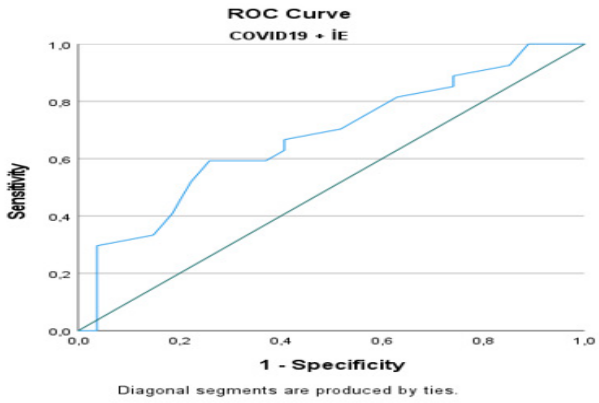

Figure 1. Albumin: COV-SE ROC curve
COV-SE: COVID-19 with non-sepsis secondary infection, ROC: Receiver operating characteristic

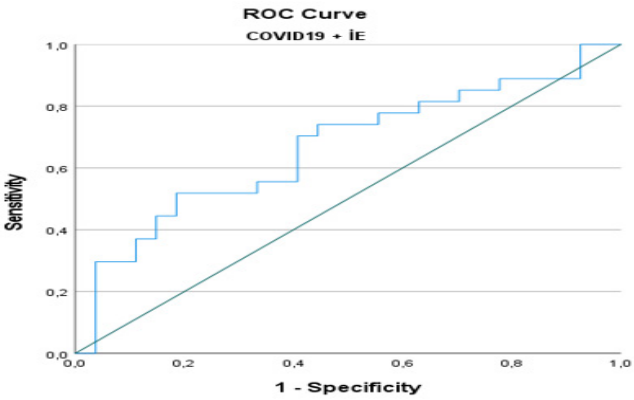

Figure 2. RAR: COV-SE ROC curve
RAR: Red cell distribution width/albumin, COV-SE: COVID-19 with non-sepsis secondary infection, ROC: Receiver operating characteristic

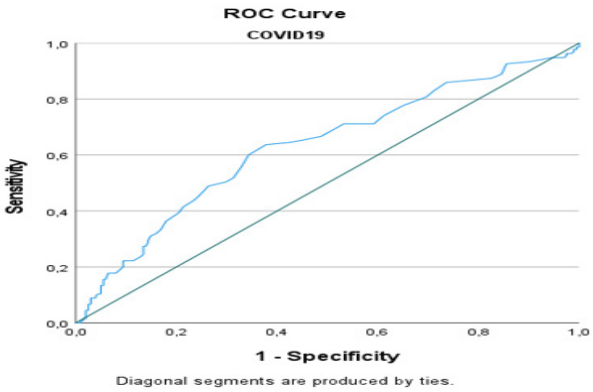

Figure 3. RDW: COV ROC curve
RDW: Red cell distribution width, COV: Isolated COVID-19, ROC: Receiver operating characteristic

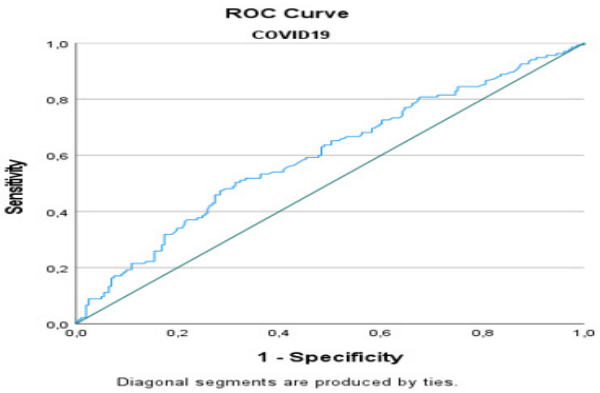

Figure 4. RAR: COV ROC curve
RAR: Red cell distribution width/albumin, COV: Isolated COVID-19, ROC: Receiver operating characteristic

Table 4. Predictive probabilities of measurements regarding mortality status in groups

	Cut-off value	Sensitivity	Specificity	NPD-	PPD+	Accuracy
Albumin: COV-SE	33.5	0.593	0.741	0.304	0.335	0.333
RDW: COV	14.35	0.637	0.621	0.718	0.531	0.628
RAR: COV	0.4236	0.504	0.787	0.673	0.519	0.613
RAR: COV-SE	0.4886	0.519	0.666	0.629	0.737	0.667

RDW: Red cell distribution width, RAR: RDW/albumin, COV: Isolated COVID-19, COV-SE: COVID-19 with non-sepsis secondary infection

Univariate logistic regression identified the following as significant predictors of survival: group allocation (COV, p=0.000), age (p=0.000), comorbidity count (p=0.004), CKD (p=0.001), heart failure (p=0.017), WBC (p=0.015), lactate (p=0.000), albumin (p=0.002), RAR (p=0.000), and CRAR (p=0.009). COV-S status increased mortality 4.254-fold, comorbidity count ≥4 by 3.259-fold, CKD by 2.533-fold, and heart failure by 2.394-fold. Increased WBC, PRC, lactate, age, RAR, and CRAR, as well as decreased albumin, were associated with higher mortality (**Table 5**).

Multivariate logistic regression (X^2=126.627; p=0.000; R^2=0.315) found group allocation (COV, p=0.032), age (p=0.000), and lactate (p=0.000) as significant predictors. Sepsis increased mortality 2.770-fold; higher lactate and age also raised mortality risk (**Table 6**).

DISCUSSION

The severity of COVID-19 is determined by viral load, inflammation, and the patient's immune response. Advanced age and underlying comorbidities (such as diabetes and hypertension) contribute to increased disease severity by promoting excessive inflammatory responses and impaired viral clearance.[21] In our study, the mean age of deceased patients (70.01±15.36) was significantly higher than that of survivors. A comorbidity count of four or more increased mortality 3.259-fold, the presence of chronic renal failure increased mortality 2.533-fold, and heart failure increased mortality 2.394-fold.

In our study, several demographic and clinical factors—particularly age, comorbidity burden, CKD, heart failure,

Table 5. Univariate logistic regression analysis results

Variable	Reference group	B	sh	p	OR	95% CI for OR	
						Lower	Upper
	Group			0.000**			
COV group	COV-S	1.448	0.277	0.000**	4.254	2.472	7.320
	COV-SE	0.398	0.294	0.176	1.489	0.837	2.649
Gender	Male	0.154	0.188	0.412	1.166	0.808	1.685
Age		0.037	0.006	0.000**	1.038	1.025	1.051
	Number of comorbidities			0.004*			
	1	0.785	0.315	0.013*	2.192	1.181	4.068
Number of comorbidities	2	0.523	0.302	0.084	1.686	0.932	3.050
	3	0.807	0.318	0.011*	2.242	1.203	4.179
	≥ 4	1.181	0.318	0.000**	3.259	1.747	6.079
HT	Yes	0.052	0.185	0.777	1.054	0.734	1.513
DM	Yes	0.077	0.196	0.695	1.080	0.736	1.584
CAD	Yes	0.334	0.234	0.154	1.396	0.882	2.209
CKD	Yes	0.930	0.285	0.001*	2.533	1.448	4.431
Asthma	Yes	0.192	0.372	0.606	1.212	0.585	2.511
COPD	Yes	0.406	0.337	0.228	1.501	0.775	2.906
Stroke	Yes	0.585	0.399	0.142	1.794	0.822	3.918
Malignancy	Yes	0.461	0.311	0.138	1.585	0.862	2.915
HF	Yes	0.873	0.366	0.017*	2.394	1.167	4.909
WBC		0.043	0.018	0.015*	1.044	1,009	1.081
PRC		0.041	0.016	0.009*	1.042	1.010	1.075
Lactate		0.625	0.113	0.000**	1.868	1.496	2.332
CRP		0.001	0.001	0.258	1.001	0.999	1.003
Albumin		-0.053	0.017	0.002*	0.948	0.917	0.981
CAR		0.066	0.035	0.061	1.068	0.997	1.143
RAR		4.226	0.897	0.000**	68.427	11.784	397.343
CRAR		0.006	0.002	0.009*	1.006	1.001	1.010

**p<0.001 *p<0.05 indicates significant effect, p>0.05 indicates no significant effect; Logistic regression. OR: Odds ratio, CI: Confidence interval, COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, HT: Hypertension, DM: Diabetes mellitus, CAD; Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, HF: Heart failure, CRP: C-reactive protein, CAR: CRP/albumin, RAR: RDW/albumin, CRAR: CRP×RDW/albumin, WBC: White blood cell, PRC: Procalcitonin

Table 6. Multivariate logistic regression analysis results

Variable	Reference group	B	sh	p	OR	95% CI for OR	
						Lower	Upper
	Group			0.032*			
COV group	COV-S	1.019	0.393	0.010*	2.770	1.282	5.985
	COV-SE	0.066	0.340	0.845	1.069	0.548	2.082
Age	Age	0.036	0.008	0.000**	1.036	1.020	1.052
	Number of comorbidities			0.485			
	1	0.606	0.365	0.096	1.834	0.897	3.747
Number of comorbidities	2	0.101	0.349	0.773	1.106	0.558	2.192
	3	0.230	0.380	0.545	1.259	0.598	2.652
	≥ 4	0.232	0.407	0.568	1.261	0.568	2.800
CKD	Yes	0.592	0.351	0.091	1.808	0.909	3.593
HF	Yes	0.214	0.444	0.629	1.239	0.519	2.961
PRC		-0.024	0.021	0.252	0.977	0.938	1.017
WBC		0.013	0.022	0.556	1.013	0.971	1.057
Lactate		0.753	0.137	0.000**	2.124	1.625	2.776
Albumin		0.016	0.039	0.683	1.016	0.941	1.097
CAR		-0.209	0.291	0.473	0.812	0.459	1.435
RAR		2.071	2.437	0.395	7.933	0.067	942.194
CRAR		0.014	0.019	0.469	1.014	0.977	1.053

*p<0.001 *p<0.05 indicates significant effect, p>0.05 indicates no significant effect; Logistic regression, OR: Odds ratio, CI: Confidence interval, COV: Isolated COVID-19, COV-S: COVID-19 with sepsis, COV-SE: COVID-19 with non-sepsis secondary infection, CKD: Chronic kidney disease, HF: Heart rate, CAR: CRP/albumin, RAR: RDW/albumin, CRAR: CRP×RDW/albumin, WBC: White blood cell, PRC: Procalcitonin

elevated WBC and lactate levels, and low albumin—were associated with increased mortality. These findings align with the established understanding that advanced age and multimorbidity contribute to impaired immune response and poorer outcomes in COVID-19. The strong effect of lactate on mortality is consistent with evidence linking hyperlactatemia to global tissue hypoxia and septic cardiometabolic stress.

Although CRP, CAR, RDW, RAR, and CRAR were significantly different between survivors and non-survivors, only age, lactate, and sepsis remained independently predictive in multivariate analysis. This pattern indicates that while inflammatory biomarkers provide supportive prognostic information, they may not outperform major clinical determinants. Similar to previous reports by Kim et al.[30] and Shan et al.,[31] albumin-based ratios (particularly RAR) demonstrated meaningful predictive value, but their contribution diminished after adjustment for established risk factors. This suggests that these ratios are most informative when combined with classical clinical indicators rather than used in isolation.

Furthermore, the ROC analysis revealed that the performance of these biomarkers differed according to clinical subgroups. RDW and RAR showed fair discrimination in patients with COV, whereas albumin and RAR performed better in patients with secondary infections. These findings reflect the dynamic nature of inflammatory responses and emphasize that biomarker utility may vary by phenotype. Overall, our results highlight the importance of integrating clinical variables with simple laboratory indices to improve risk stratification among ICU patients with COVID-19.

Various prognostic scoring systems, such as the widely used APACHE II scale, are employed in ICUs to estimate mortality risk.[22] Consistent with prior findings, our cohort showed significantly higher APACHE II scores in non-survivors (25.11±15.16) compared to survivors (11.86±8.45).

Since demographic factors alone cannot reliably predict COVID-19 prognosis,[23] early prognostic biomarkers are needed to guide clinical decisions. Serum albumin plays roles in the transport of ions, drugs, and metabolites, the maintenance of osmotic balance, and exhibits antioxidant properties.[24] Hypoalbuminemia in critically ill patients is multifactorial and can be attributed to increased capillary permeability, decreased protein synthesis, reduction in total serum albumin mass, expansion of distribution volume, and elevated expression of vascular endothelial growth factor.[25] A similar phenomenon has been observed in COVID-19 disease; a meta-analysis of 11 studies showed that the mean serum albumin at admission was 3.50g/dl in severe cases and 4.05g/dl in non-severe cases.[26]

The RAR, LDH, cerebrovascular disease, congestive heart failure, and coronary artery disease have all been identified as independent risk factors for mortality in COVID-19.[27] Uncontrolled inflammation associated with elevated inflammatory markers, especially CRP, also plays a significant role.[13]

Kalabin et al.[13] investigated the prognostic value of the CAR in mechanically ventilated and non-ventilated COVID-19 patients. Although CAR were significantly higher in ventilated and deceased patients compared to their counterparts, multivariate logistic regression analysis demonstrated that the ratio was not an independent predictor of mortality (OR 1.21, 95% CI 0.96–1.51, p=0.06). Similarly, Li et al.[14] examined admission albumin and CRP levels in 465 COVID-19 patients. They found that the CAR was

significantly elevated in patients with severe disease or death (3.29 [2.02–5.26]) compared to those discharged (0.72 [0.10-1.70]; p<0.001). The optimal cutoff for predicting disease progression was determined to be 1.843 (sensitivity 91.1%, specificity 78.0%).

