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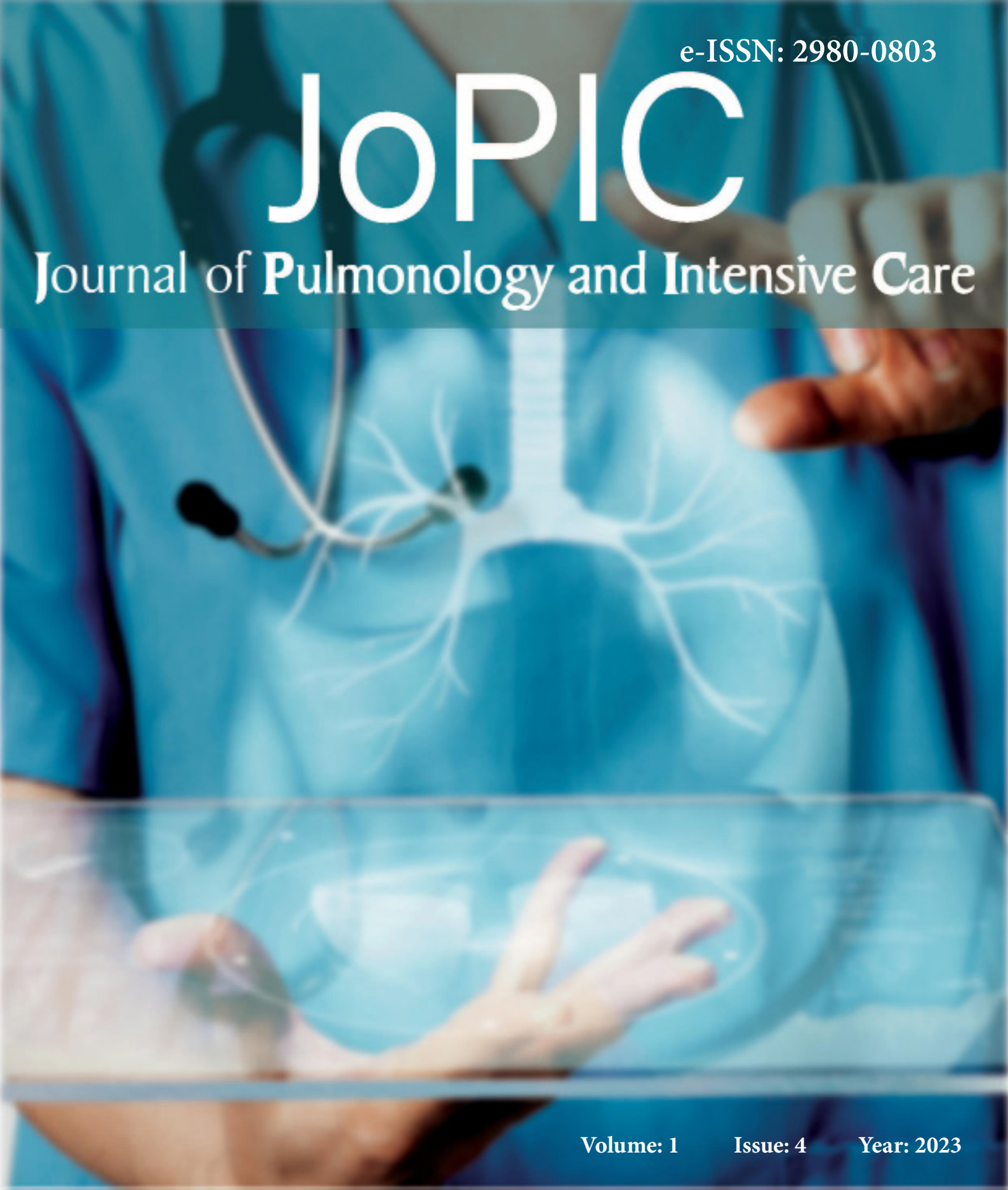

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EDITORIAL

Dear Colleagues,

As of November 2023, we have published the fourth issue of Journal of Pulmonology and Intensive Care (JoPIC) under the shield of Medihealth Academy. In addition to all researchers, referees and editorial board who contributed to the preparation of the journal; we would like to thank the printing team for their effort in preparing it for publication. Our main purpose in realizing the idea of this journal is to create a new platform for resarch that we believe will contribute to the literature in the fields of Chest Diseases and Intensive Care, as well as to increase the motivation of researchers with fast and effective article evaluation and publication processes. This fourth issue includes four original research, and a case report. Periodicals are popular with their readers and researchers. In the upcoming period, with your support, our goal is for JoPIC to be indexed in nationally and internationally accepted scientific indexes. I would like to thank you in advance for your contribution.

Assoc. Prof. Dr. Berna AKINCI ÖZYÜREK
Editor in Chief

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Original Article

DOI: 10.51271/JOPIC-0019

The role of clinical pulmonary infection score and some infection biomarkers in diagnosis and follow up in hospital acquired pneumonia

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ABSTRACT

Aims: Early diagnosis and treatment affect mortality in hospital-acquired pneumonia (HAP). Therefore, clinicians need some objective parameters for guiding treatment. The aim of this study was to determine the course of "clinical pulmonary infection score" (CPIS), C-reactive protein (CRP) and procalcitonin (PCT) in patients under treatment as well as the relationship of these parameters with each other and mortality.

Methods: This single-center, prospective, cross-sectional study focused on cases of HAP in hospitalized patients. In patients with HAP; CPIS, CRP and PCT assays were assessed on the first day. Appropriate treatment was initiated according to Turkish Thoracic Society HAP Task Force recommendations. On the 3rd day, CPIS evaluation and on the 4th day CRP and PCT analysis were repeated. All the patients' one month mortality rates were recorded.

Results: Among the 25 patients, there were 14 females. The mean age was 66±15 years. The mean duration for HAP development was 9.4±8.2 days. With a cutt-off value of 65 for age CPIS, CRP, PCT, length of hospital stay and mortality rate was not found different ($p>0.05$), however as the age increased HAP development duration significantly decreased ($r=-0.416$, $p=0.03$). We demonstrated a significant change between the first and the follow-up values of fever ($p=0.046$), leukocyte ($p<0.001$), PaO_2/FiO_2 ($p=0.016$), secretion presence ($p<0.001$), culture positivity ($p<0.001$) as well as total CPIS ($p=0.030$). However, there wasn't a significant difference in CRP and PCT levels. We couldn't show any relation between CPIS domains, total CPIS, CRP, PCT, HAP development duration and mortality rates.

Conclusion: Monitoring HAP treatment according to CPIS was found better than CRP and PCT. However, these parameters had no effect on mortality. For more accurate comments, studies with more patients are needed.

Keywords: C-reactive protein, clinical pulmonary infection score, hospital-acquired pneumonia, procalcitonin

INTRODUCTION

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs either 48 hours after hospital admission, excluding cases within the incubation period upon admission, or within the 48 hours following discharge from the hospital.[1,2]

The microorganisms responsible for HAP, underlying conditions, risk factors, and pneumonia onset timing can vary. Despite being the second most common nosocomial infection, HAP has the highest mortality rate. Early and appropriate treatment significantly reduces mortality. Thus, prompt initiation of suitable empirical treatment following diagnostic sampling is crucial. Adjustments to antibiotic therapy based on sputum culture results can follow empiric treatment.

Specific infection markers have potential utility in both diagnosing and monitoring HAP.[3] A decline in initial C-reactive protein (CRP) levels over time is indicative of a positive prognosis. Notably, Procalcitonin (PCT) has been recognized as a valuable indicator for assessing both the diagnosis and prognosis of HAP.[3]

The Clinical Pulmonary Infection Score (CPIS) is a comprehensive tool used to diagnose Ventilator-Associated Pneumonia (VAP), a subset of HAP, and guide antibiotic treatment decisions. CPIS combines six clinical and laboratory parameters, including body temperature, white blood cell count, lung

radiograph results, secretion presence, PaO_2/FiO_2 ratio, and sputum culture. The Turkish Thoracic Society (TTS) Adult Hospital-Acquired Pneumonia Diagnosis and Treatment Consensus Report emphasizes investigating CPIS's suitability for diagnosing and managing HAP, especially VAP, within the HAP context.[4]

METHODS

Study population

This single-center, prospective, cross-sectional study was conducted at a university hospital from January to November 2010. It focused on cases of HAP in hospitalized patients. HAP was diagnosed in patients who developed pneumonia 48 hours after admission, excluding cases with an incubation period at admission. Diagnostic criteria followed the Turkish Thoracic Society's guidelines, including new chest X-ray infiltrations and at least 2 of the following: fever>38°C, leukocytosis/leukopenia, purulent secretion, and reduced oxygenation. Participants included newly diagnosed, non-pregnant women, and individuals aged 18 and older. Data were collected from medical records of 25 participants. Those previously diagnosed with and treated for HAP were excluded.

The following factors: age, fever, white blood cell count, PaO_2/FiO_2 ratio, CRP, PCT, time to development of HAP and length of hospital stay were numerically divided into two groups for statistical group analysis.

- Age: < 65 years and ≥ 65 years
- Fever: < 38.4˚C and ≥ 38.4˚C,
- White blood cell count: < 11000 and ≥ 11000,
- PaO_2/FiO_2: < 240 and ≥ 240,
- CPIS: ≤6 and >6,
- CRP: <10.4 and ≥10.4,
- PCT: <0.05 and ≥0.05,
- Time to development of HAP: < 5 days and ≥ 5 days,
- Length of hospital stay: < 10 days and > 10 days

Other parameters were divided into two groups according to whether they were present in the patients or not.

Ethical Consideration

The study was carried out with the permission of the Scientific Research Evaluation and Ethics Committee of our university hospital (Date: 04/01/2010, Decision No: 0002). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Outcome parameters

Initially, patient demographics were recorded, followed by medical histories and physical exams. Recorded parameters included body temperature, white blood cell count, sputum characteristics, lung X-ray results, PaO_2/FiO_2 ratio, CRP, and PCT levels. On day one, lower respiratory tract secretions were sent to the microbiology lab.

Peripheral blood samples in EDTA tubes were assessed for white blood cell count using the Beckman-Coulter laser system in the hematology lab. For CRP, blood samples were centrifuged for 5 minutes at 4000 rpm using a NUVE centrifuge, and the serum was analyzed via BN PROSPEC nephelometry. PCT values were determined using the ELFA method on the MIMIVIDAS device in the biochemistry lab.

For the determination of partial arterial oxygen pressure (PaO_2) value in the PaO_2/FiO_2 ratio, arterial blood samples were collected from the ulnar or femoral artery using a heparinized blood gas syringe. The samples were analyzed using the ion-selective method on the Roche Omni C Cobas b121 device in the biochemistry laboratory. The fractioned of inspired oxygen (FiO_2) value is a percentage value and shows the percentage of oxygen in the air that the patient has taken. For the FiO_2 value, if any oxygen replacement therapy was performed, the oxygen flow rates received by the patients were recorded in lt/min.

For stable patients, postero-anterior (PA) chest radiographs were taken with the patient in a standing position using the Trophy Radiology N500 HFS unit in the radiology department. Unstable patients who were unable to stand received anteroposterior (AP) chest radiographs using the SEDECAL SP-HF-40 mobile X-ray unit while lying down.

On the first day, respiratory secretion samples (sputum from non-intubated patients and endotracheal aspirate - ETA - from intubated patients) were collected and examined in the microbiology lab. Gram staining was used to assess quality and dominant microorganisms. Qualified sputum samples (≥25 leukocytes and ≤10 epithelial cells) were selected for microscopic examination. Bacteria were identified using standard microbiological techniques, with unidentified bacteria identified using BBL Crystal GP and Crystal E/NF ID kits or the BD Phoenix automated identification system.

In 1991, Pugin and colleagues developed the CPIS based on 6 clinical and laboratory data points, including fever, leukocyte count, presence and purulence of tracheal secretions, oxygenation, chest radiography findings, and positive or negative sputum culture (Table 1).[5] The total CPIS score is calculated by summing all the scores obtained by the patients according to the parameters in the table. Research has demonstrated a sensitivity and specificity of 93% and 96%, respectively, for pneumonia when CPIS>6.5 For this reason, we used a cut-off of 6 in our study.

Table 1. Clinical Pulmonary Infection Score (CPIS)[5]

Variables	Score 0	Score 1	Score 2
Temperature ˚C	≥36.5 and ≤38.4	≥38.5 and ≤38.9	≥39 or ≤36
Blood leukocytes µ/L	≥4000 and ≤11000	<4000 or >11000 *	
Tracheal secretions	None	Present, not purulent	Present, purulent
Oxygenation: PaO_2/FiO_2 mmHg	>240 or ARDS		<240 and not ARDS
Pulmonary radiography	No infiltration	Diffuse or patchy infiltrate	Localized infiltrate
Culture of tracheal aspirate	Pathogenic bacteria cultured ≤ 1 or no growth	Pathogenic bacteria cultured > 1**	

*: band forms ≥ 500=+ 1 point, **: same pathogenic bacteria seen on the Gram stain=+ 1 point

After the initial assessment, the total CPIS was calculated based on data including fever, white blood cell count, PaO_2/FiO_2, chest X-ray findings, secretion characteristics and microbiological culture results and empirical antibiotic treatment was initiated according to the recommendations of the guidelines. On the third day of treatment, the patients' body temperatures, white blood cell counts, secretion characteristics, PaO_2/FiO_2 values and chest radiograph findings were re-evaluated. To investigate the presence of microbiological growth, another secretion sample was collected. On the fourth day, only hs-CRP and PCT levels were checked again.

Patients were then followed until discharge and their health status was monitored. Patients were re-evaluated during the first month after diagnosis. If patients were discharged within one month of HAP diagnosis, they were contacted by telephone for assessment. Alternatively, if patients were still being in hospital during the first month after HAP diagnosis, they were assessed at the bedside to collect information on their health status.

Statistical Analysis

Following the collection of data from 25 patients, statistical analysis was conducted. For parametric variables, the Student's t test was used for dependent groups and for non-parametric variables the Wilcoxon test was used. Non-parametric correlations were analysed using the Spearman correlation test. To determine mortality rates within the groups and compare other ratios, the Chi-square test and Fisher's exact test were employed. Values with $p<0.05$ were considered statistically significant.

RESULTS

Out of the 25 patients included in the study, 14 (56%) were female. The mean age was 65.6 ± 15.16 years. Of the patients, 13 (52%) were hospitalized in the general ward, while 12 (48%) were under intensive care unit monitoring and treatment. Among them, 24 (96%) were admitted to internal medicine departments or intensive care units, and only 1 patient (4%) was in the intensive care unit of the surgical clinic.

When examining the comorbid diseases of the patients, diabetes mellitus (DM) was present in 1 (4%) patient, cardiovascular disease in 4 (16%) patients, structural lung disease (bronchiectasis) in 1 (4%) patient, chronic obstructive pulmonary disease (COPD) in 9 (36%) patients, chronic kidney disease in 2 (8%) patients, neurological disease in 12 (48%) patients, malignancy in 3 (12%) patients, and a history of respiratory failure in 5 (20%) patients.

The time interval from hospital admission to the development of HAP was analyzed for all patients, with an average of 9.4 ± 8.2 days. This interval was 4 days or earlier for 11 (44%) patients, and 5 days or later for 14 (56%) patients.

Table 2 displays the age, gender, some laboratory values, initial and follow-up data, and one-month mortality information for all cases.

Table 2. Age, gender, some laboratory values, and mortality information of the cases

			Initial			Follow-up			
No	Age	Gender	CPIS	CRP	PCT	CPIS	CRP	PCT	1-month mortality
1	24	F	8	7.20	0.15	8	6.59	0.05	Surviving
2	75	F	1	20.60	0.14	1	-	0.05	Surviving
3	57	F	5	20.60	37.83	3	8.49	0.39	Surviving
4	65	F	3	8.28	0.46	3	3.60	0.74	Surviving
5	63	F	6	0.50	0.31	3	0.50	0.05	Surviving
6	27	F	4	31.20	0.05	4	11.20	0.05	Surviving
7	77	M	4	10.30	0.05	2	10.30	0.06	Surviving
8	83	F	8	10.30	0.12	7	10.30	0.23	Surviving
9	65	M	5	10.30	1.17	5	10.30	4.19	Surviving
10	54	M	5	10.30	1.20	3	10.30	0.95	Surviving
11	55	F	6	-	0.11	6	10.30	0.06	Exitus
12	70	M	4	4.41	0.58	2	10.30	0.42	Surviving
13	55	M	5	4.46	0.39	2	4.33	0.05	Surviving
14	77	M	8	10.30	0.37	7	10.30	0.82	Surviving
15	68	M	5	10.30	12.76	5	10.30	97.99	Surviving
16	85	F	5	10.30	0.05	3	10.30	0.05	Surviving
17	82	F	5	10.30	0.27	3	10.30	0.06	Exitus
18	62	M	7	10.40	1.98	5	10.40	0.66	Surviving
19	80	F	3	10.40	0.29	3	10.40	0.14	Surviving
20	75	M	8	10.40	7.46	4	10.40	0.32	Surviving
21	81	F	5	10.40	0.08	1	10.40	0.08	Exitus
22	55	M	6	10.40	0.06	6	10.40	0.05	Exitus
23	65	F	7	10.40	38.00	10	10.40	16.65	Surviving
24	63	M	7	10.40	2.99	3	10.40	3.33	Surviving
25	67	F	8	10.10	35.80	4	5.25	23.80	Exitus

CPIS, clinical pulmonary infection score; CRP, C-reactive protein; F, female; PCT, procalcitonin; M, male.

Considering the wide age range of the patients in the study, ranging from 24 to 85, they were divided into two groups: those under 65 and those aged 65 and above. The relationship between these groups and parameters such as CPIS, CRP, PCT values, time to HAP development, length of hospital stay, and 1-month mortality rates were examined. In this analysis of age being categorized as under 65 and 65 and above, no significant relationship was found between any parameter and the time to HAP development.

Furthermore, we aimed to investigate the relationship between the 2 most common comorbid diseases and CPIS, CRP, PCT values, time to HAP development, length of hospital stay, and 1-month mortality rates. No significant differences were found based on the presence of COPD or neurological diseases in relation to these parameters.

The means and p-values of the 6 CPIS parameters at the beginning and follow-up are shown in Table 3. Among these parameters, fever, white blood cell count, PaO_2/FiO_2 ratio, microbiological growth, and secretion data demonstrated statistically significant changes between initial and follow-up measurements. Only X-ray findings did not exhibit statistically significant changes. During follow-up, improvements were observed in body temperature, white blood cell count, presence and purulence of secretion, while an increase was observed in PaO_2/FiO_2 values and microbiological growth rates.

Table 3 Changes in CPIS parameters at baseline and follow-up

CPIS parameters		Initial	Follow-up	p value
Fever (Mean ± SD)		37.06±1.05	36.7±0.62	0.046*
Leukocyte Median (IQR)		15160 (11980-17800)	11250 (8150-14620)	0.001*
PaO_2/FiO_2 Median (IQR)		210(152-230)	265(205-310)	0.016*
Secretion (%)	Absent	6 (%24)	9 (%36)	0.001*
	Present. not purulent	4 (%16)	6 (%24)	
	Present. purulent	15 (%60)	10 (%40)	
Infiltration on chest radiograph n (%)	Present	19 (%76)	19 (%76)	>0.05
	Absent	6 (%24)	6 (%24)	
Microbiological growth n (%)	Present	7 (%28)	9 (%36)	0.01*
	Absent	18 (%72)	16 (%64)	

CPIS, clinical pulmonary infection score; n, number.

The PaO_2/FiO_2 ratio was found to have the most significant impact on the initial CPIS value among the six parameters studied (p=0.024 ve r=-0.45). No significant relationship was observed with the other parameters. In terms of microbiological examination, 28% of the patients had growth in their lower respiratory tract secretion samples at the time of diagnosis. However, this increased to 36% in the follow-up sample collected on the third day. Of the patients, 12% had *Pseudomonas aeruginosa* growth both at diagnosis and in the follow-up sample, and the same was observed for Acinetobacter spp. in another 12% of patients. In 12% of patients, there was no growth in the secretion on the first day, but Acinetobacter spp. was only grown in the follow-up. Only one patient had *Staphylococcus aureus* growth at the time of diagnosis, which did not persist in the follow-up sample. Additionally, a statistically significant difference in the CPIS value was found between patients with growth and those without (Table 4).

Table 4. Relationship between the presence of sputum bacterial growth and CPIS value

		CPIS		Total	p value
		≤ 6 n (%)	> 6 n (%)		
Microbiological Growth	Present	2 (%29)	5 (%71)	7 (%28)	0.008*
	Absent	15 (%83)	3 (%17)	18 (%72)	
Total		17 (%68)	8 (%32)	25 (%100)	

CPIS, clinical pulmonary infection score; n, number.

No statistically significant difference was found between the baseline and follow-up values of CRP and PCT, whereas a statistically significant difference was found between CPIS at diagnosis and CPIS at follow-up (Table 5). In addition, when the baseline and follow-up values of CPIS and the baseline and follow-up values of these 2 inflammation markers were analysed among themselves, no statistically significant difference was found between the baseline CPIS value and baseline CRP, baseline PCT values and between the follow-up CPIS and follow-up CRP, follow-up PCT values (Table 6).

Table 5. Changes in CPIS, CRP, PCT values at follow-up compared to baseline

	Initial	Follow-up	p value
CPIS (Mean±SD)	5.52±1.82	4.12±2.22	0.030*
CRP (Median±IQR)	10.30 – 10.10/10.40	10.30 – 8.90/10.40	0.128
PCT (Median±IQR)	0.37- 0.12/2.49	0.23 – 0.05/0.89	0.200

CPIS, clinical pulmonary infection score; CRP, C-reactive protein; PCT, procalcitonin; SD, Standard deviation; IQR, Interquartile range.

Table 6. The relationship of CPIS at diagnosis (A) with initial CRP, PCT values and at follow-up (B) CPIS with follow-up CRP, PCT values

A	Initial CPIS	B	Follow-up CPIS
Initial CRP	p= 0.563 r= - 0.124	Follow-up CRP	p= 0.473 r= 0.154
Initial PCT	p= 0.156 r= 0.292	Follow-up PCT	p= 0.204 r= 0.263

CPIS, clinical pulmonary infection score; CRP, C-reactive protein; PCT, procalcitonin.

When the factors affecting the time to development of HAP were investigated, only a statistically significant correlation was found between age and the time to development of HAP, and the time to development of HAP was shorter with increasing age. Apart from age, no significant correlation was found between fever, leukocyte, PaO_2/FiO_2 value, presence of COPD, CPIS value, baseline CRP, PCT levels and duration of hospitalization and the time to develop HAP (Table 7).

In our study, the patients were divided into 2 groups with a hospitalization period of less than 10 days and more than 10 days, and the relationship between age, fever, leukocyte, PaO_2/FiO_2, presence of secretion, lung radiography findings, CPIS, CRP, PCT values and the duration of HAP development was analysed. In this analysis in which all parameters were grouped according to certain threshold values, no statistically significant relation was found between any parameter and the duration of hospitalization. Only CRP level was found to be higher, although not statistically significant, in patients who were hospitalized for a long time

(more than 10 days). Finally, the association of 1-month mortality rates with 6 CPIS parameters, total CPIS value, CRP, PCT, duration of HAP development, presence of COPD and presence of Acinetobacter spp. was analysed, and none of these parameters were found to be significantly associated with 1-month mortality.

Table 7. Relationship between some demographic, clinical and laboratory data and the development time of HAP

Baseline data	Association with HAP development time (p and r values)
Age	p= 0.03* and r= -0.416*
Body temperature	p= 0.859 and r= -0.038
Leukocyte count	p= 0.632 and r= -0.101
PaO_2/FiO_2	p= 0.495 and r= 0.143
Presence of COPD	p= 0.087 and r= 0.280
CPIS	p= 0.210 and r= -0.260
CRP	p= 0.198 and r= 0.273
PCT	p= 0.295 and r= -0.137
Length of hospital stay	p= 1.0 and r= 0.242

COPD, chronic obstructive pulmonary disease; CPIS, clinical pulmonary infection score; CRP, C-reactive protein; HAP, hospital acquired pneumonia; PCT, procalcitonin.

DISCUSSION

This study aimed to evaluate the use of the CPIS clinical scoring system, CRP and PCT biomarkers in monitoring HAP treatment and their relationship with each other and short-term mortality rate. No significant correlation was found between patient demographics, biomarker levels, and mortality rates. However, improvements in fever, leukocyte count, secretion quality, and CPIS values were observed with antibiotic treatment.

HAP is a leading cause of mortality in hospital-acquired infections. In Turkey, the frequency of HAP has been reported to be 15-22%, but it varies depending on the clinic where the patient is hospitalized.[6] Patients treated in intensive care units are at a higher risk of developing HAP, with the incidence being 5-10 times higher compared to other patients. In a study conducted in Turkey, this rate reached 20 times higher in intensive care unit patients.[6] The possibility of recto-pulmonary contamination and colonization leading to HAP is high in patients in need of care and those in intensive care units. The risk factors for developing HAP include patient-related factors, infection control factors, medical interventions during hospitalization, and the infectious agent. Advanced age is one of the patient-related factors that contribute to higher rates of HAP and increased mortality. Some authors correlate the high incidence of pneumonia in elderly people with the presence of comorbid diseases and longer hospital stays rather than chronological age.[7] However, age is still an important risk factor in patients with non-ventilated HAP, which is thought to be due to some physiological and immunological changes resulting from the aging process.[8]

Apart from age, there are several risk factors specific to the development of HAP, increased mortality and the development of disease with multidrug-resistant pathogens.[9,10] A study conducted by Fortaleza identified age over 65, antacid use, and central nervous system (CNS) diseases as risk factors for healthcare-associated pneumonia.[8] Another study by Dandagi listed mechanical ventilation, prolonged coma or decreased level of consciousness, supine position, aspiration, comorbid diseases, hospitalization diagnosis, prolonged intensive care unit stay, use of positive end-expiratory pressure during mechanical ventilation, severe disease status, multiple organ dysfunction, advanced age, malnutrition, use of nasogastric tube, use of paralytic agents, use of antacids, male gender, enteral nutrition, and immunosuppression as risk factors for nosocomial pneumonia.[11] Gastmeier's study found age, gender, duration of hospitalization, type and size of hospital, intubation, and the use of central venous catheter as risk factors for nosocomial pneumonia-related death.[12] In our study, it was observed that 60% of patients who died in the one-month follow-up were over 65 years old, but due to the small number of patients, no statistically significant difference was found in relation to advanced age and mortality.