Among hospitalized pregnant women with COVID-19, those requiring intensive care had significantly lower albumin (2.25±0.31 vs. 2.95±0.47, p=0.000) and higher CAR (5.13±2.01 vs. 1.00±1.00, p=0.000). For CAR, a cutoff of 1.8 delivered 100% sensitivity and 86.5% specificity for predicting ICU need.[28]

Uzum et al.[29] found, in 272 COVID-19 patients, lower albumin and higher CRP and CAR in severe cases. The CAR cutoff of 21.52 had a moderate ability to predict ICU admission (80.4% sensitivity, 55.7% specificity).

In our cohort, survivors had significantly higher albumin levels (35.73±5.35) than non-survivors (34.06±6). Survivor and non-survivor CRP and CAR were, respectively, 116.04±87.68 vs. 124.99±83.15 and 3.36±2.67 vs. 3.82±2.67. Despite higher ratios in the deceased, our multivariate analysis found CAR was not a statistically significant independent predictor (OR 8.12, 95% CI 0.46-1.43, p=0.47).

Kim et al.[30] identified CAR as an independent predictor of mortality in patients with severe sepsis or septic shock. Shan et al.[31] reported that RAR offered good accuracy for 28-day mortality in adult septic patients (AUC=0.695). In our study, age, comorbidity count, CKD, heart failure, WBC, lactate, and albumin were significant predictors of survival; presence of sepsis increased mortality 4.254-fold. These findings align with prior literature and emphasize the importance of integrated clinical and laboratory risk assessment advocated by Kim[30] and Shan.[31]

RDW reflects the variability in red blood cell size and is known to increase with systemic inflammation.[32] Ramachandran et al.[15] found that 49.7% of 294 COVID-19 patients had high RDW (>14.6%) at admission; these patients had higher in-hospital mortality, though the difference was not statistically significant. Jandaghian et al.[33] observed that survivors' mean RDW was lower than non-survivors (13.9±1.88 vs. 15.3±2.7; p<0.0001), and that patients with RDW>14.5% had a 3.1-fold higher risk of death (OR 3.1; 95% CI 2.6-3.8).

Ertekin et al.[19] found that mechanical ventilation and vasopressor need correlated with significantly higher RDW and RAR levels. Elevated RDW (>55.2%) and low albumin (<2.87) were strongly associated with mortality (98.5% sensitivity, 96.2% specificity for RDW; 83.2% sensitivity, 88.6% specificity for albumin/RAR).

In our study, albumin and RAR were significant predictors for survival in the COVID-SE group, and RDW and RAR in the COV group (p<0.05). COVID-SE albumin and RAR cutoffs were 33.5 and 0.4886, respectively; COV RDW and RAR cutoffs were 14.35 and 0.4236.

We also evaluated the effect of CRAR on survival. While survivors had significantly lower CRAR values, ROC analysis showed CRAR did not have significant predictive value (p>0.05).

Limitations

Our study's single-center, retrospective design limits the generalizability of findings to other patient populations and hinders definitive conclusions regarding causal relationships. The study was conducted at one center, and variability in patient profiles, treatment approaches, and laboratory methods among centers may constrain the broad applicability of results. The patient sample was recruited between January-May 2021, so SARS-CoV-2 variant and pandemic phase influences cannot be excluded, and results might not apply to other variant periods. Unequal sample sizes in patient subgroups—particularly the lower number of secondary infection cases compared to COVID sepsis and COVID groups—may reduce statistical power and limit subgroup analysis interpretations. This study evaluated only outcomes during ICU and hospital stays, not long-term prognosis or functional results. Another important limitation is that treatment protocols were not systematically recorded. Detailed information regarding the use of corticosteroids, antiviral agents, immunomodulatory therapies, vasopressors, and mechanical ventilation strategies was not available, and these therapies may directly affect inflammatory markers and clinical outcomes. Additionally, patients' nutritional status and the use of albumin replacement therapy were not documented. Because albumin levels and albumin-based ratios (CAR, RAR, CRAR) can be influenced by nutritional intake and exogenous albumin administration, the absence of these data may limit the interpretation of albumin-related prognostic markers.

CONCLUSION

Sepsis dramatically increases mortality in COVID-19 ICU patients, especially among older individuals with higher APACHE II scores. RDW and RAR are strong mortality predictors in isolated cases, while albumin and RAR matter more for those with secondary infections. Age, lactate, and sepsis are the main independent risk factors; CAR and CRAR alone are not reliable. Early detection of sepsis and aggressive intervention are vital to reduce mortality in this high-risk group.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Ethics Committee of Clinical Researches No. 1 at Ankara Bilkent City Hospital (Date: 23.03.2022, Decision No: E1-22-2487).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

REFERENCES

1. Mahdi BM, Almukhtar M. Role of vaccines against COVID-19 pandemic. *SLAS Discovery*. 2023;28(8):355-357. doi:10.1016/j.slasd.2023.07.002
2. Xie NN, Zhang WC, Chen J, Tian FB, Song JX. Clinical characteristics, diagnosis, and therapeutics of COVID-19: a review. *Curr Med Sci*. 2023;43(6):1066-1074. doi:10.1007/s11596-023-2797-3
3. Henry BM, Benoit JL, Benoit S, et al. Red blood cell distribution width (RDW) predicts COVID-19 severity: a prospective, observational study from the Cincinnati SARS-CoV-2 emergency department cohort. *Diagnostics (Basel)*. 2020;10(9):618. doi:10.3390/diagnostics10090618
4. Bouayed MZ, Laaribi I, Chatar CEM, et al. C-reactive protein (CRP): a poor prognostic biomarker in COVID-19. *Front Immunol*. 2022;14(13):1040024. doi:10.3389/fimmu.2022.1040024
5. Suleiman AS, Islam MA, Akter MS, et al. A meta-meta-analysis of co-infection, secondary infections, and antimicrobial resistance in COVID-19 patients. *J Infect Public Health*. 2023;16(10):1562-1590. doi:10.1016/j.jiph.2023.07.005
6. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect*. 2020;26:1622-1629. doi:10.1016/j.cmi.2020.07.016
7. Ghahramani S, Tabrizi R, Lankarani KB, et al. Laboratory features of severe vs. non-severe COVID-19 patients Asian populations: systematic review and meta-analysis. *Eur J Med Res*. 2020;25(1):30. doi:10.1186/s40001-020-00432-3
8. Danarti R, Limantara NV, Rini DLU, et al.Cutaneous manifestation in COVID-19: a lesson over 2 years into the pandemic. *Clin Med Res*. 2023;21(1):36-45. doi:10.3121/cmr.2023.1598
9. Karimi A, Shobeiri P, Kulasinghe A, Rezaei N. Novel systemic inflammation markers to predict COVID-19 prognosis. *Front Immunol*. 2021;12:741061. doi:10.3389/fimmu.2021.741061
10. Yao Z, Zhang Y, Wu H. Regulation of C-reactive protein conformation in inflammation. *Inflamm Res*. 2019; 68:815-823. doi:10.1007/s00011-019-01269-1
11. Ho KM, Lee KY, Dobb GJ, Webb SA. C-reactive protein concentration as a predictor of in-hospital mortality after ICU discharge: a prospective cohort study. *Int Care Med*. 2008;34:481-487. doi:10.1007/s00134-007-0928-0
12. Rathore SS, Oberoi S, Iqbal K, et al. Prognostic value of novel serum biomarkers, including C-reactive protein to albumin ratio and fibrinogen to albumin ratio, in COVID-19 disease: a meta-analysis. *Rev Med Virol*. 2022:e2390. doi:10.1002/rmv.2390
13. Kalabin A, Mani VR, Valdivieso SC, Donaldson B. Does C-reactive protein/albumin ratio have prognostic value in patients with COVID-19. *J Infect Developing Countries*. 2021;15(8):1086-1093. doi:10.3855/jidc.14826
14. Li Y, Li H, Song C, et al. Early prediction of diseaseprogression in patients with severe COVID-19 using C-reactive protein to albumin ratio. *Disease Markers*. 2021;2021:6304189. doi:10.1155/2021/6304189
15. Ramachandran P,Gajendran M, Perisetti A, et al. Red blood cell distribution width in hospitalized COVID-19 patients. *Front Med*. 2022;7(8):582403. doi:10.3389/fmed.2021.582403
16. Mutlu NM, Peket TT, Soyal OB, et al. Red cell distribution width in diagnosis of brain death. *Transplantation Proceedings*. 2019;51(7):2189-2191. doi:10.1016/j.transproceed.2019.04.072
17. Hong WS, Rudas A, Bell EJ, ChiangJN. Association of red blood cell distribution width with hospital admission and in-hospital mortality across all-cause adult emergency department visits. *JAMIA Open*. 2023;6(3):ooad053. doi:10.1093/jamiaopen/ooad053
18. Chandler CM, Reid MC, Cherian S, Daniel E SabathDE, Edlefsen KL. Comparison of blood counts and markers of inflammation and coagulation in patients with and without COVID-19 presenting to the Emergency Department in Seattle, WA. *Am J Clin Pathol*. 2021;156(2):185-197. doi:10.1093/ajcp/aqab052
19. Ertekin B, Acar T. The relationship between prognosis and red cell distribution width (RDW) and RDW-albumin ratio (RAR) in patients with severe COVID-19 disease. *Int J General Med*. 2022:15:8637-8645. doi:10.2147/IJGM.S392453
20. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143. doi:10.1097/CCM.0000000000005337
21. Zhu Y, Sharma L, Chang D. Pathophysiology and clinical management of coronavirus disease (COVID-19): a mini-review. *Front Immunol*. 2023;14:1116131. doi:10.3389/fimmu.2023.1116131
22. Bloria SD, Chauhan R, Sarna R, Gombar S, Jindal S. Comparison of APACHE II and APACHE IV score as predictors of mortality in patients with septic shock in intensive care unit: a prospective observational study. *J Anaesthesiol Clin Pharmacol*. 2023;39(3):355-359. doi:10.4103/joacp.joacp_380_21
23. Budak F, Korkmaz Ş. General evaluation regarding the COVID-19 pandemic process: the example of Turkey. *J Social Res Management*. 2020;1:62-79. doi:10.35375/sayod.738657
24. Belinskaia DA, Voronina PA, Shmurak VI, Jenkins RO, Goncharov NV. Serum albumin in health and disease: esterase, antioxidant, transporting and signaling properties. *Int J Molecular Sci*. 2021;22(19):10318. doi:10.3390/ijms221910318
25. Saravi B, Goebel U, Hassenzahl LO, et al. Capillary leak and endothelial permeability in critically ill patients: a current overview. *Intens Care Med Experimental*. 2023;11(1):96. doi:10.1186/s40635-023-00582-8
26. Aziz M, Fatima R, Lee-Smith W, Assaly R. The relationship between low serum albumin and severe COVID-19: a systematic review and meta-analysis. *Crit Care*. 2020;24:255. doi:10.1186/s13054-020-02995-3
27. Kalın BS, Solmaz İ. Prognostic role of red cell distribution width/albumin ratio and lactate dehydrogenase level in COVID-19 patients. *Ege J Med*. 2022;61(1):38-43. doi:10.19161/etd.1085634
28. Yılmaz N, Tosun F, Cömert E, Duran M, Tuna VD. The relationship of CRP/albumin ratio level and prognosis in pregnant COVID-19. *Nigerian J Clin Practice*. 2022;25(10):1745-1750. doi:10.4103/njcp.njcp_244_22
29. Uzum Y, Turkkan E. Predictivity of CRP, albumin, and CRP to albumin ratio on the development of intensive care requirement, mortality, and disease severity in COVID-19. *Cureus*. 2023;15(1):e33600. doi:10.7759/cureus.33600
30. Kim MH, Ahn JY, Song JE, et al. The C-reactive protein/albumin ratio as an independent predictor of mortality in patients with severe sepsis or septic shock treated with early goal-directed therapy. *PLoS ONE*. 2015;10(7):e0132109. doi:10.1371/journal.pone.0132109
31. Shan X, Li Z, Jiang J, et al. Prognostic value of red blood cell distribution width to albumin ratio for predicting mortality in adult patients meeting sepsis-3 criteria in intensive care units. *BMC Anesthesiol*. 2024;24(1):208. doi:10.1186/s12871-024-02585-8
32. Yoo JW, Ju S, Lee SJ, Cho YJ, Lee JD, Kim HC. Red cell distribution width/albumin ratio is associated with 60-day mortality in patients with acute respiratory distress syndrome. *Infect Dis*. 2020;52(4):266-270. doi:10.1080/23744235.2020.1717599
33. Jandaghian S, Vaezi A, Manteghinejad A, et al. Red blood cell distribution width (RDW) as a predictor of in-hospital mortality in COVID-19 patients; a cross sectional study. *Arch Academic Emerg Med*. 2021;9(1):e67. doi:10.22037/aaem.v9i1.1325

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Determinants of survival in acute pulmonary thromboembolism: real-life data from a 3-level health institution

Hatice Çetindoğan[1], Nesrin Öcal[2], Deniz Doğan[2], Cantürk Taşçı[2], Yakup Arslan[2], Derya Doğan[3]

[1]Department of Chest Diseases, Ankara Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Ankara, Turkiye
[2]Department of Chest Diseases, Gülhane Faculty of Medicine, University of Health Sciences, Ankara, Turkiye
[3]Department of Chest Diseases, Ankara Etlik City Hospital, Ankara, Turkiye

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Corresponding Author: Hatice Çetindoğan, cetindoganh@gmail.com

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ABSTRACT

Aims: Given that pulmonary thromboembolism is a prevalent cause of cardiovascular mortality, identifying quick and accessible diagnostic-prognostic markers for pulmonary thromboembolism may significantly contribute to mortality reduction. In this study, we aimed to determine to what extent diagnosis-prognosis markers of patients are predictive of survival, based on real-life data.