Chronic and comorbid conditions including cancer, COPD, chronic lung diseases, heart diseases, and renal failure impact infection progression in HAP and VAP patients.[13] Effective VAP treatment depends on microbial diagnosis, accurate antibiotics, comorbidities, patient response, and organ function.[14] In a 7-year Vallés study on HAP, poor prognosis linked to septic shock with specific microorganisms and COPD.[15] Deng's research identified risk factors for elderly HAP development, including intensive care unit admission, extended COPD history, immunosuppression, antibiotics, mechanical ventilation, and CNS disease.[16] Our study indicated COPD patients had shorter HAP development and longer hospital stays, aligning with literature.

Central nervous system diseases compromise cough and swallowing reflex, facilitating microorganism entry into the lower respiratory tract,[17] especially risky for non-ventilated HAP.[8] A randomized study with 563 patients revealed advanced age, prolonged mechanical ventilation, neurological disease, and low PaO_2/FiO_2 ratio at the 3rd day as risk factors for clinical decline.[18] In our study, 12 patients (48%) had prior neurological diseases. Of them, 7 (58%) had early HAP development, and 9 (75%) stayed in hospitals over 10 days. Neurological disease correlated with HAP onset and extended hospital stays, while did not affect mortality significantly, possibly due to limited patient numbers. Disease severity and risky conditions in non-neurological patients might explain the mortality outcome.

Diagnosing HAP in patients with comorbid diseases can be challenging. To help with diagnosis and treatment guidance, the use of CPIS, a clinical scoring system primarily used for VAP, is recommended. CPIS scores above 6 in VAP patients can indicate a higher likelihood of pneumonia. The main purpose of CPIS is to evaluate and guide treatment. In Luna's study, the change in CPIS values over the first and third days was analyzed in patients with clinical and bacteriological confirmed VAP.[19] The study found that CPIS values gradually decreased during follow-up, with a more significant decrease in surviving patients compared to non-surviving patients. Lower mortality rates were observed in patients with CPIS values below 6 on the third or fifth day after VAP onset. Another study investigated the contribution of CPIS in the treatment of suspected pneumonia in intensive care patients.[20] CPIS was used as a decision-making factor for starting or terminating antibiotic treatment, however, it was discovered that 42% of patients diagnosed with pneumonia by clinicians had CPIS values of 6 or less on the first day. Today, CPIS is still used to manage the antibiotic treatment. In a quasi-experimental study, integrating procalcitonin and

CPIS reduced inappropriate antibiotics for severe Coronavirus disease 2019 (COVID-19) cases, but not for moderate ones.[21] In our study, HAP was not diagnosed according to CPIS, and there were 17 (68%) patients with an initial CPIS of 6 or less and 29% of these patients had microbiological growth. These findings suggest that CPIS alone is not as useful a marker for the diagnosis of HAP as hoped, and this is supported by the literature. In our study, when each parameter was analysed individually in the CPIS values at the beginning of treatment and on the 3rd day of treatment, significant improvement was observed with treatment in terms of fever, leukocytes, PaO_2/FiO_2 and presence of secretion. In addition, PaO_2/FiO_2 ratio was found to be the most effective parameter among 6 parameters on the initial CPIS value. In terms of the presence of infiltration on chest radiography, no change was observed at the beginning of treatment and at the control. This finding is compatible with the general knowledge that the response to treatment is primarily clinical, followed by radiological improvement. However, in terms of microbiological growth, there was an increase in the number of patients with growth in the control compared to the first day. These findings support the more appropriate use of CPIS in HAP treatment follow-up.

In intensive care units (ICUs) worldwide, infections significantly contribute to morbidity and mortality. Vincent et al.[22] conducted a one-day study on 13,796 patients, finding 51% infected and 71% on antibiotics. Respiratory infections constituted 64%, with positive cultures in 70% of cases. Longer ICU stays correlated with higher infection rates, especially for drug-resistant bacteria (Methicillin-resistant *Staphylococcus aureus*, *Acinetobacter*, *Pseudomonas* spp. and *Candida* spp.). Infected patients had more than twice the ICU mortality (25% vs. 11%) and hospital mortality (33% vs. 15%) compared to non-infected patients.[22] In our study, only 28% of patients showed microbiological culture positivity at diagnosis, including *Pseudomonas aeruginosa, Acinetobacter* spp., and *Staphylococcus aureus*. No statistically significant links were found between culture positivity and hospitalization duration or 1-month mortality rate. This could be due to limited cases and growth instances, and potential issues during sample collection and transport. Most patients being followed outside chest diseases clinics might contribute.

Many studies have been conducted to compare CRP with PCT in clinical practice. Simon discovered that PCT levels were more sensitive (88% vs 75%) and specific (81% vs 67%) than CRP in discriminating bacterial inflammation from noninfectious sources of inflammation in adults in a meta-analysis of 12 investigations.[23] Holm demonstrated that while PCT was not superior to CRP in detecting individuals with pneumonia, it was superior to CRP in distinguishing Mycoplasma pneumoniae from other bacterial diseases.[24] In our study, no significant change was seen between CRP and PCT values at baseline and follow-up, however there was a decrease in PCT values that did not achieve statistical significance.

PCT is a serum biomarker that has showed efficacy in distinguishing between viral and bacterial infections, and is frequently utilized in critically sick patients as a guide to antibiotic de-escalation/discontinuation.[25] CRP is an acute-phase inflammatory protein, also plays a key role in identifying and evaluating bacterial infections.[25] However, it is known that the use of both alone is not fully adequate for diagnosis, treatment decision-making, or prediction of morbidity and mortality. As a result, composite biomarkers with high accessibility, such as the combination of neutrophil/lymphocyte count ratio, CRP, and leukocyte count may assist in early diagnosis and severity assessments. So, there are studies in the literature that evaluated CPIS, CRP and PCT together. In a study of 20 suspected VAP patients PCT, CRP and CPIS values were evaluated intermittently.[26] Patients with a microbiologically verified diagnosis of VAP had a higher PCT value than those without a documented diagnosis. PCT had the highest sensitivity and specificity (78% and 97%, respectively), CPIS showed the same sensitivity but lower specificity (80%), whereas CRP had the lowest sensitivity (56%) but comparatively higher specificity (91%). In the end, when PCT levels below the threshold values are paired with CPIS, the rate of false positivity in the diagnosis of VAP is reduced.[26] In our study, no significant difference was found between baseline and follow-up CPIS, CRP and PCT parameters in terms of sensitivity and specificity values to support the diagnosis of HAP, and no statistically significant result was found when the relationship between CPIS, CRP and PCT was analyzed. However, when all parameters were evaluated alone, a statistically significant difference was found in the follow-up values of fever, leukocytes, PaO_2/FiO_2, secretion, microbiological growth and CPIS compared to the baseline values. This result supports that clinical parameters are more useful in follow-up than laboratory data such as CRP and PCT. The fact that PCT values decreased after treatment, although not significantly, suggests that CRP is the least recommended parameter to be used in follow-up.

Long hospitalization is a risk factor for HAP, which can increase the duration of hospitalization, treatment costs, and mortality. Elderly patients are particularly vulnerable to complications associated with hospitalization, such as nosocomial infections, loss of function, immobility, and confusion. Pneumonia and urinary tract infections are the most common nosocomial infections.[27] In our study we found that only CRP levels were significantly higher in patients with long hospital stays, but no significant relationships were found between other parameters and duration of hospitalization. The main reason for prolonged hospitalization was the primary diagnosis and underlying diseases of the patients. In a study PCT, CRP, and clinical scores (CPIS, etc) were compared in patients with healthcare-associated infections, and it was found that the increase in PCT, CRP, and clinical score levels were correlated with mortality rates.[3] In contrast, in our study, lower CRP level was not associated with 1-month mortality, but the CRP and PCT levels remained elevated in most patients who died within 1 month.

Study Limitations

The most prominent limitation of our study is that it is a single-centre study with a small number of participants. Some patients did not provide sufficient and high-quality lower respiratory tract samples, such as sputum, particularly on the initial day of HAP diagnosis. Finally, the fact that some of the patients were hospitalized in clinics other than Chest Diseases may also have had a negative impact on sample collection.

CONCLUSION

As a result of our study, when the CPIS clinical scoring system and PCT and CRP biomarkers were examined in terms of monitoring HAP therapy, the most relevant parameter

to be employed in monitoring was determined to be CPIS. PCT came in second, whereas CRP was not determined to be an acceptable marker for follow-up. No parameter was found to be useful in predicting mortality. However, further investigations on more instances are needed to establish more certain conclusions.

ETHICAL DECLARATION

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Manisa Clinical Researches (Date:04.01.2010, Decision No: 0002).

Informed Consent: All patients voluntarily signed the informed consent form.

Reviewer Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The role of malondialdehyde in the evaluation of the treatment response in acute pulmonary thromboembolism

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ABSTRACT

Aims: To facilitate the early diagnosis of the related patient group by investigating the level of Malondialdehyde (MDA) in high-risk pulmonary thrombo embolism (PTE). In addition, it was aimed to see the effect of treatment after acute PTE on oxidative stress and to evaluate whether it is associated with the development of chronic thrombus.

Methods: This study was conducted prospectively in 44 patients diagnosed with PTE in single-center. At the time of diagnosis, after 6 months of follow-up and treatment, the MDA levels of the patients were evaluated together with the controlled tests.

Results: MDA level was found to be a determinant in the estimation of high-risk PTE. The average MDA levels of the patients included in the study were found to be 9.64±3.76 before PTE treatment and 4.74±2.48 after treatment. The average MDA level after treatment was found to be 5.15±2.90 in patients whose thrombus persisted, and 3.77±1.99 in patients with resolution. There were significant differences between groups. In addition, It was observed that MDA levels measured at the time of diagnosis and after treatment were higher in patients in whom thrombus resolution could not be achieved after treatment.

Conclusion: MDA level is a guiding parameter in high-risk PTE. In addition, the continuation of oxidative stress in the case of chronic thrombus may be important in the remodeling of the precapillary pulmonary artery.

Keywords: Acute pulmonary thrombo embolism, chronic thrombo embolism, malondialdehyde, oxidative stress

INTRODUCTION

Pulmonary thromboembolism is a disease with high mortality that develops as a result of obstruction of the pulmonary artery (PA) and/or its branches by materials originating from another part of the body (thrombus, air, fat, tumor cells, amniotic fluid, septic materials, etc.).[1] The mean annual incidence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and PTE, ranges from 23-269/100,000.[2]

In acute PTE cases, "risk classification", which evaluates the risk of 30-day mortality, should be done in order to make the treatment approach correctly. High-risk PTE accounts for less than 5% of all patients with an early hospital mortality of at least 15%.[3]

Thrombus resolution may take up to two months after acute PTE.[4] In a study, patients with PTE were re-evaluated 6 months later and chronic thrombus was reported in approximately 50% of them.[4] While PTE in which large-diameter vessels with no thrombus resolution are involved results in chronic period vascular remodeling, PTE in which small-diameter vessels are involved results in chronic period proliferation and abnormal endothelial function.[5] In addition, the thrombus existing in the vascular bed is organized and plays a key role in the remodeling of the precapillary pulmonary artery by causing changes in the medial and intimal layers of the pulmonary arteries. These changes in the pulmonary artery can result in pulmonary hypertension.

Free radicals are molecules that have one or more unpaired electrons in their final orbital and are therefore highly unstable.[6] In a healthy microorganism, there is a certain balance between the formation and elimination of free radicals. This situation is called oxidative balance. Reactive oxygen products, which are formed as a result of the deterioration of this balance in favor of oxidants, react with the unsaturated bond structures of cholesterol and fatty acids in the cell membrane, forming peroxidation products and causing changes in the chemical and physical structure of the cell membrane.

The most toxic one of the compounds formed as a result of lipid peroxidation are aldehydes. As a result of this reaction, cytotoxic and mutagenic MDA and 4-hydroxynonenal are

formed. MDA has a toxic effect by binding to amino groups of proteins, phospholipids and nucleic acids. It can easily pass through the cell membrane and react with the structural components of DNA. This causes mutagenic, carcinogenic and genotoxic effects.[7] This high reactivity and longevity of MDA have made it one of the most frequently used parameters to measure the peroxidation level.

Oxidative stress develops in the organism as a result of instability, hypoperfusion, hypoxia and ischemia caused by pulmonary thromboembolism.[8] Studies have shown that oxidative stress plays a role in the remodeling of the precapillary pulmonary arteries. Determination of the diagnostic value of oxidative stress in chronic thromboembolic disease (CTED) and chronic thromboembolic pulmonary hypertension (CTEPH) is quite remarkable in the development of new treatment protocols.

The average MDA level after treatment was found to be 5 in patients whose thrombus persisted, and 3.77 in patients with resolution. There were significant differences between groups.

METHODS

This study was designed as a single-center prospective study in a cohort of patients who applied to the Ministry of Health, Health Sciences University, Dışkapı Yıldırım Beyazıt Health Application and Research Center (SUAM) and were diagnosed with PTE after the evaluation of the Chest Diseases Clinic.

This study was approved by the ethics committee with the decision of the University of Health Sciences, Dışkapı Yıldırım Beyazıt SUAM Clinical Researches Ethics Committee dated 16.03.2020 and numbered 84/16 and was carried out following the ethical principles determined by the Declaration of Helsinki.

Patients who refused to participate in the study, had chronic thrombus at the time of diagnosis, had previously been diagnosed with pulmonary hypertension, had uncontrolled metabolic disease, were diagnosed with acute coronary syndrome or acute cerebrovascular disease, had uncured malignancy, or newly diagnosed cancer, had rheumatological disease at the time of acute attack, had interstitial lung disease or chronic obstructive pulmonary disease, patients under 18 years of age and pregnant women were not included in the study. When all these requirements were met, patients who agreed to participate in the study were included in the study.

The study was carried out between 18.03.2020 and 30.06.2021 and a total of 78 patients were included in the study. 10 patients who died, 4 patients who were diagnosed with cancer after the examinations, and 11 patients who did not come to their follow-ups were excluded from the study. 9 patients were not included in the study because under pandemic conditions they wanted to be followed up in another center close to their residence. According to the G-Power analysis, we determined the minimum sample size as 44 patients, and the study was terminated after reaching a sufficient number of patients.

Study Method

Demographic characteristics such as age and gender, smoking histories, comorbidities and symptoms at admission, vital values, imaging tests (chest radiography, CTPA and/or ventilation-perfusion scintigraphy), transthoracic echocardiography (TTE) and compression Doppler ultrasonography (CDU) results, laboratory values (complete blood count, biochemical tests, coagulation tests, d-dimer, pro-BNP, troponin, blood gas values) and medical treatments of patients diagnosed with PTE between the specified dates and meeting the inclusion criteria were analyzed through the in-hospital information management system (HIMS) and the Ministry of Health E-Nabız System. In order to determine the MDA level at the time of diagnosis, 2 tubes of blood samples were taken from the patients, and they were centrifuged and stored under appropriate conditions in the Health Sciences University, Ankara Dışkapı Yıldırım Beyazıt SUAM, Medical Biochemistry Clinic.

After the 6th month in the treatment of the patients, imaging examinations (chest radiography, CTPA and/or V/P scintigraphy) and TTE, CDU were re-evaluated. MDA level was checked.

Sample Collection and Analysis Methods

Blood samples taken from the selected patients by venipuncture method into the tube containing BD Vacutainer SSTII Advance serum separating gel at the appropriate time were centrifuged at 1500g for 10 minutes and stored at -20°C by placing in capped Eppendorf tubes. On the ELISA working day, the frozen sera were removed from -20°C and allowed to reach room temperature, then vortexed and studied in accordance with the kit insert.

It was studied with ELISA washing device (BioTek ELx50) and ELISA reading device (BioTek Epoch) by using CAYMAN TBARS (product code:10009055) USA 2021 kits.

Statistical Analysis

Existing studies related to the research topic were evaluated and based on these, the minimum number of patients for which statistically significant results could be obtained was found to be 44 when Alpha 0.05 test power was calculated as 0.65 for 80% AUCROC MDA null hypothesis using the "G-Power" program.

Data were analyzed with SPSS version 21.0 (IBM®, Chicago, USA). The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk test). Normally distributed numerical variables were analyzed with the "T test in Independent Groups" between the two groups, with "ANOVA" between the three groups, and the numerical variables that did not show normal distribution were analyzed with the "Mann Whitney U test" between the two groups and with the "Kruskal Walls" between the three groups. Intragroup analyzes were evaluated using the "Peer t test" in those with normal distribution. Nominal data were evaluated between the two groups using the "Pearson Chi-square test" or the "Fisher's Exact test". The area under the curve (AUC) in the ROC analysis was evaluated to determine the factors that were determinative for the prediction of high-risk PTE, and the data were expressed at a 95% confidence interval. The correlations of normally distributed numerical variables were analyzed with the "Pearson correlation test", and the numerical variables that did not show normal distribution were analyzed with the "Spearman correlation test". In the statistical analyzes of the study, comparisons with a p value below 0.05 were considered statistically significant.

RESULTS

44 patients were included in the study. The mean age of the patients was 54.1±14 years. The male and female gender ratios were equal. At least one acquired risk factor was detected in 75% of the patients. Immobilization and COVID-19 (22.7%) were the most common risk factors. Demographic characteristics of the patients are given in Table 1.

Table 1. Demographic characteristics and risk factors distribution of patients

	All Patients (n=44)	
Age	Mean±SD	54.1±14
Gender	n(%)	
Female		22 (50)
Male		22 (50)
Risk Factors	n(%)	33 (75)
Immobilization		10 (22.7)
COVID-19		10 (22.7)
Obesity		8 (18.6)
History of venous thromboembolism		7 (15.9)
Presence of fracture in the lower extremity		2 (4.5)
Long term travel		2 (4.5)
Major surgical intervention		1 (2.3)
Oral contraceptive usage		1 (2.3)
Congestive heart failure		1 (2.3)

Comorbidity was present in 54.5% of the patients included in the study. The most common comorbidities were diabetes mellitus (18.2%) and hypertension (15.9%). The most common symptoms were Shortness of breath (%79) and chest pain (%28). The distribution of patients according to symptoms is shown in Table 2.

Table 2. Distribution of patients according to symptoms

Symptoms		All Patients (n=44)	<65 Age	≥65 Age	p
Dyspnea *	n(%)	35 (79.5)	26 (78.8)	9 (81.8)	0.829
Chest Pain*	n(%)	28 (63.6)	22 (66.7)	6 (54.5)	0.469
Leg Pain**	n(%)	8 (18.2)	8 (24.2)	0	0.170
Cough**	n(%)	6 (13.6)	4 (12.1)	2 (18.2)	0.630
Palpitation**	n(%)	6 (13.6)	5 (15.2)	1 (9.1)	1.000
Hemoptysis **	n(%)	5 (11.4)	5 (15.2)	0	0.309
Syncope **	n(%)	4 (9.1)	4 (12.1)	0	0.558
Fatigation **	n(%)	4 (9.1)	1 (3)	3 (27.3)	**0.043**

*Chi-square test, **Fisher's exact test

The vital signs of the patients included in the study according to risk groups are given in Table 3.

The mean MDA level at the time of diagnosis was found to be 8.88±3.24 in the low and medium risk group of the patients participating in the study, and 13.06±4.26 in the high-risk group. There was a significant difference between the groups (p=0.003). The results are given in Table 4.

The MDA cut-off value was determined as 11.95 with 80% sensitivity and 62% specificity. MDA levels were found to be predictive for high-risk PTE (AUC: 0.773, 95% CI 0.592-0.953, p=0.017). The ROC curve for high-risk PTE prediction is shown in Figure 1.

While a significant negative correlation was observed between MDA level at the time of diagnosis and saturation a significant positive correlation was observed with ALT, AST and respiratory rate.

Table 3. Distribution of vital clinical and laboratory findings of patients by risk groups

Clinical findings		All patients (n=44)	High risk (n=8)	Medium risk (n=12)	Low risk (n=24)	p value
Systolic blood pressure (mm/Hg)	Median (min-max)	117 (80-185)	89 (80-100)	110 (90-140)	120 (97-185)	A*
Diastolic blood pressure (mm/Hg)	Median (min-max)	70 (50-107)	60 (50-72)	66.5 (60-80)	70 (58-107)	A*
Pulse(beats/min)	Median (min-max)	93 (68-131)	115 (83-131)	97 (78-129)	89.5 (68-110)	A*
Respiratory rate	Median (min-max)	20 (14-35)	24 (18-35)	20 (14-28)	18 (16-24)	A**
Saturation	Median (min-max)	92 (40-98)	82.5 (40-95)	90 (80-95)	94 (83-98)	A**
Laboratory findings						
Ph	Median (min-max)	7.4 (7.18-7.52)	7.39 (6.73-7.48)	7.42 (7.29-7.52)	7.40 (7.33-7.48)	A**
Lactate (mg/dL)	Median (min-max)	1.8 (0.7-17)	3.5 (1-17)	3.15 (0.7-4.6)	1.6 (0.7-2.6)	A*
AST (U/L)	Median (min-max)	20 (10-265)	43 (20-265)	20 (10-33)	17 (10-44)	A*
ALT (U/L)	Median (min-max)	19 (6-192)	49.5 (19-282)	16.5 (6-58)	18.5 (7-58)	A*
Troponin (ng/mL)	Median (min-max)	0.01 (0-3.07)	1.21 (0.78-3.07)	0.36 (0-0.97)	0.01 (0-0.29)	A*
ProBNP (pg/ml)	Median (min-max)	329 (5.97-10852)	2017 (1165-3220)	977 (200.6-10852)	145.5 (5.97-1821)	A*
D-Dimer (µg/mL)	Median (min-max)	4.46 (0.76-25)	7.06 (4.62-25)	4.58 (1.07-25)	2.98 (0.76-7.54)	A*

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BNP: Brain natriuretic peptide, A: High risk and low risk, *p<0.05; **p≥0.05, Kruskal Wallis test was used.

Table 4. Distribution of malondialdehyde levels by risk groups				
		Low+Medium Risk	C	P
MDA*	Mean±SD	8.88±3.24	13.06±4.26	**0.003**
MDA: Malondialdehit, *Independent group T test				

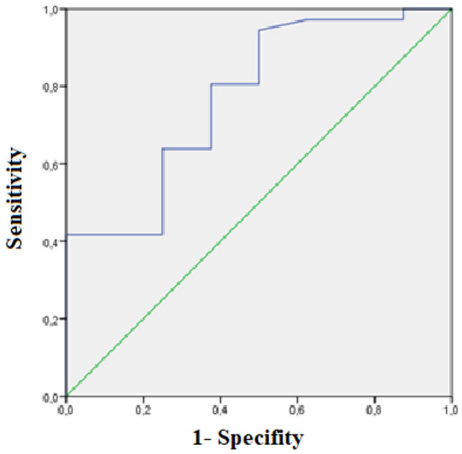

Figure 1: ROC analysis for prediction of high-risk pulmonary thromboembolism

A significant decrease was observed in MDA levels after the treatment of the patients included in the study.

The MDA levels before and after treatment in the patients included in the study are shown in Table 5.

Table 5. Malondialdehyde levels				
MDA level		Pre-treatment	Post-treatment	p value
All patients*	Mean±SD	9.64±3.76	4.74±2.48	**<0.001**
<65 years*	Mean±SD	8.8±3.85	4.2±2.31	**<0.001**
≥65 years*	Mean±SD	8.6±3.66	3.6±3.05	**<0.001**

MDA levels at diagnosis in patients whose thrombus continued after treatment were found to be higher than the other group. (p<0.001). MDA levels examined after treatment were higher in patients with chronic thrombus. (p<0.001).

It was determined that MDA levels measured at the time of diagnosis were not predictive of chronic thromboembolism (AUC:0.605, 95% CI 0.424-0.786, P=0.252).

DISCUSSION

Pulmonary thromboembolism is a life-threatening emergency condition with a high mortality rate despite effective treatment as a result of occlusion of the pulmonary arterial bed. Although the widespread use of BTPA and d-dimer provides some convenience in diagnosis, it makes the diagnosis difficult due to the variability in the clinical picture. In addition, most deaths occur in the first hour in high-risk PTE requiring emergency reperfusion therapy.[9] For this reason, early diagnosis and appropriate treatment are life-saving.

Pulmonary thromboembolism is often considered a disease of advanced age.[10] In a study, the average age was found to be 60.2 years.[11] The mean age of the patients participating in our study was 54.1 years. The low mean age is due to the fact that PTE is more mortal in older patients, they do not continue their follow-up, and they are not included in the study because their comorbidities contribute to oxidative stress.

There is no certainty that sex difference affects the incidence of pulmonary thromboembolism. However, the overall incidence is often thought to be equal for both sexes.[12] In our study, male and female sex ratios were found to be equal, in line with the literature.

Approximately 75% of patients with pulmonary thromboembolism had at least one underlying risk factor.[13] In our study, 75% of the patients had at least one acquired risk factor, in line with the literature. The most frequently reported risk factors in the GARFIELD VTE study were previous operation, recent hospitalization, and lower extremity fracture, respectively.[11] The most common risk factors in our study were COVID-19 and immobilization. This difference in risk factors is due to the fact that our study was conducted under pandemic conditions.

The clinical picture in pulmonary thromboembolism is highly variable. It can take place in a wide spectrum ranging from an asymptomatic picture to sudden death. In the study by Özsu et al.[14], in which they evaluated the national data of PTE, the two most common symptoms were found to be dyspnea and pleuritic chest pain, respectively. In our study, the two most common symptoms were dyspnea and chest, similar to the literature.