Methods: Data from patients hospitalized with the diagnosis of pulmonary thromboembolism were retrospectively investigated. The demographic, clinical, and radiological findings were analyzed. Probability, severity, and mortality score determinations of patients with acute PE were analyzed using the Charlson Comorbidity Index, Pulmonary Embolism Severity Index, and Simplified Pulmonary Embolism Severity Index scores.

Results: The data of 300 patients were evaluated. The mortality rate was 11%. The mortality group had an elevated mean age compared to the survival group (p=0.035). Hospital death was 7.3%, highest in the 9th and 6th decades (p=0.025 and p=0.036). The mortality rate was 26.6% in patients with thrombus in the pulmonary artery trunk (p=0.01). The presence of right heart strain on echocardiography was correlated with mortality. (p<0.05). The mean Pulmonary Embolism Severity Index and Simplified Pulmonary Embolism Severity Index scores also showed an important difference between survival groups (p=0.028 and p=0.021). Although the mean Charlson Comorbidity Index score tended to be higher among the non-survivors, this numerical difference did not achieve statistical significance (p>0.05). Mortality was significantly higher in those with a high 30-day early mortality score compared to those in all groupse (p=0.02).

Conclusion: Demographic and clinical characteristics are closely related to the survival of patients with pulmonary thromboembolism. An individual approach to patients diagnosed with pulmonary thromboembolism will provide management above all scores.

Keywords: Demographic, risk, Pulmonary Embolism Severity Index, Charlson Comorbidity Index, prognosis

INTRODUCTION

Pulmonary thromboembolism (PE) is a widely prevalent condition morbidity and mortality that affects the pulmonary and cardiovascular systems. Although the acute PE mortality rates have decreased with the widespread clinical use of diagnosis and treatment algorithms in the guidelines published in recent years, the incidence of PE is gradually increasing.[1] PE is still the third most common acute cardiovascular disease globally after myocardial infarction and stroke.[2] Given that numerous differential diagnoses can mimic the presenting signs and symptoms of PE, maintaining a high index of clinical suspicion is the paramount initial step in the diagnostic process. Possible delays in diagnosis are among the most important points in terms of mortality. In many post-mortem evaluations, PE findings were found in individuals who were not clinically diagnosed while alive.

A timely diagnosis and a prognosis assessment for determining how the patient should be followed up may be at least as effective on survival as the clinical findings of the patient. Thus, a rapid and easy diagnostic approach will play a key role in reducing mortality.

Individualized patient management based on demographic, clinical, and radiological findings may be an appropriate

approach in this respect. The most logical way to achieve all this is to benefit from real-life data. However, data on this subject are limited.

More real-life data are needed to demonstrate the principles of the individualized approach.[2,3] Clinical guidelines offer us some scoring systems in terms of PE probability and prognosis, such as Well's probability scoring, Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI) scores, and 30-day early mortality risk groups determined according to the ESC/ERS pulmonary embolism guideline. PESI is a clinical risk score used to assess the 30-day mortality risk in patients with acute pulmonary embolism (PE). sPESI is an easier and faster version of PESI (**Table 1, 2**).[4,5]

Table 1. Pulmonary Embolism Severity Indexes (PESI, sPESI)[1,4,5]

Parameter	PESI score	sPESI score
Age	Age/year	>80 age is one point
Malignancy	30	1
Male gender	10	-
Chronic pulmonary disease	10	1
Chronic cardiac disease	10	1
Systolic blood pressure <100 mmHg	30	1
Pulse ≥110/min	20	1
Respiratory rate ≥30/min	20	-
Respiratory rate ≥30/min	20	-
Arterial O_2 saturation <90%	20	1
Change in mental status	30	1
	Low risk Class I: ≤65 Class II: 66-85 High risk Class III: 86-105 Class IV: 106-125 Class V: >125	Low risk: 0 High risk: ≥1

However, it may not be correct to evaluate the data obtained from these scorings in the same way for every patient. Patient characteristics, especially demographic findings and comorbidities, weaken the validation of these scorings.

The Charlson Comorbidity Index (CCI) is a validated prognostic scoring system used to measure a patient's comorbidity burden, assigning a specific weight (point) to each comorbid diagnosis. As the total CCI score increases, so does the patient's risk of mortality and rehospitalization. CCI measures disease burden and evaluates more than 17 comorbidities, including cardiovascular disease, malignancies, chronic lung and neurological diseases, and connective tissue diseases (**Table 3**).[6]

Table 3. Charlson Comorbidity Index[6]

Score	Comorbidity
1	Coronary artery disease
1	Congestive heart failure
1	Chronic pulmonary disease
1	Peptic ulcer
1	Peripheral vascular disease
1	Mild liver failure
1	Cerebrovascular disease
1	Connective tissue disease
1	Diabetes mellitus
2	Hemiplegia
2	Moderate or severe renal failure
2	Diabetes mellitus causing end-organ failure
2	Any tumor diagnosed 5 years ago
2	Leukemia
2	Lymphoma
3	Moderate or severe liver failure
6	Metastatic solid tumor
6	AIDS (not just HIV+)

The central purpose of this analysis is to examine the clinical utility of probability and risk scoring systems and to determine to what extent diagnosis-prognosis markers of patients are predictive of survival, based on real-life data.

METHODS

Ethics

The study was carried out with the permission of the Health Sciences University Gülhane Training and Research Hospital Scientific Researches Evaluation and Ethics Committee (Date: 05.11.2020, Decision No: 2020-430). All processes involving human subjects were executed in strict conformity with the principles outlined in the Declaration of Helsinki and prevailing ethical guidelines.

Methodological Blueprint and Participants

The files and data of adult patients diagnosed with acute PE in the chest diseases clinic between October 1, 2016, and October 1, 2020, were subjected to retrospective review. Patients with a definite diagnosis of PE and whose data could be accessed

Table 2. PE severity and early (in-hospital or 30-day) mortality risk stratification[1,4,5]

Early mortality risk group		Risk parameters and scores			
		Shock or hypotension	Clinical parametres PESI 3, 4, 5 sPESI ≥1	Right heart dilatation dysfunction findings (on ECHO or CTA)	Cardiac troponin(>0.04 ng/ml) elevation
High		+	+	+	+
Intermediate	High	-	+	+	+
	Low	-	+	One (+) or both (-)	
Low		-	-	-	No evaluation is required, if requested it should be negative

PE: Pulmonary embolism, PESI: Pulmonary Embolism Severity Index, sPESI: Simplified PESI, ECHO: Echocardiography, CTA: Computed tomography-angiography

reliably were included. Patient files were analyzed in terms of clinical, laboratory, and radiological findings.

Patients were Categorized as Follows as PE Diagnosis Methods

Computed tomography-angiography (CTA), ventilation/perfusion scintigraphy (V/Q), and/or clinical+echocardiography (ECHO)±Doppler ultrasonography (USG) findings. The Well's scores (which evaluate the likelihood of pulmonary embolism) and PESI and sPESI scores (which evaluate the risk of early mortality after diagnosis) of the patients at the time of diagnosis were recalculated in light of the data obtained from the file scan. CCI scores were also calculated by examining comorbidities from patient files and medical histories in electronic records. The survival and mortality of the patients during the diagnosis and treatment of PE were recorded. Findings were compared and analyzed between survival and mortality groups. These examinations were also discussed in terms of age groups, comorbidity groups, and clinical and radiological findings.

Statistical Analysis

The data analysis was performed on the entire dataset using the dedicated IBM SPSS Statistics platform (Version 22.0; Armonk, NY, USA, 2013) .The compatibility of continuous variables with normal distribution was evaluated by the Kolmogorov-Smirnov test. The Mann-Whitney U test or Student's t-test was used depending on whether the groups were normally distributed or not. The correlations of the obtained numerical parameters were analyzed. A value of $p < 0.05$ was evaluated as sympathetically important.

RESULTS

A total of 600 patients with a preliminary diagnosis of PE were hospitalized in the chest diseases clinic between October 1, 2016, and October 1, 2020. It was determined that the data of 445 of them could be accessed and 300 of them could be included in the study. Exclusion criteria: Inability to access the patient file or incomplete/insufficient clinical data. Pregnancy (due to different clinical evaluation processes). Hospitalization with a preliminary diagnosis of PE, but an alternative diagnosis has been confirmed (e.g., pneumonia, aortic dissection, malignant embolism, chronic thromboembolic disease). Patients hospitalized due to the development of acute complications during the treatment process with a diagnosis of PE. In case of duplicate records of the same patient during the study period (**Figure 1**).

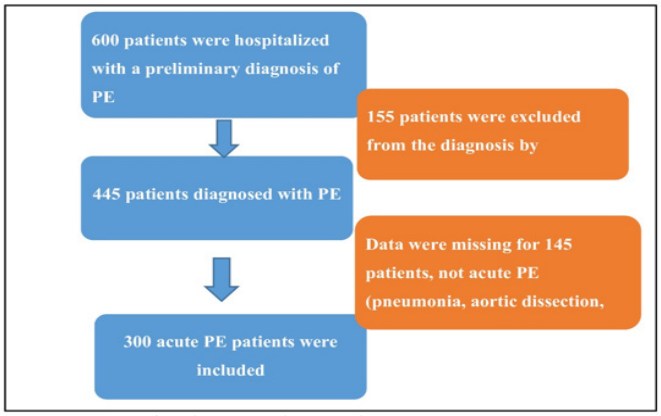

Figure 1. Patients' inclusion-exclusion scheme

Baseline characteristics of patients: The mean age of the patients was 66.1±17.6 years (20-96). When the gender distributions were examined, it was observed that 51.3% (n=154) of all patients were female, 48.7% (n=146) were male, and the mean age in women was significantly higher (69.3±16.2 and 62.6±18.4 years, respectively; p=0.001). Out of 300 patients, 278 (89%) resulted in survival, while 22 (11%) resulted in mortality. The mean age was significantly different between the mortality and survival groups (70.1±17.6 vs. 65.7±17.6 years, p=0.035).

When patients were examined in terms of survival according to decades of age, it was observed that the highest mortality rates were observed in patients in the 9th and 6th decades (p=0.025 and p=0.036, respectively) (**Figure 2**).

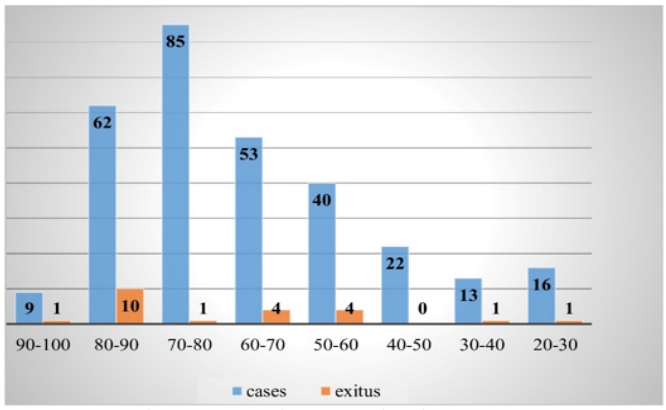

Figure 2. Mortality rates according to age decades

When patients were examined in terms of survival according to decades of age, it was observed that the highest mortality rates were observed in patients in the 9th and 6th decades (comorbidities were investigated both for all patients and for the mortality group).

The distribution of comorbidities in order of frequency was as follows: diabetes mellitus (DM) in 23.7%, malignancy (active or in remission) in 22.7%, chronic obstructive pulmonary disease (COPD) in 12.3%, chronic kidney disease (CKD) in 11%, atrial fibrillation (AF) in 7.7%, and cerebrovascular event in 7% (p=0.025 and p=0.036, respectively).

Among the comorbidities in the mortality group, 17.3% had AF, 15.1% had CKD, 10.8% had COPD, 10.2% had malignancy, and 7.1% had DM. AF and CKD were significantly more common in the mortality group (p=0.02).

Among all patients, immobility was the most common risk factor, with a rate of 42.7%. This was followed by cancer and surgery in the last 4 weeks (17.7% and 10%, respectively). The distribution of predisposing factors in the general population and mortality group is summarized in **Table 4**.

Conditions that make up the "other" risk factors included COVID-19 infection, minor surgery, antiphospholipid antibody syndrome, Osler-Weber-Rendu syndrome, heavy smoking, and secondary polycythemia (**Table 4**).