It was shown that mortality is higher in PTE patients with high troponin levels.[15] In the study conducted by Lankeit et al.[16], it was stated that the negative predictive value of the high-sensitivity troponin test being normal is 98% in determining the poor prognosis. In our study, troponin levels were found to be significantly lower in the low-risk group in line with the literature.

It was reported that elevated natriuretic peptides are associated with early mortality.[17] Chen et al.[18] stated that NT-proBNP is a very sensitive marker in determining right ventricular dysfunction and mortality, and mortality is significantly reduced if it is detected in low levels. In our study, natriuretic peptide levels were found to be significantly lower in the low-risk group, in line with the literature.

The most toxic one of the compounds formed as a result of lipid peroxidation are aldehydes. As a result of this reaction, cytotoxic and mutagenic MDA is formed. It can easily pass through the cell membrane and react with the structural components of DNA. The high reactivity of MDA has made it one of the most frequently used parameters to measure peroxidation level and oxidative stress. Oxidative stress plays a role in many diseases, including VTE.[19]

It has been shown that increased oxidative stress in ischemic cerebrovascular disease causes cellular damage by uncontrolled increase of inflammatory mediators.[20] In the study by Özkul et al.[21], MDA levels were correlated with clinical outcomes, and an increase in MDA level was associated with more severe disease clinically. Similarly, in our study, high-risk PTE cases were shown to have higher MDA levels compared to other groups, which we think is of vital importance in the early diagnosis of the patient group to be given reperfusion therapy.

In the study by Aykal et al.[22], it was stated that the oxidative balance shifted towards the oxidant side in VTE patients. In a study evaluating MDA in PTE, it was shown that there was a significant increase in MDA level compared to the control group.[23] In the study of Halıcı et al.[24], it was shown that MDA was higher in acute PTE patients compared to the control group, and it still remained high after one month of treatment. In our study, it was shown that the

MDA level in patients with chronic thrombus is high at the time of diagnosis, as well as remained elevated at the end of treatment. As a result of these results, we think that it can be a guide for the evaluation of antioxidant treatments in patients with ongoing thrombus burden.

Pulmonary arterial hypertension (PAH) is a disease of unknown etiology. It has been shown that an increase in ROS levels reduces the bioavailability of nitric oxide, leading to the development of PAH. In the study of Reis et al.[25], it was shown that the increase in MDA level in PAH patients plays a vital role in the progression of pulmonary hypertension. In the study of Smukowska et al.[26], it was shown that MDA levels increase in CTEPH. All these results show that oxidative stress plays an important role in the remodeling of the precapillary pulmonary arteries.

Acute PTE is mostly considered to be a reversible disease, and patients are considered to be completely cured with appropriate anticoagulant therapy. However, in the study of Morris[27], it was reported that more than half of the patients had residual perfusion defects in their control visits 6 months after acute PTE. In our study, it was determined that thrombus persisted in 36.4% of the patients after 6 months of treatment. Since right heart catheterization was not performed in these patients, they could not be evaluated in terms of PH. However, considering that the presence of chronic thrombus is a risk factor for the development of CTEPH, we think that close follow-up is important in patients with continuing MDA elevation.

CONCLUSION

It has been shown that oxidative stress is higher in high-risk PTE compared to other risk groups. MDA can be used as a reliable biomarker in this patient group to avoid delay in treatment. In cases where resolution cannot be achieved completely in acute PTE, the continuation of oxidative stress is an important condition in the remodeling of the precapillary pulmonary artery.

In addition, no other long-term study evaluating the oxidative stress in acute PTE could be seen in the literature. For this reason, we think that our study will shed light on more comprehensive studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Dışkapı Yıldırım Beyazıt SUAM Clinical Researches (Date: 16.03.2020, Decision No: 84/16).

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Role of serum melatonin level in COVID-19 mortality and hospital admission

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ABSTRACT

Aims: Coronavirus disease 2019 (COVID-19) is a zoonotic virus that presents itself with a broad spectrum of respiratory involvement. Without any specific treatment, various treatment modalities and markers for severity have been suggested. This study aimed to investigate the role of melatonin in the severity of COVID-19 infection, with the hypothesis that melatonin levels correlated with mortality, ward and intensive care unit (ICU) admission.

Methods: The study was performed as a single-center prospective cohort. Patients evaluated at the emergency ward for COVID-19 suspicion were defined as the study population. Those who had at least one COVID-19 RT-PCR positivity and did not have a history of cranial operation, being a shift worker, or under melatonin treatment were chosen. Ninety-six patients who had all the criteria fulfilled were deemed suitable for the study. Descriptive analysis for demographic data, Spearman correlation, and Mann-Whitney test for nonparametric evaluation were used.

Results: Eighty patients were considered suitable after excluding 16 patients, primarily due to improper melatonin sampling times. A positive correlation was seen between melatonin levels and intensive care admission, which was not observed in ward admission or overall mortality. This implicates the possibility of melatonin being used as a marker for the severity analysis of COVID-19.

Conclusion: With limited sensitivity, melatonin may be used to evaluate ICU admission. Its role regarding ward admission and overall mortality remains limited.

Keywords: Critical care, COVID-19, melatonin, mortality

INTRODUCTION

Corona viruses (COV) are an RNA virus, which is zootonic in nature. They often present in humans with respiratory involvement, varying from mild upper respiratory symptoms to acute respiratory distress syndrome. Coronavirus Disease 2019 (COVID-19), aptly named for its emergence in 2019 at Wuhan, China; represents the extreme end of its spectrum, with high virulence and mortality. With no specific treatment in sight, vaccination studies appear to be the only viable approach to disease control.[1]

Various suggestions and treatment modalities have been discussed for reducing the severity of COVID-19 infection. Melatonin is a topic of discussion with a potential role in inflammatory syndromes and sepsis.[2-6] It is expected to act as a limiting factor in the cytokine storm of COVID-19 by its antioxidant and anti-inflammatory effects. Reduction in melatonin levels in the elderly can also contribute to the severity of the disease in this age group. In experimental models, melatonin was proven protective against inflammatory and oxidative stress.[5] Studies have also shown the antiviral properties of melatonin against other viruses.[6-7] The role of melatonin in COVID-19 infection remains an issue of discussion, as currently available data can only allow assumptions.

The goal of the study was to investigate the role of melatonin in COVID-19 infection. The study hypothesized that decreased melatonin levels would increase overall mortality and contribute to hospital admission requirements.

METHODS

The study was performed as a single-center cohort study after approval from the Ethical Committe of Dışkapı Training and Research Hospital (Date: 17.05.2021, Decision No: 111/02). It was planned and prepared according to the Guidelines

for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). The enlistment period of the study was between June 1st and December 1st; however, earlier cessation of the period was to be considered if an adequate number of patients were accepted. An estimated duration was assumed to be two months, which included one month of follow-up. This assumption was made after investigating the number of COVID-19 patients applied to the emergency ward in the last three months. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients older than 18 years old and with at least one confirmed positive COVID-19 reverse transcription polymerase chain reaction (RT-PCR) were considered eligible for the study. Exclusion criteria were patients' refusal to participate, being under melatonin treatment for any reason, being a shift worker, and having a history of any cranial operation. Informed consent was received from the patients, both written and verbal. The additional blood sample required for the study was planned to be taken alongside the routine requested blood samples. The routine samples consisted of a standardized COVID-19 panel, which included complete blood count, liver and renal function tests, inflammatory markers from serum, and arterial blood sampling for the evaluation of desaturation and lactate.

For standardization purposes, blood samples for melatonin levels were only received from samples provided between 08:00 AM and 10:00 AM. The blood samples were then transported in a standard vacutainer blood collection tube within 30 minutes to be centrifuged at a 1000 rate per minute for fifteen minutes. These samples were stored at -70°C and later transported to the laboratory of biochemistry department for enzyme-linked immuno-sorbent assay (ELISA) testing.

Regarding follow-up methodology, patients admitted to either the COVID-19 ward or intensive care units (ICU) were evaluated for mortality. This evaluation period was up to one month, starting from the initial diagnosis. Patients who were deemed suitable for outpatient follow-up were also subject to the exact duration of follow-up. Survival data of the patients' was to be received from the national database, which reports if the patient is alive whenever the records are accessed. This database was used for this purpose and not for additional data.

Mortality was accepted as the primary outcome of this study. Hospitalization requirement for the ward and/or ICU was the secondary outcome, with the ICU admission reflecting a worse prognosis. Vital signs, comorbidities, age, gender, and elevated white blood cell count were accepted as independent parameters due to their role in pneumonia scoring systems. Lactate levels were also accepted as another independent parameter, with computed thoracic tomography findings accepted as confounding parameters, as these findings mainly were used to evaluate how many lobes were involved rather than a separate parameter itself.

CURB-65 and pneumonia severity index (PSI) were the predictors for which the overall mortality comparison would be made to verify any possible correlation. Quick Sequential Organ Failure Assessment (qSOFA) scoring was used to predict ICU admission. Melatonin level was the primary diagnostic criterion hypothesized to affect mortality and hospital admission. CURB-65, PSI and qSOFA were also the main factors utilized in emergency service for requirement of ICU admission.

The hospital computer system, emergency ward records, and the study's patient chart, which included the data mentioned above, were utilized as data sources, the hospital computer system, emergency ward records, and the study's patient chart. The study patient follow-up chart consisted of a single form in Microsoft Word format. This form allowed a quick overview of the patient and was the primary data source for statistical analysis. The hospital computer system and hand-written records were referred for validation if data was missing from this form.

Selection bias was presumed due to the nature of the study. It was addressed as, besides the evaluation of melatonin level, no difference in treatment or presence of additional exposure was present. An average of 100 patients was expected to be enlisted and followed in this prospective study. Estimated loss during patient enlistment was assumed to be around 10% due to blood sampling techniques, logistics of transportation, and rapid deterioration, which would prevent an optimal evaluation. Assuming a mean melatonin level of 10(±5) ng/ml among healthy populations from epidemiologic studies, to validate an increase or decrease of 20%, 49 patients were deemed the minimal amount for a power of 80% and type-1 error of 0.05.[8]

Vital signs and blood sample results consisted of quantitative variables. Subgrouping was then performed to placate these variables as qualitative variables for their role in pneumonia scoring systems.

Descriptive statistics were used for demographic data, with the results being reported with case counts (n), median, and percentile distribution when appropriate. Kolmogorov-Smirnov was used for normality analysis. Spearman correlation and Mann-Whitney test were utilized to correlate two nonparametric results, depending on the parameter's type. No subgroups were defined for this study.

In case of missing data for any data regarding patients, removal from the study was planned. It was the choice as neither mean imputation nor available case validation would have been sufficient, given the combination of nominal and scale variables. To illustrate, the absence of a vital sign would also affect pneumonia scoring systems and further complicate the analysis, thus necessitating the removal of the patient if any data was missing. Due to the study's design, no loss to follow-up was expected. International Business Machines (IBM) Statistical Product and Service Solutions (SPSS) Edition 23 was the choice of statistical program in this study.

RESULTS

Patients were considered as candidates after the initial emergency ward evaluation. A total of 846 patients were evaluated at the COVID-19 emergency service isolation ward. Four percent (n=36) of patients had repeated admission; thus, the unique admission number was reduced to 816. Nearly half of the group was excluded from the study (n=458, 56%), as they either did not have a COVID-19 RT-PCR result, had a former positivity that could not be confirmed, did not stay in the ward long enough for a test result or were diagnosed by imaging modalities. The remaining 358 patients were eligible for the study. Most of the patients (n=362, 79% of the eligible group) refused to participate in the study or were not in a state to be informed about the study directly.

Ninety-six patients who had agreed to participate verbally and in writing were then accepted to the study as the final

group. However, 14 patients (14%) were removed, despite being initially suitable, due to either differences in blood sampling techniques or inadequate transportation. An additional patient was removed due to exitus before being admitted to any ward, and one patient was removed due to severe sepsis, which affected the blood sampling methodology (Figure 1).