We observed that 63 (21%) of the patients diagnosed with PE were screened for genetic thrombophilia according to their indications (non-provocable/idiopathic PE, recurrent PE,

Table 4. Mortality rates for each risk factor

Risk factor	n (%)	Mortality, n (%)*
Atrial fibrillation	17 (5.7)	1 (5.8)
Pregnancy	3 (1)	0
Surgery in the last 4 weeks	30 (10)	0
Active cancer	53 (17.7)	6 (11.3)
Malignancy in remission	13 (4.3)	0
Immobility	128 (42.7)	14 (10.9)
Bone fracture	21 (7)	2 (9.5)
Short trip	6 (2)	0
Other **	10 (3.3)	2 (20)

*Death rates are calculated based on the number of patients in each risk factor group
**Other: COVID-19, minor surgery, antiphospholipid disease, Osler Weber Rendu, smoker and secondary polycythemia

young age, etc.). Among the 18 patients with homozygous mutations, the FV-Leiden mutation was the first, with a rate of 46.2%.

Findings related to PE: The most common symptoms were dyspnea (87.1%) and chest pain (54.6%). While the mortality rate was significantly lower in patients presenting with chest pain, it was significantly higher in those presenting with syncope (p=0.025 and p<0.001 respectively).

The diagnostic methods of the patients were determined. 227 (75.7%) patients were diagnosed with CTA, 63 (21.0%) patients were diagnosed with V/Q scintigraphy, and 21 (7.0%) patients were diagnosed with clinical+ECHO±Doppler USG findings. 101 (33.7%) of the patients diagnosed with PE had concurrent acute DVT. The percentages represent the frequency of use of diagnostic modalities. Some patients, particularly in cases of diagnostic uncertainty, were evaluated with more than one method (e.g., CTA+ECHO or CTA+V/Q scintigraphy). Therefore, the distribution of patients by diagnostic method exceeds 100% overall. Percentages reflect the relative rates of use of the diagnostic methods used, not mutually exclusive patient groups. We found that the thrombus localization in our PE cases was associated with mortality. The mortality rate was high in those with thrombus in the pulmonary artery trunk (26.6%) (p=0.01).

ECHO was performed on 217 of 300 patients in the study population. Patients who underwent echocardiography may be more clinically stable, have more comorbidities, or be more suitable for evaluation. Reasons for patients not undergoing echocardiography: Clinical instability/hemodynamic disturbance, inadequate image quality (obesity, chest wall deformity, mechanical ventilation), referral to rapid CT pulmonary angiography and postponement of echocardiography during the diagnostic process, early discharge or transfer of the patient, limited device/operator access. Right heart dilatation was reported in 6.3% of the patients who underwent ECHO, tricuspid regurgitation in 69.1%, and global hypokinesia in 12.0%. In 148 patients whose sPAP could be measured with ECHO, the mean sPAP was 46.4±21.4 mmHg. Patients with normal Pab values were not recorded. Patients with Pab values above 30 were included in the study. Patients with increased right heart load were included in the measurements. Of course, considering that sPAP is calculated indirectly from the tricuspid velocity, it is reasonable to think that most patients in whom sPAP cannot be measured do not have high pressures. In this respect, this rate may not reflect the full patient population. Systolic pulmonary artery pressure (sPAP), right heart dilatation, and global hypokinesia findings indicating right heart strain showed significant differences in terms of survival. sPAP was higher in the mortality group.

While the mean sPAP was 41.8±22.4 mmHg in survivors, it was 51.3±31.1 mmHg in the mortality group (p=0.037). The mortality rates in those with and without right heart dilatation were 11.8% and 1.6%, respectively (p=0.021); and the mortality rates in those with and without global hypokinesia were 25.0% and 5.8%, respectively (p=0.007).

PESI and sPESI scores were significantly different between survival and mortality groups (p=0.028 and p=0.021, respectively). There was a higher mortality rate in those with higher CCI and age-adjusted CCI scores, but the difference was not significant (p>0.05). The prognosis of patients according to the early mortality risk groups was also analyzed (**Table 2**). The frequency of death was significantly higher in the high-risk group than in all groups (p=0.02).

The relationship between the laboratory test results of the patients at the time they were diagnosed with PE and survival was also analyzed. Among the parameters, only high D-dimer was associated with mortality. Pro-BNP and cardiac enzymes were also higher in the mortality group, but the difference was not statistically significant.

The correlations between the obtained data were also analyzed. Accordingly; significant correlations were found between sPAP and age (r=0.185 and p=0.006), sPAP and PESI score (r=0.156 and p=0.022), D-dimer and age (r=0.117 and p=0.034), D-dimer and PESI score (r=0.141 and p=0.034), age and PESI score (r=0.579 and p<0.001), PESI and WELLS score (r=0.265 and p<0.001), and PESI and length of hospital stay (r=0.136 and p=0.019).

DISCUSSION

The real-life data obtained in this study show that advanced age, presenting with syncope, high D-dimer level, central location of thrombus, detection of right heart strain findings on echocardiography, presence of comorbidities, high PESI and sPESI scores, and being in a high early mortality risk group are significantly associated with mortality in patients with acute PE. Based on these results, an individualized approach and close follow-up in patients with these risk factors may provide positive gains in prognosis.When the studies in the literature are examined, meticulous and successful PE management has a significant effect on the patient's prognosis.

While a mortality rate of up to 30% is observed in untreated acute PE, the mortality rate in PE diagnosed and treated in a timely manner has been reported as 8%.[8] In a study conducted in Germany, the in-hospital mortality rate of patients hospitalized with a diagnosis of acute PE between 2005 and 2015 was reported as 16.6%.[9] In our study, this rate was 7.3%, and it is seen that we have made positive progress in survival with the developments in PE diagnosis and treatment modalities.

In recent studies, old age is considered a risk factor for both the risk of developing PE and PE-related mortality.[10,11] This claim was largely confirmed in our study.

While patients aged 60 years and over constituted 75.0% of all cases, elderly patients constituted 72.7% of cases resulting in mortality. On the other hand, no significant difference was found when we examined the mortality rates of the elderly and young patient groups separately (7.1% vs. 8.0%).

It has been reported in the literature that many comorbidities are frequently seen in this patient group.[12,13] Studies are showing that COPD exacerbation and AF may be risk factors for PE frequency and mortality. On the other hand, the cause-and-effect relationship between PE and AF is complex.[14,15] While thrombus formation can be triggered by AF, acute PE itself can also trigger the development of AF. The hypothesis that PE can cause AF has a pathophysiological basis. A sudden increase in pulmonary vascular resistance can cause loading of the right ventricle and thus an increase in right atrial pressure. This can lead to atrial arrhythmias such as AF.[15] It has been reported that the risk of VTE is increased in patients with active cancer.[16,17] Similar to the literature, malignancy and AF were frequently detected in our study. When we performed subgroup analysis for the mortality group, the order of comorbidity frequency was AF, chronic kidney disease, chronic obstructive pulmonary disease and malignancy.

Many risk factors that increase the incidence of PE have been identified. Depending on the presence of these risk factors, patients are classified as unprovoked and provoked PE.[1] Whether the risk factor is permanent or transient is also important. Recent history of lower extremity fracture, history of hospitalization for heart failure or AF in the last 3 months, hip or knee prosthesis, major trauma, myocardial infarction in the last 3 months, and spinal cord injury have been identified as the strongest risk factors.[1,17] The fact that our study population was predisposed to immobility, advanced age, and multiple comorbidities was also found to be consistent with the literature.

Genetic thrombophilia is one of the well-known PE risk factors. However, the literature on this subject is very limited. Until the early 2000s, only a weak gene locus had been definitively identified as being associated with VTE. Most of these variants involved strong genetic risk factors such as antithrombin or protein C deficiencies, which increase the risk of VTE by almost 10% in heterozygous carriers. However, since these genotypes are found in less than 1% of the population, this type of thrombophilia represented a very small group of patients. Since PE usually occurs as a complication of DVT, hereditary risk factors are generally thought to be common to these two entities. However, the prevalence and risk associated with many risk factors such as Factor V Leiden or activated protein C resistance differ between DVT and PE. The Factor V Leiden paradox suggests that the rs6025 polymorphism increases the risk of DVT more than the risk of PE.[18,19] These results emphasize the need to consider DVT and PE as different phenotypes in VTE genetic studies. In our study results, the FV-Leiden mutation ranked first among patients with homozygous mutation. DVT was present in 12 of our 18 patients with the FV-Leiden mutation. This situation was considered consistent with the literature. Considering these data, it seems appropriate to investigate genetic thrombophilia in patients with unprovoked PE in the presence of DVT.

In patients with suspected PE diagnosis, laboratory tests and PE probability scores should be evaluated first. In this respect, D-dimer, a fibrin degradation product, is considered quite guiding in hemodynamically stable patients. In the diagnostic approach to PE, d-dimer is a test with high specificity in exclusion.[20,21] However, the relationship between D-dimer elevation and prognosis is not clear. According to our results, D-dimer levels were above the expected values according to age in patients diagnosed with PE. We also detected significantly higher D-dimer levels in the mortality group compared to the survivors. These results indicate that D-dimer may have not only a diagnostic but also a prognostic role.

Mortality risk scoring is recommended as a guide in treatment planning in PE patients.[22] PESI, sPESI, and early mortality risk scores recommended in current guidelines are still used in clinical practice. In our study, these scores and additional CCI scores of the patients were examined. The mean PESI and sPESI scores showed a significant difference between survival and mortality groups. There are several studies on whether the CCI score can be used to predict acute and long-term outcomes in patients with acute PE.[6,7] Although the CCI was higher in the mortality group in our study, this difference was not statistically significant.

Hemodynamic status is the most important determinant of PE prognosis. The instability of the patients at the time of presentation is also related to this situation. Right ventricular dysfunction, which is the basic mechanism of hemodynamic collapse in patients with PE, is one of the early mortality indicators in patients with acute PE. Cardiac arrhythmias and conduction disorders due to right ventricular overload have been identified as possible causes of syncope in PE.[23] It has been reported that detection of thrombus in the main pulmonary artery is more common in patients with PE presenting with syncope.[24-26] In our study, the mortality rate was found to be the highest in patients presenting with syncope and was evaluated in accordance with the literature. ECHO is also quite insignificant in the assessment of the risk of hemodynamic deterioration. In this respect, it is a very important part of the diagnosis and treatment algorithms of patients with PE. Our study results also showed that ECHO findings are closely related to mortality and clearly support this idea.

Limitations

Our study is retrospective and single-center. This limits the number of patients. Collecting data from patient records increases the risk of missing, inconsistent, or incorrect data. This may result in some important variables (e.g., sPAP, which cannot be measured in all patients, or some laboratory tests) being excluded from the analysis. Nevertheless, the goal of presenting real-world data is important and instructive for such studies.

CONCLUSION

The real-life data presented in this study validated the usefulness of the scores recommended by current guidelines in determining the probability, severity, and mortality risk of PE. However, it was also concluded that an individual approach that includes the patients' own baseline characteristics, localization of thrombus, and echocardiographic findings of PE is a better guide. The most important limitation of our study is that it was designed retrospectively. Multicenter, prospective studies with a larger number of cases may clarify this issue more clearly.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Health Sciences University Gülhane Training and Research Hospital Scientific Researches Evaluation and Ethics Committee (Date: 05.11.2020, Decision No: 2020-430).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

REFERENCES

1. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41(4):543-603. doi:10.1093/eurheartj/ehz405
2. Barco S, Valerio L, Gallo A, et al. Global reporting of pulmonary embolism-related deaths in the World Health Organization mortality database: vital registration data from 123 countries. *Res Pract Thromb Haemost*. 2021;5(5):e12520. doi:10.1002/rth2.12520
3. Kalch A, Albani A, Küchler C, et al. Evidence-based health information about pulmonary embolism: assessing the quality, usability and readability of online and offline patient information. *PEC Innov*. 2022;1:100103. doi:10.1016/j.pecinn.2022.100103
4. Martinez Licha CR, McCurdy CM, Maldonado SM, Bakhos CT. Current management of acute pulmonary embolism. *Ann Thorac Cardiovasc Surg*. 2020;26(2):65-71. doi:10.5761/atcs.ra.19-00158
5. Konstantinides SV, Barco S, Lankeit M, et al. Management of pulmonary embolism: an update. *J Am Coll Cardiol*. 2016;67(8):976-990. doi:10.1016/j.jacc.2015.11.061
6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8
7. Ng AC, Chow V, Yong AS, Chung T, Kritharides L. Prognostic impact of the Charlson Comorbidity Index on mortality following acute pulmonary embolism. *Respiration*. 2013;85(5):408-416. doi:10.1159/000342024
8. Turetz M, Sideris AT, Friedman OA, et al. Epidemiology, pathophysiology, and natural history of pulmonary embolism. *Semin Intervent Radiol*. 2018;35(2):92-98. doi:10.1055/s-0038-1642036
9. Kröger K, Moerchel C, Moysidis T, Stang A. Incidence rate of pulmonary embolism in Germany: data from the federal statistical office. *J Thromb Thrombolysis*. 2010;29(3):349-353. doi:10.1007/s11239-009-0396-1
10. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation*. 2018;137(12):e67-e492. doi:10.1161/CIR.0000000000000558
11. Corrigan D, Prucnal C, Kabrhel C. Pulmonary embolism: the diagnosis, risk-stratification, treatment and disposition of emergency department patients. *Clin Exp Emerg Med*. 2016;3(3):117-125. doi:10.15441/ceem.16.146
12. Pérez-Nieto OR, Gómez-Oropeza I, Quintero-Leyra A, Hernández-Castillo R, Vázquez-Rodríguez S. Hemodynamic and respiratory support in pulmonary embolism: a narrative review. *Front Med (Lausanne)*. 2023;10:1123793.
13. Krajewska A, Ptaszynska-Kopczynska K, Kiluk I, et al. Paroxysmal atrial fibrillation in the course of acute pulmonary embolism: clinical significance and impact on prognosis. *Biomed Res Int*. 2017;2017:5049802. doi:10.1155/2017/5049802
14. Koracevic G, Atanaskovic V. Is atrial fibrillation a prognosticator in acute pulmonary thromboembolism? *Med Princ Pract*. 2010;19(2):166. doi:10.1159/000273082
15. Sohara H, Amitani S, Kurose M, et al. Atrial fibrillation activates platelets and coagulation in a time-dependent manner: a study in patients with paroxysmal atrial fibrillation. *J Am Coll Cardiol*. 1997;29(1):106-112. doi:10.1016/s0735-1097(96)00427-5
16. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122(10):1712-1723. doi:10.1182/blood-2013-04-460121
17. Otten HM, Mathijssen J, ten Cate H, Nieuwland WA. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. *Arch Intern Med*. 2004;164(2):190-194. doi:10.1001/archinte.164.2.190
18. Lee EJ, Dykas DJ, Leavitt AD, et al. Whole-exome sequencing in evaluation of patients with venous thromboembolism. *Blood Adv*. 2017;1(10):1224-1237. doi:10.1182/bloodadvances.2017005249
19. Meißner L, Schürmann P, Dörk T, , et al. Genetic association study of fatal pulmonary embolism. *Int J Legal Med*. 2021;135(1):143-151. doi:10.1007/s00414-020-02441-7
20. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA*. 2014;311(11):1117-1124. doi:10.1001/jama.2014.2135
21. Sikora-Skrabaka M, Skrabaka D, Ruggeri P, et al. D-dimer value in the diagnosis of pulmonary embolism-may it exclude only? *J Thorac Dis*. 2019;11(4):172-664. doi:10.21037/jtd.2019.02.88
22. Kohn CG, Mearns ES, Parker MW, Hernandez AV, Coleman CI. Prognostic accuracy of clinical prediction rules for early post-pulmonary embolism all-cause mortality: a bivariate meta-analysis. *Chest*. 2015;147(4):1043-1062. doi:10.1378/chest.14-1888
23. Duplyakov D, Kurakina E, Pavlova T, Shchukin Y. Value of syncope in patients with high-to-intermediate risk pulmonary artery embolism. *Eur Heart J Acute Cardiovasc Care*. 2015;4(4):353-358. doi:10.1177/2048872614527837
24. Sanchez O, Trinquart L, Colombet I, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. *Eur Heart J*. 2008;29(12):1569-1577. doi:10.1093/eurheartj/ehn208
25. Watts JA, Marchick MR, Kline JA. Right ventricular heart failure from pulmonary embolism: key distinctions from chronic pulmonary hypertension. *J Card Fail*. 2010;16(3):250-259. doi:10.1016/j.cardfail.2009.11.008
26. Fremont B, Pacouret G, Jacobi D, et al. Prognostic value of echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism: results from a monocenter registry of 1,416 patients. *Chest*. 2008;133(2):358-362. doi:10.1378/chest.07-1231

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The effect of CPAP treatment on pulmonary function, anxiety/depression and life quality in obstructive sleep apnea syndrome

Emine Keleş[1], Ebru Damadoğlu[2], Ahmet Uğur Demir[3]

[1]Department of Chest Diseases, Ankara Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Ankara, Turkiye
[2]Department of Allergy and Immunology, Faculty of Medicine, Hacettepe University, Ankara, Turkiye
[3]Department of Chest Diseases, Faculty of Medicine, Hacettepe University, Ankara, Turkiye

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Corresponding Author: Emine Keleş, dr.eminekeles@gmail.com

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ABSTRACT

Aims: Obstructive sleep apnea syndrome (OSAS) is a condition commonly associated with excessive daytime sleepiness and neurophysiological dysfunction and increases cardiovascular and cerebrovascular morbidity and mortality. Exercise limitation was assessed with a 6 min walk test (6MWT) in previous studies and was associated with apnea hypopnea index (AHI), body-mass index (BMI), female gender, hypertension (HT), and low FVC values. There are few studies on the effect of CPAP treatment on these parameters. In our study; the aim of this study was to evaluate the changes in pulmonary function test (PFT), 6MWT, quality of life (SF-36) and hospital anxiety / depression scale with patients who should use CPAP because of OSAS.

Methods: Patients who presented to the Sleep Clinic of the Department of Pulmonology at Hacettepe University Faculty of Medicine between 17 October 2018 and 20 December 2018 were enrolled in the study. Individuals with a diagnosis of sleep apnea who met the indication criteria for positive airway pressure (PAP) therapy underwent titration under polysomnographic supervision, and an appropriate PAP device with optimal pressure settings was prescribed. Demographic characteristics, medical history, anthropometric measurements, and polysomnography (PSG) recordings were collected for all participants. Additionally, the Short Form-36 (SF-36) questionnaire, the Hospital Anxiety and Depression Scale (HADS), the 6MWT, and baseline morning spirometry were administered. After obtaining their PAP devices and using them for one month, patients were scheduled for routine follow-up, during which spirometry, the SF-36 questionnaire, HADS, and the 6MWT were reassessed.

Results: 18 patients were included in the study. These patients; 17% were female and 83% were male and the mean age was 46.9±9. The anxiety and depression scores were significantly decreased after one month of CPAP treatment. Before CPAP treatment; anxiety was found in 4 patients and depression was found in 8 patients. One month CPAP treatment; anxiety was present 2 patients and no depression was detected in any patient. In the evaluation of exercise capacity; there was a significant increase in walking distance after CPAP treatment (548.83±60.6, 579.33±54) (p: 0,007). CPAP treatment was significantly improved in subscales of quality of life in general health, physical function, vitality (energy), social function and mental health sub parameters. There was no significant change in spirometric measurements before and after CPAP treatment and titration. There was no significant change in spirometric measurements before and after CPAP treatment and titration. In the correlation analysis, a significant relationship was found between the change in 6MWT and the change in physical function, energy, mental health and anxiety score. At the same time, a significant correlation was found between anxiety and depression improvement and quality of life subscales.

Conclusion: The study demonstrated that even short-term PAP therapy may lead to improvements in several quality-of-life subdomains, anxiety and depression scores, and exercise capacity. Considering the findings of this study, multicenter investigations involving a larger cohort of patients with OSAS, comparing CPAP therapy with alternative treatment modalities and enabling more advanced analyses, would provide a more comprehensive understanding of CPAP-related changes in pulmonary function, quality of life, anxiety and depression, and exercise capacity.

Keywords: Sleep apnea, obstructive, exercise test, quality of life, pulmonary function tests, anxiety, depression, continuous positive airway pressure

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of upper airway obstruction during sleep, often accompanied by a reduction in arterial oxygen saturation.[1] The major symptoms include excessive daytime

sleepiness, witnessed apnea, and loud snoring.[2] Repeated apneic events result in hypoxemia and/or hypercapnia, which, through peripheral and central chemoreceptor mechanisms, lead to increased sympathetic activation, excessive daytime somnolence, cognitive dysfunction, predisposition to depression, and constitute a risk factor for several comorbidities, particularly cardiovascular diseases. The gold-standard treatment modality for OSAS is positive airway pressure (PAP) therapy.[3]

Patients with OSAS frequently experience reductions in daily activity levels due to excessive sleepiness, fatigue, and often increased body weight. Nocturnal hypoxemia impairs skeletal muscle oxidative metabolism, resulting in reduced exercise capacity compared to healthy individuals. Studies have shown that exercise limitation is independent of body composition and is primarily associated with the severity of sleep disturbance.[4] In the literature, exercise limitation has been demonstrated using cardiopulmonary exercise testing (CPET), and regular PAP therapy has been shown to lead to significant improvement in exercise performance.[5]

In this study, we aimed to evaluate the effects of PAP therapy on functional capacity, exercise capacity, and emotional status in patients diagnosed with OSAS. Functional capacity was assessed using the pulmonary function test (PFT), exercise capacity with the six-minute walk test (6MWT), and emotional state using the Hospital Anxiety and Depression Scale (HADS) and the Short Form-36 (SF-36) quality of life questionnaire. Although similar studies exist in the literature, no previous research has evaluated these three parameters simultaneously.

METHODS

Ethics

Ethical approval for this study was obtained from the Hacettepe University Clinical Researches Ethics Committee (Date: 17.10.2018, Decision No: 2018118-21 (KA-I80107)) and the Turkish Medicines and Medical Devices Agency. All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants prior to enrollment.

This prospective observational study was conducted at the Department of Pulmonary Medicine, Hacettepe University Faculty of Medicine, Sleep Disorders Outpatient Clinic, between October 17 and December 20, 2018.

Study Population

A total of 52 patients who underwent polysomnography (PSG) and were diagnosed with OSAS requiring PAP therapy, based on the 2012 American Academy of Sleep Medicine (AASM) scoring criteria, were initially enrolled. The Apnea–Hypopnea Index (AHI), expressed as the number of apnea and hypopnea events per hour, was used to determine OSAS severity:

- Mild OSAS: AHI 5–15/hour
- Moderate OSAS: AHI 15–30/hour
- Severe OSAS: AHI>30/hour

The indication for PAP therapy was determined by a multidisciplinary sleep council comprising specialists in neurology, otorhinolaryngology, pulmonary medicine, and dentistry. Eligible patients underwent overnight PSG with titration to determine the optimal therapeutic pressure.

Before hospitalization, patients' demographic characteristics, medical histories, height, weight, and PSG data were recorded. Baseline assessments included the SF-36 quality of life questionnaire, HADS, 6MWT, and PFT. During titration nights, PSG recordings were performed under technician supervision using a 55-channel system (Alice 6). Pressure titration was adjusted according to apneic and hypopneic events, and optimal PAP pressure was determined based on AASM 2012 scoring rules.

Patients were prescribed PAP devices at the determined pressure and instructed to use them for one month. At follow-up, PFT, HADS, SF-36, and 6MWT were repeated. Device data were downloaded to assess average nightly usage duration, mask leakage, and residual AHI.

Inclusion Criteria

- Age ≥18 years
- Diagnosis of OSAS confirmed by PSG with PAP therapy indication
- Absence of known chronic pulmonary disease (COPD, asthma, bronchiectasis, lung cancer, etc.)
- Voluntary participation with informed consent

Exclusion Criteria

- Pregnancy
- Obesity hypoventilation syndrome
- Psychiatric disorders
- Contraindications to PFT or 6MWT, including:
- Unstable angina
- Myocardial infarction within the previous month
- Active endocarditis, myocarditis, or pericarditis
- Uncontrolled arrhythmia with hemodynamic compromise
- Syncope history
- Severe symptomatic aortic stenosis
- Uncontrolled heart failure
- Acute pulmonary embolism or infarction
- Lower extremity thrombus
- Suspected aortic dissection
- Pulmonary edema
- Uncontrolled asthma
- Resting oxygen saturation ≤85% on room air
- Acute respiratory failure
- Acute non-cardiopulmonary illness affecting exercise performance (e.g., infection, renal failure, thyrotoxicosis)
- Mental impairment preventing cooperation

Pulmonary Function Test (PFT)

After recording patients' height, weight, and age, they were allowed to rest for 15 minutes before testing. Spirometry was performed using a portable device (Medwelt SP10). Parameters measured included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), and mid-expiratory flow rate (FEF25–75%). All values were expressed as percentages of predicted values based on patient demographics. Pulmonary function testing was performed in accordance with the American

Thoracic Society/European Respiratory Society (ATS/ERS) criteria.

Six-Minute Walk Test (6MWT)

Before the test, patients rested for 15 minutes. Baseline blood pressure, heart rate, oxygen saturation, and dyspnea score were recorded. The test was conducted in a 30-meter corridor under supervision, during which patients were instructed to walk at the fastest pace possible for six minutes. Fatigue, dyspnea, and oxygen saturation were continuously monitored. The test was terminated early if severe dyspnea, dizziness, pallor, or a marked drop in oxygen saturation occurred. After six minutes, vital signs and perceived dyspnea were reassessed, and total distance walked was recorded and adjusted for age, sex, height, and body weight. 6MWT was performed in accordance with the ATS/ERS criteria.

Quality of Life Assessment (SF-36)

The SF-36 questionnaire, consisting of 36 items, evaluates eight health-related quality-of-life domains: physical functioning (10 items), role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), social functioning (2 items), mental health (5 items), vitality (4 items), bodily pain (2 items), and general health perceptions (5 items). Each domain is scored from 0 (worst) to 100 (best). Based on the established normative data and discriminative characteristics of the SF-36 in the Turkish population, the questionnaire was administered to patients diagnosed with sleep apnea before and after one month of CPAP treatment use.[6] The test was administered face-to-face by directing the questions to the patient, and the responses provided were recorded.