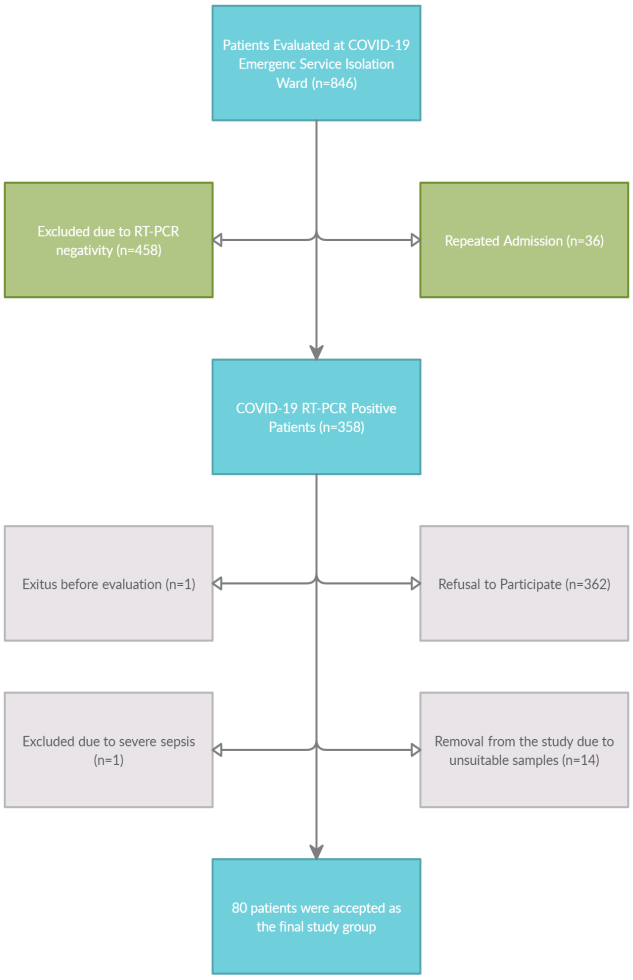

Figure 1. Patient evaluation flow chart

The demographic evaluation showed that 43 (53,8%) patients were male and 37 (46,3%) females, with an average age of 64. Thirty-seven (46,3%) were vaccinated twice; those who had at least one vaccination for COVID-19 comprised half of the patients (n=40). All vaccination types available in the country regardless of subtype were accepted as a positive vaccination history, with two vaccination history being deemed adequate for vaccination. Fifteen patients (18,8%) had impaired mental condition, and 64 (80%) had computer tomography findings consistent with COVID-19 pneumonia.

The most commonly observed comorbidities were diabetes mellitus, hypertension, and coronary artery disease. (n=19, 15 and 6, respectively). Twenty-one patients had no known disease, with 19 having at least one and 12 having two known diseases. Thirty-nine (48.7%) were retired at the time of admission, 22 (27.5%) were unemployed, and the remaining 19 (%23.7) patients were non-shift workers (Table 1).

Regarding hospitalization, two patients were discharged from the emergency service, while 52 (65%) required admission to the COVID-19 ward. The remaining 26 (n=32,5%) had to be followed up under intensive-care conditions. Ten patients (12.5%) had at least one complication during treatment. Seventeen patients (21.3%) were lost in overall mortality within the one-month follow-up period (Table 2).

Table 1. Demographic Information

Parametres		Number	Percentage (%)
Gender	Male	43	53.8
	Female	37	46.3
	Total	80	100
Age	Average	63	
	SD	14	
	Total	80	
Mental Status	Normal	65	81.3
	Abnormal	15	18.8
	Total	80	100
Vaccination History	None	40	50
	1 Dosage	3	3.8
	2 Dosage	37	46.3
	Total	80	100
COVID-19 CT Findings	Present	64	80
	Absent	16	20
	Total	80	100
Comorbidities	DM	19	23
	HT	15	18
	CAD	6	7
Occupational Status	Retired	39	48.7
	Unemployed	22	27.5
	Non-shift Worker	19	23.7
	Total	80	100

SD: Standart deviation, **CT**: Computed tomography, **DM**: Diabetes mellitus, **HT:** Hypertension, **CAD**: Coronary artery disease

Table 2. Hospitalization, complications and mortality

Parametres		Number	Percentage (%)
Treatment localization	Outpatient	2	2.5
	Ward	52	65
	Intensive care	26	32.5
	Total	80	100
Progression	Complication	10	12.5
	Mortality	17	21.3

Complication definition: Complications mentioned here include three cases of cerebrovascular events and one case of the following disease; acute kidney injure, delirium, liver injury, decompensated heart failure, myocardial infarctus and peptic ulcer perforation

A positive correlation was seen between melatonin levels and ICU admission. (p=0.005) This correlation was validated by the evaluation of other parameters which were related to ICU admission. Desaturation, respiratory rate, elevated WBC, lactate levels, and increased CURB-65, qSOFA, and PSI scores were found statistically significant in the same analysis. No correlation was found between melatonin levels and mortality, which again was verified by the scoring systems (Table 3).

In the Receiver Operating characteristic (ROC) analysis, a correlation between melatonin levels and ICU admission was demonstrated. (p=0.005, and area under curve=0.696) As melatonin levels increased, a lower admission to the ICU was observed (Figure 2).

Table 3. Mortality and hospital admission analysis

Parametres			Mortality	Ward Admission	ICU Admission
Spearman correlation between parametres	**Melatonin**	Correlation coefficient	-0.150	**.296****	**-.318****
		Sig. (2-tailed)	0.186	0.008	0.004
	Lactate	Correlation coefficient	0.213	-0.197	**.238***
		Sig. (2-tailed)	0.058	0.081	0.034
	WBC	Correlation coefficient	0.158	**-.357****	**.331****
		Sig. (2-tailed)	0.161	0.001	0.003
	CURB65	Correlation coefficient	.267*	**-.280***	**.258***
		Sig. (2-tailed)	0.017	0.012	0.021
	PSI	Correlation coefficient	.271*	**-.357****	**.341****
		Sig. (2-tailed)	0.015	0.001	0.002
	qSOFA	Correlation coefficient	0.203	**-.453****	**.479****
		Sig. (2-tailed)	0.072	0.000	0.000

*: Correlation is significant at the 0.05 level (2-tailed), **: Correlation is significant at the 0.01 level (2-tailed), **WBC**: White blood cell, **PSI**: Pneumonia severity index, **qSOFA**: Quick sequential organ failure assessment, **ICU**: Intensive care unit

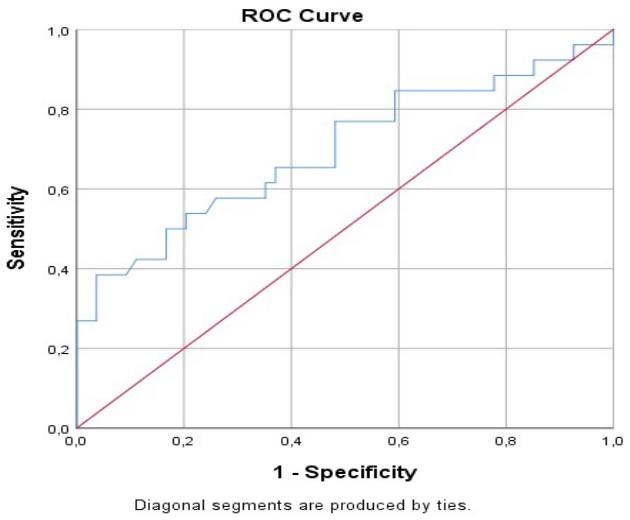

Figure 2. ROC curve of melatonin and intensive care admission

DISCUSSION

Melatonin levels were found relevant in ICU admission, while no statistical correlation was observed in overall mortality. These results show that the study's hypothesis was only partially correct, being limited to pointing out the localization of treatment rather than its prognosis. The melatonin levels also vary differently, and only at a high threshold does it predict ICU admission. This need for a high level of melatonin requirement might explain why supplemental melatonin intake was found effective in some studies rather than an increased basal level already present in the patients.[7,9] A randomized controlled study is underway by Garcia et al.[10] to investigate melatonin's role in symptomatic and asymptomatic patients. A similar trial has been prepared for patients in the ICU for the role of melatonin in the improvement of clinical parameters.[11]

While no reports have been presented as of this manuscript that supports melatonin's role in mortality reduction of COVID-19 infection, its role in lowering inflammatory markers has been reported at a dosage of 5-25 mg/day.[7,12] This dosage appears to be higher than the previously mentioned randomized controlled study's dosage plan. In summary, it can be concluded that while the elevation of melatonin levels may have a protective effect, the exact cut-off is yet to be proven in the currently available literature. Admitting melatonin to a particular group or as a general prophylaxis to the whole population without screening is another topic to be debated.

The study's main limitation was the limited population size caused by reduced COVID-19 levels in the surrounding area of the single-center hospital. This limitation was further worsened by the refusal of participation in most patients. This refusal was mainly attributed to the patients' and their families' stance against medical studies, which occurred in a similar prospective study of ours with up to 90% refusal of participation. We tried to avoid selection bias by preventing direct interaction between the study group's doctors and those who had offered the study. In a similar approach, all patients and/or their families who had applied to the COVID-19 emergency ward were offered to participate in the study. By this, we had hoped to prevent the selection of "stable" patients among the general population.

Another limitation of the study was a lack of a control group (patients suitable for outpatient follow-up) and a lack of repeated melatonin sampling for the patients. The control group exclusion was mainly due to different evaluation and routine inspection methods for outpatient follow-up, as these patients are not often required for an equally detailed routine laboratory work-up and imaging. Follow-up melatonin sampling could have provided additional information but was not planned as initial melatonin testing was utilized during COVID-19 routine evaluation, and repeated testing could not be put on a schedule for patients with varying follow-up periods.

Melatonin may be used as a marker for COVID-19 severity, albeit with limited sensitivity. Its role in mortality remains insignificant, while being statistically relevant in evaluating ICU admission may prove helpful. Combining melatonin with other markers or limiting its usage to a specific age group may be considered an option for better sensitivity and specificity. Further studies, especially those with higher recruitment rates and longer follow-up duration, are required to discuss the generalizability of melatonin as a marker for hospital admission evaluation. Additional studies, such as those already underway, would also allow a better dosage schedule if melatonin is considered as a prophylaxis method.

ETHICAL DECLARATION

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Dışkapı Training and Research Hospital (Date: 17.05.2021, Decision No: 111/02).

Informed Consent: All patients signed and free and informed consent form.

Reviewer Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The relationship between level of procalcitonin and mortality in patients who have been followed for solid organ malignancy with febrile neutropenia

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ABSTRACT

Aims: Previous studies have demonstrated that certain laboratory indicators play a crucial role in the identification of infections and prognosis assessment in individuals afflicted with febrile neutropenia. The concentration of procalcitonin exhibits an elevation in the presence of bacterial and fungal infections, while remaining unaltered in the context of viral illnesses. The objective of this study was to assess the efficacy of procalcitonin as a diagnostic tool for detecting infection and predicting prognosis in patients with febrile neutropenia.

Methods: The present investigation involved a retrospective analysis conducted at a single center, focusing on a cohort of 61 patients who received treatment for febrile neutropenia. The study encompassed the analysis of patients' age, gender, current circumstances, and laboratory test results. Procalcitonin levels were evaluated in first day of hospitalization.

Results: The age range of the patients in the study varied from 18 to 84 years, with a median age of 58. Out of the whole sample, 29 individuals (47.5%) were female, while 32 individuals (52.5%) were male. Out of the total sample size, 27 patients (44.2%) were diagnosed with lung cancer, 13 patients (21.3%) were diagnosed with breast cancer, and 4 patients (14%) were diagnosed with testicular cancer. Out of the total patient population, 24 individuals exhibited microbiologically confirmed infections, while 9 patients presented with clinically characterized infections. Out of the total number of cases, 10 cases, accounting for 16.3% of the sample, led to fatality. The median procalcitonin values were 1.5 ng/ml in patients diagnosed with microbiologically confirmed infection and 0.6 ng/ml in those diagnosed with clinically suspected infection. Furthermore, it is worth noting that the median procalcitonin value among individuals with fever of unknown origin was found to be 0.6 ng/ml, with statistical significance indicated by a p-value of less than 0.001. The median procalcitonin level was found to be 17.70 ng/ml in instances resulting in mortality, whereas it was 0.56 ng/ml in cases without mortality ($p<0.001$).

Conclusion: We determined that procalcitonin must be routinely used in order to show enfection and mortality in patients with febrile neutropenia. Because procalcitonin is a sufficient and appropriate examination to show infection and mortality so it can be beneficial to decide treatment method, and hospitalization. Procalcitonin may also be more useful in predicting the prognosis of patients with febrile neutropenia.

Keywords: Febrile neutropenia, procalcitonin, oncology, infection, malignancy

INTRODUCTION

In cancer patients, the administration of intense and high-dose chemotherapy treatments can lead to the development of infectious complications that carry significant morbidity and death rates. Consequently, this issue presents itself as a crucial clinical concern. Bacterial and fungal infections are the primary contributors to both morbidity and mortality in individuals within this patient population.[1]

Distinguishing between fevers caused by infection and those caused by non-infectious factors poses a challenge in neutropenic individuals. In many instances, inflammation and infection may manifest with less pronounced clinical indications and symptoms than anticipated. Consequently, fever may serve as the sole discernible indicator of an infection. Determining the underlying cause of a fever may not always be feasible. The etiology of fever in neutropenic individuals is detectable in a mere 30-50% of cases, either through clinical or microbiological means. Conversely, in the other instances, the source of fever remains elusive and cannot be determined.

The timely identification and proper management of infections in individuals with febrile neutropenia are of utmost significance. Nevertheless, the insufficiency of clinical

and microbiological data in these individuals is a significant challenge in the diagnostic methodology.[2-4] The utilization of broad-spectrum empiric anti-bacterial medication has become a customary method for monitoring neutropenic patients with fever due to various justifications. Nevertheless, it is well acknowledged that this approach gives rise to other issues, including the development of resistance, secondary infections, financial implications, and potential toxicity.