Hospital Anxiety and Depression Scale (HADS)

HADS is a 14-item self-report instrument used to evaluate the risk and severity of anxiety and depression. Odd-numbered items assess anxiety, and even-numbered items assess depression. Scores ≥10 on the anxiety subscale and ≥7 on the depression subscale indicate a high risk for each condition. The Turkish validity and reliability study of the HADS was used as a reference, and the scale was administered to patients diagnosed with sleep apnea both before PAP therapy and after the first month of treatment.[7] The test was administered face-to-face by directing the questions to the patient, and the responses provided were recorded.

Statistical Analysis

All data analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (SD) for normally distributed data, or as median [minimum–maximum] and 25th–75th percentiles for non-normally distributed data. Categorical variables were presented as numbers and percentages. Normality was tested with the one-sample Kolmogorov–Smirnov test. Paired-sample t-tests were used for normally distributed paired data; the Wilcoxon signed-rank test for non-normally distributed data; and McNemar's test for categorical paired comparisons (e.g., anxiety presence before vs. after therapy). Correlations between variables were assessed using Pearson's correlation coefficient. p-value of <0.05 was considered statistically significant.

RESULTS

This study was conducted at the Department of Pulmonary Medicine, Hacettepe University Faculty of Medicine, between October 17 and December 20, 2018. During this period, 52 patients diagnosed with moderate or severe OSAS who required PAP therapy underwent overnight PSG with titration in the sleep laboratory. However, after applying the exclusion criteria, the study was completed with 18 eligible volunteer patients (**Figure**).

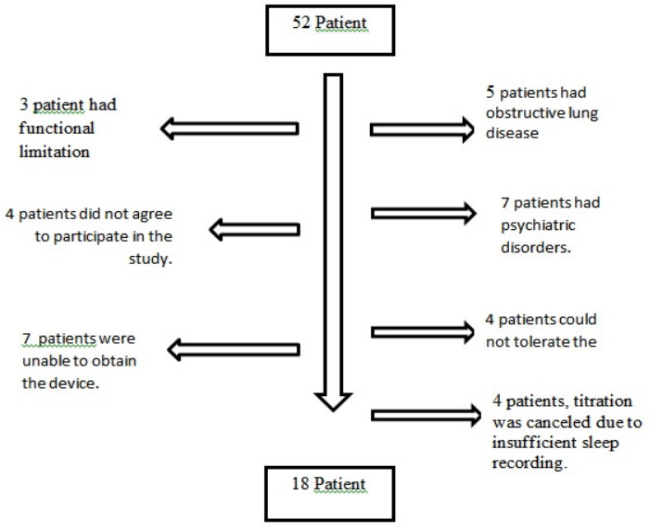

Figure. The patient selection and exclusion process in the study has been illustrated schematically

Patient Characteristics

The demographic and clinical characteristics of the study group are summarized in **Table 1**. The mean age was 46.9±9.0 years, and 83.3% (n=15) of participants were male. Six patients (33.3%) were current smokers, 5 (27.8%) were former smokers, and 7 (38.9%) had never smoked. The median smoking history was 15 pack-years (range: 5-60).

Table 1. Demographic and clinical characteristics of the study population

Sex (n=18)	**n (%)**
Female	3(16.7)
Male	15(83.3)
Age±SD (years)	46.94±9.03
Smoking status (n=18)	
Current smoker	6 (33.3)
Former smoker	5 (27.8)
Never smoked	7 (38.9)
Smoking (pack-years)	15 (5-60)*
Comorbid diseases	
Hypertension	5 (27.8)
Diabetes mellitus	3 (16.7)
Venous thromboembolism	1 (5.6)
Pulmonary hypertension	1 (5.6)
Epilepsy	2 (11.1)
None	3 (16.7)

SD: Standard deviation. Median, minimum, and maximum values are provided

Comorbidities included hypertension (HT) in 5 patients (27.8%), diabetes mellitus in 3 (16.7%), venous thromboembolism in 1 (5.6%), pulmonary HT in 1 (5.6%), and epilepsy in 2 (11.1%). Three patients (16.7%) had no comorbid disease.

Baseline body composition parameters are presented in **Table 2**. The mean body-mass index (BMI) was 31.2±4.1 kg/m², indicating that half of the participants were overweight and half were obese. The mean neck circumference was 41.5±2.9 cm, and mean abdominal circumference was 111.2±8.8 cm.

Table 2. Baseline anthropometric measurements of the study population

Body measurements (n=18)	Mean±SD	Median (25-75 per)
Weight (kg)	93.28±12.8	94.5 (80-99.5)
Height (cm)	173.11±9.5	173.5 (167-178.5)
BMI (kg/m²)	31.16±4.1	30.41 (27.64-34.80)
Neck circumference (cm)	41.5±2.9	41.5 (40-43)
Abdominal circumference (cm)	111.22±8.8	110.5 (105.2-116

BMI: Body-mass index, Per: Percentile, SD: Standard deviation

Polysomnographic and Titration Findings

Polysomnographic parameters and titration results are shown in **Table 3**. Among the patients, 11% (n=2) were classified as having moderate OSAS and 89% (n=16) as severe OSAS.

The mean AHI during diagnostic PSG was 55.3±21.5 events/hour, which decreased to 6.98±6.5 events/hour during PAP titration (p<0.001). Minimum and mean oxygen saturations increased significantly after titration (p<0.001 for both). The duration of sleep spent with oxygen saturation below 90% decreased significantly after titration (p<0.001).

The lowest heart rate significantly increased during titration (p<0.001), while the highest heart rate significantly decreased (p=0.001). Total sleep time and sleep stage percentages did not differ significantly between the diagnostic and titration PSG recordings.

At the one-month follow-up after initiation of PAP therapy, device-derived data were examined. Thirteen patients had devices with data-recording capability. The mean AHI among these patients was 2.3 events/hour. One patient exhibited a mean AHI of 15.3 events/hour, necessitating an increase of 2 cmH_2O in the device pressure. It was also noted that 50% of the patients (n=9) demonstrated PAP adherence exceeding 80%.

Quality of Life Assessment

Comparison of pre- and post-PAP therapy SF-36 subscale scores is shown in **Table 4**. Significant improvements were observed in physical functioning (p=0.009), general health (p=0.005), vitality (p=0.003), social functioning (p=0.007), and mental health (p=0.007) domains after one month of PAP therapy. No statistically significant changes were detected in role limitations due to physical problems, bodily pain, or role limitations due to emotional problems. Subgroup analysis of patients with ≥80% PAP adherence (n=9, 50%) revealed no significant differences in SF-36 subscale scores compared with the overall cohort.

Table 4. Comparison of SF-36 quality-of-life subscales before and after PAP therapy

SF-36 subscales	Pre-PAP	Post-PAP	p value
Physical functioning	80.28±14.29	89.72±11.04	0.009
Role limitations due to physical health	69.44±41.62	81.94±30.68	0.156
Pain	79.17±19.93	86.94±17.81	0.084
General health	56.67±26.12	67.5±23.21	0.005
Vitality (energy)	49.72±29.33	69.44±20.71	0.003
Social functioning	75±26.08	93.05±14.36	0.007
Role limitations due to emotional problems	70.37±35.96	79.63±28.33	0.298
Mental health	69.33±26.53	82.89±12.63	0.007

SF-36: Short Form Quality of Life, PAP: Positive airway pressure

Anxiety and Depression

According to the HADS assessment, the mean anxiety score decreased significantly from 8.33±5.6 before PAP therapy to 4.44±3.7 after one month (p=0.003).

Table 3. Comparison of polysomnographic and PAP titration parameters

Polysomnography characteristics			Polisomnography+titration		p value
	Mean±SD	Median (25-75 per.)	Mean±SD	Median (25-75 per.)	
Apnea–Hypopnea Index	55.29±21.5	52.55 (42.77-65.9	6.98±6.5	5.5 (1.45-11.1)	<0.001
Total sleep time (min)	358.96±35.3	357.15 (331.7-392.97)	324.47±96	331.7 (260.7-408.8)	0.186
Sleep efficiency (%)	85.23±8.8	87.35 (78.95-91.82)	69.63±16.7	73.4 (59-81.3)	0.002
Lowest oxygen saturation (%)	76.05±10.2	80 (72.75-82.5)	87.38±5.1	88.5 (85.5-91)	<0.001
Mean oxygen saturation (%)	92.9±1.6	93.15 (91.55-94.1)	94.55±1.6	94.5 (93-95.2)	<0.001
REM(%)	13.8±5.1	15.46 (8.95-17.97)	15.16±7.8	15.96 (9.62-21.62)	0.621
Stage 1 sleep (%)	8.92±4.6	9.44 (5.1-11.78)	7.53±6.5	4.55 (1.92-13.03)	0.533
Stage 2 sleep (%)	61.04±12.2	57.34 (52.72-62.69)	65.84±12.1	65.88 (60.18-69.59)	0.291
Stage 3 sleep (%)	16.23±8.8	18.65 (9.31-23.04)	11.16±8.8	8.84 (5.46-17.68)	0.058
Sleep latency (min)	4.73±8.1	2.03 (1.45-5)	16.85±15.6	9.96 (5.11-26.67)	0.011
Time spent with SpO_2 <% 90 (%)	21.91±17.6	17.34 (3.72-36.53)	1.06±2.3	0.14 (0.02-0.86)	<0.001
Mean heart rate (beats/min)	68.41±6.6	66.05 (65.1-72.85)	67.63±8.4	66.5 (61-73)	0.481
Lowest heart rate (beats/min)	40.33±14.2	40.2 (25.45-53.5)	55.55±7.2	54 (49-59.2)	<0.001
Highest heart rate (beats/min)	118.46±26.7	112.5 (91.5-148)	90.94±12.3	86.5 (82-100.7)	0.001

PAP: Positive airway pressure, SD: Standart deviation, Per: Percentile, Min: Minute (Paired-Sample T test and non parametric Wilcoxon's signed-rank test)

Similarly, the mean depression score decreased from 6.11±3.9 to 2.89±3.0 (p=0.001). Before treatment, 44% of patients (n=8) met the HADS criteria for depression, whereas no patients were classified as depressed after PAP therapy.

Pulmonary Function and Exercise Capacity

Pre-and post-treatment pulmonary function and exercise parameters are presented in **Table 5**. A significant increase in six-minute walk distance (6MWD) was observed following PAP therapy (548.8±60.6 m vs. 579.3±54 m, p=0.007).

Table 5. Pulmonary function and exercise performance before and after PAP therapy

	Pre-PAP	Post-PAP	p value
6MWT (meter)	548.83±60.6	579.33±54	0.007
FVC (%)	101.05±20.1	93.69±28.3	0.131
FEV1 (%)	98.05±18.1	95.33±17	0.074
FEV1/FVC	79.76±6.3	79.96±5.5	0.771
PEF (%)	98.55±17.6	100±19.7	0.659
FEF25/75 (%)	87.33±25.6	85.05±24.6	0.433

6MWT: 6 minute walk test, PAP: Positive airway pressure, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, PEF: Peak expiratory flow, orced expiratory flow between 25% and 75% of forced vital capacity

No significant changes were found in spirometric parameters (FVC, FEV_1, FEV_1/FVC, PEF, or FEF25–75).

Correlation Analysis

Correlation analysis demonstrated significant relationships between:

- Age and post-treatment changes in physical functioning, physical role limitation, general health, vitality, mental health, and anxiety scores ($p<0.05$);
- BMI and post-treatment changes in physical functioning ($p<0.05$);
- Change in 6MWD and improvements in physical functioning, vitality, mental health, and anxiety ($p<0.05$);
- PAP usage percentage and changes in pain and anxiety scores ($p<0.05$);
- AHI during diagnostic PSG and post-treatment emotional role limitation scores ($p<0.05$);
- Duration of oxygen saturation >90% during PSG and corresponding emotional role limitation improvement ($p<0.05$).

DISCUSSION

In our study, it was found that in patients with moderate to severe OSAS who required PAP therapy, a one-month period of PAP treatment significantly improved exercise capacity according to the 6MWT results, without notable changes in body composition parameters. PAP therapy also led to improvements in anxiety, depression, and several subscales of quality of life, and these improvements were shown to be interrelated. No significant changes were observed in spirometric measurements after PAP treatment.

Several risk factors have been associated with obstructive sleep apnea, including male sex, increased body weight, tobacco use, and advanced age.[8] OSAS is known to occur more frequently in men than in women. The Turkish Adult Population Epidemiology of Sleep (TAPES) study conducted in 2012 similarly demonstrated a higher prevalence of OSAS among men.[9] In that study, the mean age of 5.021 participants was 40.7±15.1 years. In our study, the male-to-female ratio was 5:1, and the mean age was 46.9±9 years, which is consistent with findings reported in the literature.

Obesity is another major risk factor for OSAS and is defined as a significant contributor to the development of respiratory disorders such as snoring and sleep apnea.[10] Young et al.[11] reported that 58% of OSAS cases were associated with a BMI≥25 kg/m². In a 2019 study, Kandasamy et al.[8] investigated the efficacy of CPAP therapy in 175 OSAS patients and found that 29.7% were overweight and 59.4% were obese, supporting previous research showing that OSAS prevalence is approximately four times higher in obese individuals. In Turkiye, the TAPES study showed that among 5.021 patients, 34.3% were overweight, 15.6% were obese, and 6.6% were morbidly obese.[9] Consistent with these findings, in our study, half of the patients were overweight and the other half obese, with a mean BMI of 31.2 kg/m². Mean neck and abdominal circumferences were also above normal limits. After one month of PAP therapy, no significant change was observed in BMI. Weight loss occurred only in patients who had made substantial lifestyle changes, while one patient with concomitant pulmonary HT and right heart failure experienced weight gain due to fluid retention. These findings suggest that long-term weight reduction programs may be an important intervention strategy for OSAS. PAP therapy alone may not be sufficient for weight loss; however, since our study evaluated short-term results, definitive conclusions cannot be drawn.

The relationship between smoking and OSAS has been evaluated in several previous studies. Multiple cross-sectional epidemiological studies have reported a significant association between smoking and both snoring and sleep apnea. In the Northern European Respiratory Health Study, even individuals who had never smoked but were exposed to passive smoking had a 1.6-fold increased risk of snoring (95% CI, 1.2–2.1), even after adjusting for BMI, age, and sex.[12] Wetter et al.[13] reported a dose-response relationship between smoking and OSAS severity, with more severe symptoms in heavy smokers, and that these symptoms improved after smoking cessation. In our study, 33% of patients were current smokers, 28% were former smokers, and 39% had never smoked. According to 2016 national data, 39.5% of the adult population in Turkiye were daily tobacco users;[14] therefore, the smoking rate in our cohort was lower than the national average.

Cholidou et al.[15] evaluated changes in 6MWT performance after six months of CPAP treatment in OSAS patients and reported a statistically significant increase after therapy. Previous studies have similarly demonstrated beneficial effects of CPAP therapy on exercise performance in OSAS patients.[16,17] Consistent with the literature, in our study, the 6MWT distance significantly increased after CPAP therapy compared with baseline (p=0.007). This improvement can be

explained by the normalization of the baroreflex mechanism, which controls heart rate and is impaired in OSAS patients.[18] Saad et al.[19] reported that reduced baseline FEV_1 in severe OSAS cases was associated with a 29.7 m decrease in 6MWT distance. However, studies on this topic remain limited. Contrary to these findings, although the 6MWT distance significantly improved in our study, spirometric parameters did not show a significant change before and after CPAP treatment. Tapan et al.[20] reported that although not statistically significant, CPAP therapy improved exercise capacity and respiratory muscle strength, enhanced quality of life, and contributed to blood pressure regulation, with minor improvement only in FEV_1. In contrast, Bonay et al.[21] reported that long-term CPAP use in OSAS patients led to decreases in FEV_1 and FEF25–75 values, possibly due to airway irritation and inflammation caused by chronic CPAP exposure. Our study did not evaluate long-term outcomes, and no significant positive or negative changes in spirometric parameters were observed after one month of CPAP therapy. Similarly, there were no significant changes in PFT results between pre/post-night measurements during titration nights. One of the reasons for the absence of significant changes in PFT results may be the short duration of therapy, which might have been insufficient for a measurable physiological response. Additionally, the patients had only recently initiated device use, and their daily usage times were relatively limited. More definitive conclusions may be obtained with a larger sample size and increased daily usage hours.

Depression has been reported in approximately 30% of patients with OSAS,[22] which negatively affects family life, social interactions, and work performance, ultimately impairing quality of life.[23,24] The relationship between psychiatric disorders and OSAS has recently been attributed to a complex feedback mechanism involving biological, metabolic, and neurological dysregulation, which contributes to psychiatric disorders, sleep fragmentation, and cardiovascular and metabolic diseases.[25] In a Turkish study conducted in 2016, Çelik et al.[26] evaluated depression and anxiety levels using the HADS before and at three months of CPAP therapy and found statistically significant improvements in both parameters. Similarly, Gupta et al.,[25] in a systematic review and meta-analysis of 33 studies, reported moderate improvements in depression, anxiety, and quality of life following CPAP treatment, but these benefits were not observed in patients with poor adherence. In our study, anxiety scores decreased significantly after CPAP treatment ($p=0.003$), and there was a statistically significant correlation between CPAP adherence and anxiety score improvement ($p=0.046$). Depression scores also decreased significantly after CPAP therapy ($p=0.001$). These findings support the beneficial effects of CPAP therapy on depressive and anxiety symptoms in OSAS patients, even within a short one-month treatment period.

Increased sleep fragmentation and reduced sleep quality have been associated with excessive daytime sleepiness, impaired quality of life, and negative health outcomes. Coman et al.[27] demonstrated significant improvements in quality of life after three months of CPAP therapy. Similarly, Irer et al.[28] reported improvements in all SF-36 subdomains after three months of treatment. Our findings are consistent with these results, indicating that CPAP therapy improves quality of life by reducing apneic events. Using the SF-36 questionnaire, we observed significant improvements in physical functioning, vitality, social functioning, general health, and mental health after one month of therapy, while changes in physical role limitation, bodily pain, and emotional role limitation were not statistically significant. Subgroup analysis of patients with ≥80% CPAP adherence yielded similar results. In patients with <80% adherence, only the vitality subscale showed significant improvement after treatment. This finding suggests that regular CPAP use may contribute to improvements in quality-of-life subscales, although the small sample size limits definitive conclusions.

In our correlation analysis, a significant relationship was found between improvement in emotional role limitation and baseline AHI. Finn et al. reported that AHI values were significantly correlated with five SF-36 domains; mental health, social functioning, physical role, physical functioning, vitality, and general health indicating that higher AHI levels were associated with poorer scores.[29] The findings of our study and others suggest that various aspects of quality of life are adversely affected by higher AHI values in OSAS patients. Moreover, our results demonstrated interrelationships between anxiety, depression, and quality-of-life subscales.

Limitations

The main limitation of our study is the small sample size, which was primarily due to patient noncompliance with therapy, inability to obtain the PAP device, or preference for alternative treatments. Additionally, only short-term (one-month) outcomes were evaluated, and long-term effects could not be assessed. Another limitation is that only CPAP and BiPAP users were included; therefore, the results could not be compared with other treatment modalities or untreated patients. Furthermore, social, familial, and personal factors independent of the disease, which may influence depression, anxiety, and quality of life, were not evaluated and may have affected the outcomes.

The strengths of our study include the simultaneous evaluation of multiple parameters, providing a comprehensive overview of the physiological, psychological, and functional challenges experienced by OSAS patients. The study demonstrated that significant improvement can be achieved even with short-term therapy. Our findings highlight that overall health and well-being should be evaluated through combined parameters, as they are interconnected.

CONCLUSION

As a result, this study demonstrated that even short-term PAP therapy can significantly improve several subdomains of quality of life, reduce anxiety and depression levels, and enhance exercise capacity in patients with OSAS. Future multicenter studies with larger patient populations and longer follow-up periods are warranted to compare CPAP with alternative treatment modalities and to further elucidate its impact on pulmonary function, quality of life, and emotional well-being.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for this study was obtained from the Hacettepe University Clinical Researches Ethics Committee (Date: 17.10.2018, Decision No: 2018118-21 (KA-I80107)).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

REFERENCES

1. Chokroverty S. Overview of sleep & sleep disorders. *Indian J Med Res.* 2010;131:126-140.
2. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. *Sleep.* 1999;22(5):667-689.
3. Kielb SA, Ancoli-Israel S, Rebok GW, Spira AP. Cognition in obstructive sleep apnea–hypopnea syndrome (OSAS): current clinical knowledge and the impact of treatment. *Neuromolecular Med.* 2012;14(3):180-193. doi:10.1007/s12017-012-8182-1
4. Peppard PE, Young T. Exercise and sleep-disordered breathing: an association independent of body habitus. *Sleep.* 2004;27(3):480-484. doi:10.1093/sleep/27.3.480
5. Lin CC, Hsu Y, Chen YH, Lin CY, Wang Y. Effect of treatment by nasal CPAP on cardiopulmonary exercise test in obstructive sleep apnea syndrome. *Lung.* 2004;182(4):199-212. doi:10.1007/s00408-004-2502-7
6. Demiral Y, Ergor G, Unal B, et al. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. *BMC Public Health.* 2006;6:247. doi:10.1186/1471-2458-6-247
7. Aydemir Ö, Güvenir T, Küey L, Kültür S. Validity and reliability of the Turkish version of the Hospital Anxiety and Depression Scale. *Turkish J Psychiatry.* 1997;8(4):280-287.
8. Kandasamy G, Reddy K, Raj S, et al. Effectiveness of nasal continuous positive airway pressure therapy in patients with obstructive sleep apnea. *Int J Health Plann Manage.* 2019;34(4):e1593-e1601. doi:10.1002/hpm.2758
9. Sadik A, Ahmet UD, Zeynep ZU, et al. Prevalence and associated factors of sleep-disordered breathing in Turkish adult population. *Sleep Biol Rhythms.* 2013;11:29-39.
10. Huang KT, Huang YJ, Chou YT, et al. The influence of obesity on different genders in patients with obstructive sleep apnea. *Sci World J.* 2014;2014:1-7. doi:10.1155/2014/487215
11. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol.* 2005;99(4):1592-1599. doi:10.1152/japplphysiol.00587.2005
12. Franklin KA, Gislason T, Omenaas E, et al. The influence of active and passive smoking on habitual snoring. *Am J Respir Crit Care Med.* 2004;170(7):799-803. doi:10.1164/rccm.200404-474OC
13. Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M. Smoking as a risk factor for sleep-disordered breathing. *Arch Intern Med.* 1994;154(19):2219-2224.
14. The Tobacco Atlas, Turkey. [Internet]. Available from: https://tobaccoatlas.org/country/turkey/. Accessed March 13, 2019.
15. Cholidou KG, Kallianos A, Papageorgiou E, et al. Heart rate recovery post six-minute walking test in obstructive sleep apnea. *Clin Res Cardiol.* 2014;103(10):805-815. doi:10.1007/s00392-014-0721-3
16. Schlosser B, Wichmann M, Teschler H. Improvement of cardiopulmonary exercise capacity in patients with obstructive sleep apnea syndrome under CPAP therapy. *Med Klin (Munich).* 2006;101(2):107-113. doi:10.1007/s00063-006-1015-y
17. Lin CC, Hsu Y, Chen YH, Lin CY, Wang Y. Effect of treatment by nasal CPAP on cardiopulmonary exercise test in obstructive sleep apnea syndrome. *Lung.* 2004;182(4):199-212. doi:10.1007/s00408-004-2502-7
18. Bonsignore MR, Marrone O, Insalaco G, Bonsignore G. Baroreflex control of heart rate during sleep in severe obstructive sleep apnoea: effects of acute CPAP. *Eur Respir J.* 2006;27(1):128-135. doi:10.1183/09031936.06.00042904
19. Ben Saad H, Ben Hassen I, Ghannouchi I, et al. Six-minute walk test data in severe obstructive sleep apnea-hypopnea syndrome under continuous positive airway pressure treatment. *Respir Med.* 2015;109(5):642-655. doi:10.1016/j.rmed.2015.03.001
20. Tapan ÖO, Yıldız T, Erdem N, et al. Effect of nasal continuous positive airway pressure therapy on the functional respiratory parameters and cardiopulmonary exercise test in obstructive sleep apnea syndrome. *Turk Thorac J.* 2016;17(1):1-6. doi:10.5578/ttj.17.1.001
21. Bonay M, Nitenberg A, Maillard D. Should flow-volume loop be monitored in sleep apnea patients treated with continuous positive airway pressure? *Respir Med.* 2003;97(7):830-834. doi:10.1016/s0954-6111(03)00039-8
22. El-Ad B, Lavie P. Effect of sleep apnea on cognition and mood. *Int Rev Psychiatry.* 2005;17(4):277-282. doi:10.1080/09540260500104508
23. Schlosshan D, Elliott MW. Clinical presentation and diagnosis of the obstructive sleep apnoea hypopnoea syndrome. *Thorax.* 2004;59(4):347-352. doi:10.1136/thx.2003.007179
24. Lacasse Y, Godbout C, Series F. Health-related quality of life in obstructive sleep apnoea. *Eur Respir J.* 2002;19(3):499-503. doi:10.1183/09031936.02.00216902
25. Gupta MA, Simpson FC. Obstructive sleep apnea and psychiatric disorders: a systematic review. *J Clin Sleep Med.* 2015;11(2):165-175. doi:10.5664/jcsm.4466
26. Celik M, Yalcin S, Ozdemir C, et al. Effect of continuous positive airway pressure treatment on depression, anxiety, and perceived stress levels in patients with obstructive sleep apnea syndrome. *Turk Psikiyatri Derg.* 2016;27(4):244-250.
27. Coman AC, Borzan CM, Todea DA, Pop CM. Obstructive sleep apnea syndrome and the quality of life. *Clujul Med.* 2016;89(3):390-395. doi:10.15386/cjmed-593
28. Irer B, Celikhisar A, Celikhisar H, Bozkurt O, Demir Ö. Evaluation of sexual dysfunction, lower urinary tract symptoms, and quality of life in men with obstructive sleep apnea syndrome and efficacy of continuous positive airway pressure therapy. *Urology.* 2018;121:66-71. doi:10.1016/j.urology.2018.08.001
29. Finn L, Young T, Palta M. Sleep-disordered breathing and self-reported general health status in the Wisconsin Sleep Cohort Study. *Sleep.* 1998;21(7):701-706.