Numerous inflammatory indicators have been examined in the assessment of infections in neutropenic individuals; however, their diagnostic utility has been determined to be restricted. The current understanding about the relevance of inflammatory indicators, particularly in the identification of patients at low risk, remains uncertain.[5] The patient population under consideration is characterized by the presence of well-established inflammatory markers, namely C-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-8 (IL-8). The limitations of CRP include its delayed rise and its association with non-infectious inflammatory conditions. Interleukin-6 (IL-6) and Interleukin-8 (IL-8) have been identified as early and highly responsive indicators in severe infections, and have been highlighted as being more effective than C-reactive protein (CRP) in diagnosing febrile neutropenic patients. Nevertheless, it is important to acknowledge that in practical applications, these methods do have certain limitations. Specifically, they are susceptible to the influence of tissue injury, exhibit low levels of specificity, and incur substantial costs.[5] Consequently, there exists a necessity for cost-efficient novel biomarkers that have the potential to be valuable in the timely detection of infections within this specific patient population. These biomarkers should be unaffected by the activity of the underlying disease, accurately reflect the severity of infections, and possess the ability to differentiate between episodes of high and low risk for prognostic purposes.

Procalcitonin (PCT) is a prohormone protein composed of 116 amino acids and is widely recognized as a biomarker for bacterial infections.[6-8] According to reports, the measurement of serum procalcitonin levels has demonstrated potential utility in the timely detection of bacterial infections and in assessing the prognosis of individuals with febrile neutropenia.[9-11] The objective of this study was to assess the correlation between the first procalcitonin level during the commencement of a febrile neutropenia episode and the occurrence of infection and mortality in individuals with solid organ cancer.

METHODS

Ethics

The present investigation adhered to the ethical principles outlined in the 1975 Helsinki Declaration, subsequently revised in 2008. The research project received approval from the Scientific Research Assessment and Ethics Committee of the Antalya Training and Research Hospital, with the assigned approval number 44/26 and the date of approval being 19/06/2014.

Patients

A retrospective analysis was conducted on the clinical and laboratory characteristics of adult cancer patients who experienced febrile neutropenic episodes after undergoing chemotherapy. These patients were admitted to the Medical Oncology Clinic of Antalya Training and Research Hospital and received antibiotic treatment between January 2013 and December 2014. During the initial phase of hospitalization, the procalcitonin level was assessed, a comprehensive medical history was obtained, thorough systemic examinations were conducted, and a minimum of two blood cultures (obtained from different veins with a 30-minute interval), urine cultures, and cultures from relevant sites potentially harboring infection (such as sputum, wound, stool, catheter, etc.) were collected based on the patient's clinical presentation. This study included patients who met the criteria for febrile neutropenia, which included having an absolute neutrophil count of 500/mm^3 or less, or having a single oral body temperature of 38.3^{0}C or 38^{0}C for more than one hour in patients with an absolute neutrophil count of 500/mm^3 or less, or between 500 and 1000/mm^3 with an expected further decrease. Patients with solid organ malignancies and patients with hematologic malignancies who did not meet these criteria were not included in the study.

Treatment and Follow-up

Following the collection of culture samples from our patients, an antipseudomonal beta lactam antibiotic, specifically piperacillin-tazobactam, was administered empirically. This antibiotic was either given alone or in combination with an aminoglycoside, specifically Amikacin 1 g/24 h IV, as per the febrile neutropenia protocol of our clinic. Additionally, patients received 5 gr/6 hours IV of a medication in accordance with our clinic's protocol. Treatment adjustments were made based on the pathogens identified during treatment or in accordance with our protocol for patients experiencing persistent fever. In cases where patients exhibited persistent fever for 5-7 days, antifungals were introduced to the treatment regimen. Antibiotics were discontinued at appropriate times following a decrease in fever and the disappearance of clinical signs of infection.

Ferbile Neutropenia Etiologic Groups

The evaluation of febrile neutropenia events was conducted on three distinct etiologic groups.

1. Microbiologically defined infection (MDI) refers to an infection when the blood culture yields positive results, but no specific clinical source of the infection can be identified. Alternatively, MDI can also encompass cases where the blood culture may be positive or negative, but the causative microorganism is detected in the clinical focus.

2. Clinically defined infection (CDI) refers to a confirmed manifestation of infection that exhibits no growth when subjected to culture analysis.

3. Fever of unknown origin (FUO) refers to a condition in which there is an absence of evidence indicating the presence of a microbiologic or clinical agent or a specific site of infection.

Statistical Analysis

The formation of groups was based on the presence of infection and death, and a statistical comparison was conducted on the collected data. The descriptive statistics were reported in terms of frequency, percentage, mean, and standard deviation (SD) values. The Fisher's exact test, also known as the Pearson chi-square test, was employed to examine the associations among categorical variables. In the examination of the disparity in measurement values between the two groups, the normality assumption was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was employed in cases when the data did not conform to a normal distribution, whereas the Student's t test was utilized when the data did conform to a normal distribution. The study employed

univariate and multivariate logistic regression analysis to examine the independent risk factors that influence prognosis. The findings were presented using Wald statistics, odds ratios, and 95% confidence intervals. Statistical significance was determined by considering p-values that were less than 0.05. The analyses were conducted using the SPSS 18.0 software suite.

Table 1. Participating patients' descriptive statistics

		n	%
Gender	Female	29	47.5
	Male	32	52.5
Age	Median (min.-max.)	58 (18-84)	
Stage	1	3	4.9
	2	9	14.8
	3	15	24.6
	4	34	55.7
Etiologic groups	Microbiologically defined infection	24	39.34
	Clinically defined infection	9	14.75
	Fever of unknown origin	**28**	**45.90**
Clinical Infections	None	39	63.9
	Dental Abscess	1	1.6
	Urinary tract infection	11	18.03
	Pneumonia	9	14.8
	Acute tonsillitis	1	1,6
Blood Culture	No growth	43	70.5
	Positive	18	29.5
Urine Culture	No growth	52	85.3
	Positive	8	13.1
	No sample	1	1.6
Sputum Culture	No growth	51	83.6
	Positive	4	6.6
	No sample	6	9.8
Tissue Culture	No growth	1	1.6
	Positive	1	1.6
	No sample	59	86.8
Diagnosis	Lung*	27	44.2
	Breast	13	21.3
	Testicular	4	6.5
	Colon	3	4.9
	Gastric	2	3.3
	Soft tissue	2	3.3
	Bone	2	3.3
	Brain	2	3.3
	Endometrial	2	3.3
	Others	4	6.55

*Non-small cell:21 Small cell:6

RESULTS

The study comprised a total of 61 participants, with ages ranging from 18 to 84 years (median age: 58). Of these participants, 29 (47.5%) were female and 32 (52.5%) were male. The majority of patients had advanced cancer. The study population exhibited a prevalence of lung cancer, breast cancer, and testicular cancer as the primary malignancies. The majority of patients exhibited clinical or microbiological evidence of infection. A total of 22 patients were identified with a clinical emphasis of infection, with urinary tract infection being the most prevalent. Blood cultures were collected from all patients, and it was found that 18 patients (29.5%) had growth in the culture. Additional descriptive characteristics of the study population can be found in Table 1. Among the agents cultivated in blood culture, 9 (50%) were identified as gram-positive, while the remaining 9 (50%) were classified as gram-negative. In urine culture, 6 (75%) of the agents were gram-negative, whilst 2 (25%) were gram-positive. Similarly, in sputum culture, 2 (50%) of the agents were gram-positive, while the other 2 (50%) were gram-negative. *Candida albicans* was identified in one of the two tissue culture samples, while the other sample exhibited no observable growth. The predominant pathogen identified in blood cultures was *Staphylococcus hominis*, while *Escherichia coli* was the most often isolated pathogen in urine cultures. Table 2 presents a comprehensive overview of the statistical data pertaining to the agents that were cultivated within the culture samples. After the administration of antibiotics, it was observed that the median length of fever was 1 day, while the median duration of neutropenia was 4 days. Furthermore, it was found that neutropenia persisted for a period of 10 days or more in only 3 instances. A mortality rate of 16.3% was observed among 10 individuals (Table 3).

Table 2. Growth results of the cultures taken

Blood culture results			
		n	**%**
Gram (+) bacteria	*Staphylococcus hominis*	5	8.2
	Staphylococcus aureus	2	3.3
	Staphylococcus epidermidis	1	1.6
	Staphylococcus warneri	1	1.6
Gram (-) bacteria	*Escherichia coli*	3	4.9
	Klebsiella peumonia	3	4.9
	Pseudomonas aeruginosa	2	3.3
	Salmonella	1	1.6
No growth		43	70.5
Urine culture results			
		n	**%**
Gram (+) Bacteria	*Staphylococcus haemolyticus*	1	1.7
	Streptococcus spp.	1	1.7
Gram (-) bacteria	*Escherichia coli*	4	6.7
	Pseudomonas aeruginosa	2	3.3
No growth		52	86.6
Sputum culture results			
		n	**%**
Gram (+) bacteria	*Staphylococcus aureus*	1	1.8
	Coagulase (-) Staphylococcus	1	1.8
Gram (-) bacteria	*Escherichia coli*	1	1.8
	Pseudomonas aeruginosa	**1**	**1.8**
No growth		**51**	**92.7**

Table 3. Several characteristics of febrile neutropenic episodes	
	n:61
Fever (°C) * [a]	38.4
Hypotension (SBP<90 mmHg) *	6(9.8%)
Pulse(beats/min) [a]	94
Neutrophil (/mm³) * [a]	200
Platelets (x1000/mm³) * [a]	93
Hemoglobin (g/dl) * [a]	9.5
Elevated liver enzymes (ALT>50 U/L) *	5(8.2%)
Renal dysfunction (GFR<60 ml/min.) *	11(18%)
Duration of fever[a fi] (day)	1
Duration of neutropenia[a fi] (day)	4
Mortality count	10(16.3%)
CRP (mg/dl)	160
ESH (mm/h)	70

*: Values monitored at the time of admission, [a]: Median, [fi]: Patients other than those who died without fever and/or recovery from neutropenia, SBP: systolic blood pressure, ALT: alanine aminotransferase, GFR: glomerular filtration rate, CRP: c-reactive protein

The study examined many factors including age, procalcitonin levels, neutrophil count, C-reactive protein levels, sedimentation rate, hemoglobin levels, blood urea nitrogen levels, creatinine levels, aspartate aminotransferase levels, alanine aminotransferase levels, presence of fever, duration of fever, and duration of neutropenia (excluding exitus) in three distinct groups: FUO, CDI, and MDI. Based on the conducted tests, it was seen that there was a significant difference between at least one group and the other group, as shown by the PRC (p=0.022) and CRP (p=0.012) values. Based on the results of the pairwise comparisons, it was determined that the observed differency can be attributed to FUO and MDI. The study observed that patients with microbiologically confirmed illnesses exhibited elevated levels of procalcitonin and C-reactive protein (p<0.05) as seen in Table 4.

A substantial statistical difference was observed in the procalcitonin levels between patients who were discharged and those who died. The study found that patients with procalcitonin levels exceeding 2 had a mortality rate of 47.1%, which was significantly higher compared to individuals with levels below 2, who had a mortality rate of 4.5% (p<0.001). Furthermore, upon analyzing the numerical value of procalcitonin, it was revealed that individuals who were ex had a significantly greater median value (p<0.001). The mortality rate among patients with clinically defined infection was 11.1%, while the mortality rate among those without clinically defined infection (FUO+MDI) was 17.3%. However, statistical analysis revealed that this difference was not statistically significant (p=0.999). The mortality rate among patients diagnosed with a microbiologically identified infection was found to be 29.2%, whereas the mortality rate for patients without a microbiologically characterized infection (FUO+CDI) was 8.1%. The observed disparity between the two percentages exhibited statistical significance, as evidenced by a p-value of 0.04. There was no statistically significant difference observed in the prognoses of patients with fever of unknown cause compared to those without fever of unknown cause (MDI+CDI) (p=0.092) (Table 5).