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Case Report

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Symptomatic unicentric Castleman disease with hilar localization mimicking malignancy: a diagnostic challenge

Ayşen Atasoy[1], Esma Sevil Akkurt[1], Özlem Düvenci Birben[1], Muhammet Ali Beyoğlu[2], Derya Yenibertiz[1]

[1]*Department of Pulmonology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkiye*
[2]*Department of Thoracic Surgery, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkiye*

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Corresponding Author: Esma Sevil Akkurt, esma.sevil@hotmail.com

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ABSTRACT

Unicentric Castleman disease (UCD) is a rare lymphoproliferative disorder that is often detected incidentally and asymptomatically. However, in some cases, mass effect or inflammatory features may cause clinical symptoms, posing a diagnostic challenge. A 43-year-old woman with a history of toxic nodular goiter presented with dyspnea. Thoracic CT revealed a 37×29 mm well-circumscribed mass in the left hilum encasing the basal branch of the pulmonary artery. PET-CT showed moderate FDG uptake (SUVmax: 6.1). EBUS-guided biopsy reported reactive lymphoid tissue. Due to diagnostic uncertainty, surgical excision was performed. Histopathology confirmed hyaline-vascular type UCD. HHV-8-associated MCD and lymphoma were excluded. This case highlights the diagnostic complexity of UCD, especially when presenting with a symptomatic hilar mass and moderate FDG uptake mimicking malignancy. Surgical biopsy remains essential for definitive diagnosis.

Keywords: Unicentric Castleman disease, hyaline-vascular type, hilar localization; FDG-PET, excisional biopsy

INTRODUCTION

Castleman disease (CD), first described by Castleman et al.[1] in 1954, is a rare lymphoproliferative disorder characterized by lymph node hyperplasia. Clinically, it is classified into two main forms: unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD).[2,3] UCD typically involves a single lymph node or nodal station and is often asymptomatic.[3] Diagnosis is usually made incidentally during imaging studies performed for other reasons. However, in rare cases, clinical symptoms may develop due to the mass effect of the lesion.[4] While the mediastinum is the most frequently reported site of involvement, hilar localization remains exceedingly rare.[5,6]

The estimated annual incidence of CD is approximately 21-25 cases per million population, with unicentric forms accounting for the majority.[2,9] A definitive diagnosis of UCD can only be established by histopathological examination, as minimally invasive biopsies are often inconclusive.[6,7] In this context, symptomatic UCD with hilar localization is exceedingly rare and may mimic malignancy during the diagnostic process. Herein, we present a case of hilar UCD encasing the pulmonary artery with moderate fluorodeoxyglucose (FDG) uptake on positron emission tomography–computed tomography (PET-CT), histopathologically diagnosed as the hyaline-vascular subtype, highlighting the diagnostic challenges and surgical management.

CASE

A 43-year-old female patient presented to the pulmonology outpatient clinic with complaints of shortness of breath. Her only known medical condition was toxic nodular goiter. She was a lifelong non-smoker. Physical examination findings were unremarkable, and pulmonary function tests were within normal limits. Laboratory tests revealed anemia, leukocytosis, and elevated C-reactive protein (CRP) levels, although there were no clinical signs of infection.

A chest X-ray showed fullness in the left hilar region. Thoracic computed tomography (CT) revealed a well-circumscribed mass measuring 37×29 mm in the left hilum, encircling 180 degrees of the basal branch of the lower lobe pulmonary artery, along with a 15×11 mm lymphadenopathy in the subcarinal area (**Figure 1**).

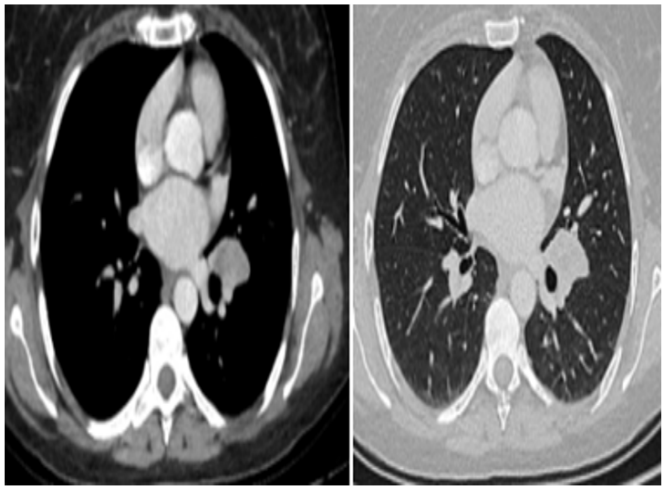

Figure 1. Thoracic computed tomography (CT) showing a well-circumscribed mass (37×29 mm) in the left hilum encircling the basal branch of the lower lobe pulmonary artery, with a 15×11 mm subcarinal lymph node

On PET-CT, a mass-like lesion of approximately 4 cm in the left hilar region demonstrated moderate FDG uptake (SUVmax: 6.1) (**Figure 2**). The differential diagnosis included tuberculosis, sarcoidosis, and lymphoma. Sampling of subcarinal and left infrahilar lymph nodes was performed via endobronchial ultrasound (EBUS). Cytological examination was consistent with a reactive lymph node pattern.

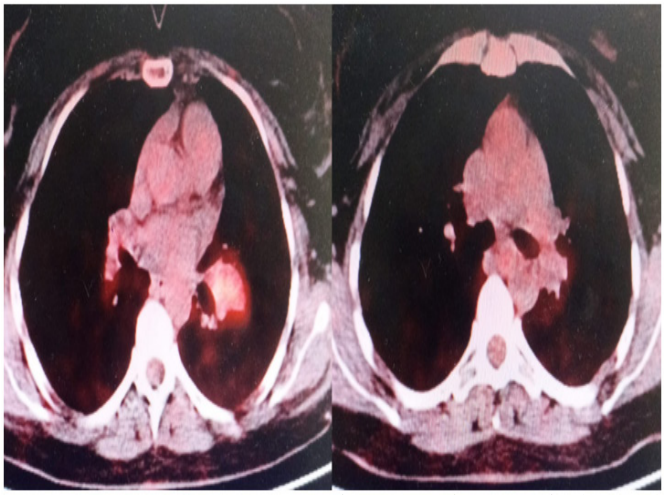

Figure 2. Positron emission tomography–computed tomography (PET-CT) demonstrating moderate fluorodeoxyglucose (FDG) uptake (SUVmax=6.1) in the left hilar mass

As the diagnosis remained inconclusive, the patient was referred to thoracic surgery, and an excisional biopsy was planned. Following surgical excision, histopathological examination confirmed the diagnosis of hyaline-vascular type CD (**Figure 3**). To exclude human herpesvirus 8 (HHV-8)–associated MCD and lymphoma, serum protein electrophoresis, immunofixation, Epstein–Barr virus (EBV) PCR, 24-hour urine protein analysis, and urine electrophoresis were performed, all of which were within normal limits. Beta-2 microglobulin level was 2.83 mg/L, and lactate dehydrogenase (LDH) was 161 U/L. Although both values were normal, elevations in these parameters may be observed in multicentric forms, helping to distinguish them from UCD. The patient was followed postoperatively without complications.

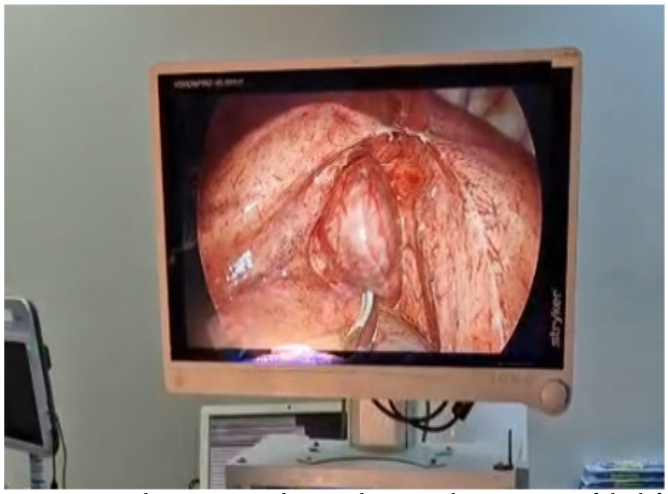

Figure 3. Bronchoscopic view showing the external compression of the left lower lobe bronchus caused by a well-circumscribed hilar mass

DISCUSSION

UCD is a rare lymphoproliferative disorder that is often asymptomatic and usually detected incidentally during radiological examinations performed for unrelated reasons.[2,3] While the mediastinum is the most common site of involvement, UCD has also been reported in various anatomical regions, such as the neck, mesentery, and retroperitoneum.[5,6] Hilar localization, particularly on the left side, is extremely rare. Only a few cases of hilar UCD have been reported in the literature, and these cases similarly presented with nonspecific respiratory symptoms and imaging findings mimicking malignancy.

Although UCD is typically asymptomatic, some patients may develop localized symptoms, such as dyspnea, chest pain, or cough, due to the mass effect of the lesion.[4,8] In our patient, dyspnea was likely related to the mass encasing the pulmonary vasculature. Laboratory findings, including leukocytosis, anemia, and elevated CRP, resembled systemic inflammatory features more commonly associated with MCD.[2,9] However, mild inflammatory responses have also been reported in some UCD cases.[9] Normal beta-2 microglobulin and LDH levels in our patient further supported the unicentric form, as elevations in these parameters are more suggestive of multicentric disease.

One of the major diagnostic challenges in our case was the presence of imaging features suggestive of malignancy. PET-CT demonstrated moderate FDG uptake (SUVmax: 6.1) within the lesion, raising suspicion for malignancy. Although PET-CT is useful for identifying metabolically active lesions, its specificity in differentiating benign from malignant conditions is limited.[10,11] Therefore, PET-CT findings alone are insufficient for definitive diagnosis.

EBUS-guided biopsy in our patient revealed only reactive lymphoid tissue, which was inadequate for diagnosis. As reported in the literature, minimally invasive biopsies have limited diagnostic yield in UCD, and excisional biopsy remains the gold standard.[6,7] In our patient, histopathological

examination following surgical excision confirmed the diagnosis of hyaline-vascular type UCD. This subtype is the most common in UCD and is associated with a favorable prognosis and low recurrence rate.[2,12] Complete surgical resection in UCD is associated with excellent long-term survival and minimal risk of recurrence.[6] In our case, total excision was achieved, the postoperative period was uneventful, and the patient remains stable under follow-up.

CONCLUSION

A left hilar mass encasing the pulmonary artery with moderate FDG uptake initially raised suspicion for malignancy; however, the definitive diagnosis of hyaline-vascular type UCD was established only after surgical excision. CD, particularly in uncommon locations, can clinically and radiologically mimic malignancy. In symptomatic cases with hilar localization and FDG uptake, the differential diagnosis should remain broad, and surgical excision should be strongly considered when minimally invasive methods are inconclusive, as it remains the gold standard for definitive diagnosis.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent has been obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

All authors made substantial contributions to the clinical documentation, interpretation, and manuscript preparation. All authors approved the final version of the manuscript.

REFERENCES

1. Castleman B, Towne VW. Case records of the Massachusetts General Hospital: Case No. 40231. *N Engl J Med.* 1954;250(23):1001-1005. doi:10.1056/NEJM195406102502308
2. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease. *Blood.* 2017;129(12):1646-1657. doi:10.1182/blood-2016-10-746933
3. UpToDate: "Unicentric Castleman disease: clinical features, evaluation, and diagnosis." Erişim: July 2025.
4. Harisinghani MG, Kalra MK, Dineen S, et al. Radiologic features of unicentric Castleman disease on CT. *Clin Radiol.* 2012;67(2):137-143.
5. Bonekamp D, Horton KM, Hruban RH, Fishman EK. Castleman disease: the great mimic. *Radiographics.* 2011;31(6):1793-1807. doi:10.1148/rg.316115502
6. Talat N, Belgaumkar AP, Schulte KM. Surgery in Castleman's disease: a systematic review of 404 published cases. *Ann Surg.* 2012;255(4):677-684. doi:10.1097/SLA.0b013e318249dcdc
7. Bowne WB, Lewis JJ, Filippa DA, et al. The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. *Cancer.* 1999;85(3):706-717. doi:10.1002/(sici)1097-0142(19990201)85:3<706::aid-cncr21>3.0.co;2-7
8. Frizzera G. Castleman's disease and related disorders. *Semin Diagn Pathol.* 1988;5(4):346-364.
9. Liu AY, Nabel CS, Finkelman BS, et al. Idiopathic multicentric Castleman's disease: a systematic literature review. *Lancet Haematol.* 2016;3(4):e163-e175. doi:10.1016/S2352-3026(16)00006-5
10. Kato Y, Kojima M, Yatsui SK. Usefulness of FDG-PET in differentiating Castleman's disease from lymphoma. *J Nucl Med.* 2018;59(suppl 1):19.
11. Ueno T, Suzui N, Tamura A, et al. FDG-PET/CT for evaluation of Castleman disease. *Cancer Imaging.* 2019;19(1):25.
12. Chen D-Y, Chen H-Y, Hou C-H, et al. Clinicopathological features and prognosis of hyaline vascular subtype unicentric Castleman disease. *J Thorac Dis.* 2020;12(12):7628-7636.