Table 5. Analysis of variables making a difference according to prognosis						
		Alive		Dead		
		n	%	n	%	p
Gender	Female	24	82.8	5	17.2	
	Male	27	84.4	5	15.6	
PRC group	≤2	42	95.5	2	4.5	**<0.001**
	>2	9	52.9	8	47.1	
PRC median (min-max)		0.56 (0.04-100)		17.70 (1.47-100)		**<0.001**
Neutrophil grup	≤100	24	80.0	6	20.0	0.508
	101-500	24	92.3	2	7.7	
	>500	3	60.0	2	40.0	
CDI	No	43	82.7	9	17.3	0.999
	Yes	8	88.9	1	11.1	
MDI	No	34	91.9	3	8.1	**0.040**
	Yes	17	70.8	7	29.2	
FUO	No	25	75.8	8	24.2	0.092
	Yes	26	92.9	2	7.1	

PRC: procalcitonin, CDI: clinically defined infection, MDI: Microbiologically defined infection, FUO: fever of unknown origin

Table 4. Analysis of the differences of infection groups according to numerical variables*							
	FUO	CDI	MDI	p	p^{1-2}	p^{1-3}	p^{2-3}
Age (year)	55 (18-84)	52 (25-70)	58.5 (21-75)	0.346			
PRC (µg/L)	0.4 (0.1-32.8)	0.6 (0.0-89.1)	1.5 (0.1-100)	0.022	0.392	0.020	0.999
Neutrophil (/mm³)	200 (0-1000)	300 (0-700)	100 (0-900)	0.308			
CRP (mg/dl)	97.5 (15-350)	132 (43-376)	196.5 (40-398)	0.012	0.262	0.011	0.999
ESH (mm/h)	56 (32-98)	70 (70-140)	84 (30-150)	0.200			
Hemoglobin (g/dL)	9.6 (5.9-13.3)	9 (8.4-11.1)	9.3 (5.4-13.8)	0.979			
BUN (mg/dL)	16.5 (4-37)	13 (2-54)	25 (7-137)	0.058			
sCrea (mg/dl)	0.8 (0.5-2.4)	0.9 (0.5-2)	1 (0.6-9.2)	0.310			
AST (U/L)	16 (10-337)	15 (8-29)	17 (7-163)	0.490			
ALT (U/L)	16 (2-219)	12 (4-43)	14.5 (6-76)	0.661			
Fever (°C)	38.4 (38.1-39.5)	38.6 (38.2-39.5)	38.4 (38-39.6)	0.257			
Fever duration (day)	1 (1-4)	1 (1-2)	1 (1-4)	0.845			
Neutropenia duration (day)	4 (1-13)	3 (2-7)	4 (2-21)	0.191			

*Median (minimum-maximum), FUO: fever of unknown origin, CDI: clinically defined infection, MDI: Microbiologically defined infection, PRC: procalcitonin, CRP: C-reactive protein, ESH: eritrocyte sedimentation rate, Sed.: sedimentation, BUN: blood urea nitrogen, sCrea: serum kreatinin, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Table 6. Univariate and multivariate analysis of whether procalcitonin levels and groups are independent risk factors in predicting prognosis

	Univariate analysis					Multivariate analysis				
	Wald	p	OR	95% C.I.		Wald	p	OR	95% C.I	
				Lower	Upper				Lower	Upper
PRC	8.166	**0.004***	1.034	1.010	1.057	2.108	0.147	1.030	**0.990**	**1.071**
PRC groups (>2/≤2)	11.272	**0.001***	18.667	3.381	103.060	6.949	**0.008***	21.460	2.195	209.773

PRC: procalcitonin, OR: odds ratio

There was no statistically significant difference observed in the procalcitonin readings between patients with (CDI) and without (MDI+FUO) clinically diagnosed infection (p=0.611). The procalcitonin values of patients diagnosed with microbiologically characterized infection (MDI) were found to be significantly higher compared to individuals without microbiologically confirmed infection (FUO+CDI) (p=0.006). Patients who presented with a fever of unclear origin exhibited significantly lower levels of procalcitonin compared to patients who did not have a fever of unknown origin (MDI+CDI) (p=0.021).

The evaluation of whether procalcitonin level serves as an independent risk factor for predicting prognosis was initially conducted by univariate analysis, which revealed a significant association with prognosis (p<0.05). The multivariate logistic regression model did not provide support for this finding. The study found that patients with a procalcitonin value above 2 had a significantly greater death probability compared to individuals with a procalcitonin value less than or equal to 2, with a relative risk of 21.46 (95% CI 2.19–209.77) (Table 6).

The locations exhibiting the greatest sensitivity and selectivity values were identified by the utilization of receiver operating characteristic (ROC) analysis, which assessed the diagnostic efficacy of procalcitonin in determining prognosis. When a threshold value of 1.44 was used for the PRC, the sensitivity and selectivity were determined to be 100% and 78.43%, respectively. Additionally, the area under the curve (AUC) was calculated to be 0.931, indicating statistical significance (Figure).

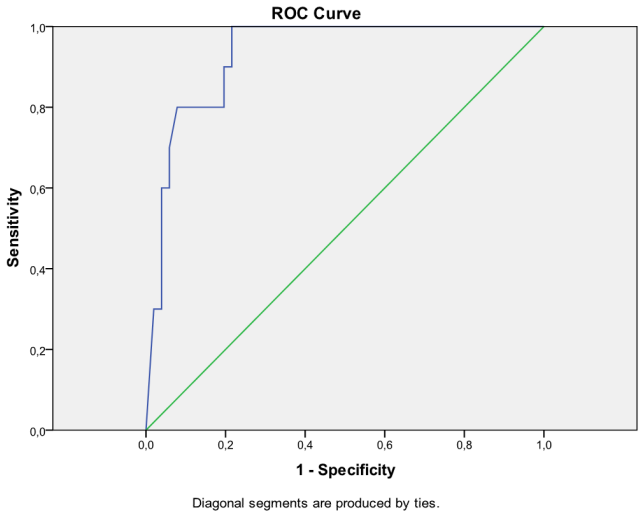

Figure. ROC curve for a cut off value of 1,44 for procalcitonin

DISCUSSION

In contemporary medical practice, the administration of high doses of chemotherapy in cancer treatment has been observed to induce immunosuppression, particularly neutropenia. Consequently, patients undergoing such treatment are rendered susceptible to the development of severe and unusual infections. Bacterial and fungal infections are identified as the primary factors contributing to morbidity and mortality in patients of this nature.[1] Due to the potential for rapid progression and high death rates associated with infection in neutropenic patients, it is imperative to promptly conduct clinical and microbiological assessments in these individuals presenting with fever. Consequently, initiating empirical antibiotic therapy without delay is crucial.[1,12,13] In the case of these individuals, distinguishing between a severe infection and the etiology of fever is frequently challenging. Inflammation and infection often manifest with less conspicuous clinical indications and symptoms than anticipated, with fever frequently serving as the sole indicator of infection in the majority of instances. Hence, there has been a demand for expedient and straightforward markers that can detect the existence of infection, aid in excluding infection, and forecast the prognosis of infected individuals. Consequently, investigations have been undertaken to address this matter.

The assessment of patient prognosis during and after episodes of febrile neutropenia has emerged as a significant focal point in recent years. In order to achieve this objective, it has been feasible to categorize individuals into two distinct groups: high risk and low risk. This classification is accomplished by taking into account a range of characteristics, such as the Multinational Association for Supportive Care in Cancer (MASCC) guidelines. Furthermore, multiple laboratory markers have demonstrated their utility in assessing the presence of infection and predicting the prognosis of these patients. The utilization of procalcitonin as a diagnostic marker for infection remains limited in the context of febrile neutropenia patients, despite its recent emergence as a potential indicator. In contrast to cytokines such as tumor necrosis factor (TNF) and IL-6, the levels of procalcitonin exhibit elevation specifically in cases of bacterial and fungal infections, while remaining unaffected in instances of other forms of inflammation, including viral infections, organ transplant rejection, and autoimmune illnesses.[14-16] Persson et al.[17] shown that the assessment of plasma procalcitonin and IL-6 levels in individuals with febrile neutropenia has the potential to provide valuable guidance for treatment decisions. Previous studies have demonstrated that this test exhibits a high degree of sensitivity and specificity when distinguishing between bacterial and fungal infections. Additionally, it has been established as a prompt and reliable method for distinguishing early invasive bacterial infections in pediatric emergency cases.[16,18] Indeed, it was discovered that its ability to predict infectious etiology in sepsis was superior to that of CRP and IL-6.[19] The findings of this study indicate that serum procalcitonin levels were substantially higher than C-reactive protein (CRP) levels (p=0.008) in febrile neutropenic adult patients with severe illness. The mean procalcitonin value was 118. In a separate comparative investigation, the efficacy of procalcitonin was

assessed in relation to other biomarkers including CRP, IL-6, IL-8, soluble TNF receptor II, and soluble IL-2 receptor levels among pediatric cancer patients. The findings of this study indicated that procalcitonin exhibited greater utility as an indicator of infection in febrile neutropenic patients compared to the aforementioned parameters.[20] Secmeer et al.[21] conducted a study wherein they examined 60 instances of febrile neutropenia. Their findings suggested that both C-reactive protein (CRP) and procalcitonin levels could serve as indicators of the infection's severity. However, procalcitonin was deemed more suitable for determining the initial course of treatment due to its earlier elevation compared to CRP. A further investigation examining the relationship between procalcitonin and CRP revealed that serum procalcitonin exhibited superior performance in detecting febrile neutropenia episodes and demonstrated a higher positive predictive value compared to CRP. In contrast, it was observed that CRP had superior efficacy in identifying such attacks, as well as a larger negative predictive value in comparison to procalcitonin.[22]

The diagnostic utility of procalcitonin in individuals with febrile neutropenia has been met with skepticism due to the potential release of procalcitonin from leukocytes. However, recent studies have demonstrated that procalcitonin synthesis and release can occur in cases of immunosuppression and leukopenia, provided there is adequate stimulation.[6,11,23] Moreover, elevated levels of procalcitonin have been observed in neutropenic patients during the initial phases of infection.[14,24,25] In a study conducted by Ruokonen et al.,[14] it was noted that there was a rapid increase in procalcitonin levels within a span of 8 hours following the initiation of fever. In the present investigation, it was observed that the procalcitonin levels of 37 patients upon admission to the hospital exceeded the established normal threshold of 0.5 ng/ml.

Elevated levels of procalcitonin have been found to be correlated with the severity of infection, making it a potential biomarker for monitoring patients with severe infections, sepsis, and multiple organ dysfunction syndrome (MODS).[6,26-30] Due to the aforementioned factors, procalcitonin has been well acknowledged as a dependable indicator in distinguishing between bacterial and non-bacterial inflammation.[7,28,30] In the conducted investigation, it was shown that individuals with a procalcitonin (PCT) level greater than 2 ng/ml exhibited a notably elevated incidence of bacterial growth in both blood and urine cultures, in contrast to patients with a PCT level equal to or less than 2 ng/ml. Furthermore, in accordance with our findings, previous research has also observed considerably elevated procalcitonin levels in febrile neutropenic patients with confirmed infection when compared to the group without bacterial infection.[9,20,25]

Evidence exists indicating a correlation between the specific bacteria responsible for infection and the levels of procalcitonin in individuals experiencing febrile neutropenia. According to the available reports, there is a notable elevation in procalcitonin levels in cases of bacteremia attributed to gram-negative bacteria.[9,11,14,20,24] Nevertheless, our study did not yield any statistically significant disparity when comparing procalcitonin levels between the gram-positive and gram-negative groups based on the microorganism type (p=0.95). This lack of significance may be attributed to the limitations of our measuring device, which reported procalcitonin values exceeding 100 ng/ml as ">100 ng/ml" and subsequently treated them as 100 ng/ml in our study.

Evidence indicates that there exists a correlation between the severity of infections in neutropenic patients and serum procalcitonin levels, comparable to those with intact immune systems.[20,23,24,26] In the present investigation, it was shown that the levels of procalcitonin exhibited a statistically significant increase in the cohort characterized by microbiologically confirmed illnesses (p=0.022). Additionally, a statistically significant elevation in mortality rates was seen within the aforementioned patient group (p=0.40). The findings of this study provided evidence to support the notion that there exists a correlation between serum procalcitonin levels and the degree of infection severity in neutropenic individuals. Moreover, it was suggested that measuring serum procalcitonin levels could serve as a valuable tool in diagnosing severe infections and assessing the prognosis of patients within this specific population.

The present study is subject to certain limitations, including its retrospective design, its execution within a singular institution, and its inclusion of a limited patient cohort.

CONCLUSION

Elevated blood procalcitonin levels were seen in 37 (60.6%) febrile neutropenic individuals upon admission. The observed increase in procalcitonin levels was determined to be notably greater in cases of MDI or CDI compared to cases of FUO. This finding suggests that procalcitonin could potentially serve as a valuable tool for promptly diagnosing known illnesses. The data indicates that there was a notable increase in mortality rates in episodes when procalcitonin levels above 2 ng/ml, so supporting the notion that elevated procalcitonin levels may be indicative of an unfavorable prognosis. Based on a comprehensive analysis of our study findings and existing literature, it is evident that the frequent utilization of procalcitonin as a significant parameter is warranted for the purpose of indicating infection and mortality rates among patients afflicted with febrile neutropenia. The inclusion of infection and mortality data in the assessment can greatly facilitate the determination of appropriate treatment modality, namely the decision between outpatient or inpatient care upon hospital admission.

ETHICAL DECLARATIONS

Ethics Committee Approval: Antalya Training and Research Hospital Scientific Research Assessment and Ethics Committee (Date: 19/06/2014, Approval No: 44/26).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Alveolitis as a result of dust chlorine exposure

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ABSTRACT

Hypersensitivity pneumonia of the lung, also called "extrinsic allergic alveolitis" or "hypersensitivity pneumonitis", is a condition in which the lung tissue becomes inflamed for reasons other than microbial causes. There may be many different reasons. Among the most common reasons were bird feeding, agricultural works and air conditioners. There are acute, subacute or chronic (slowly progressing) forms. Acute and subacute forms may recur, while the chronic form progresses and causes permanent and irreversible damage such as fibrosis and emphysema. Bird proteins, mammalian proteins, fungi, bacterial proteins and small molecular weight chemicals are generally blamed for the formation of the disease. Sometimes the causative agent may not be identified. In this case, we aimed to present a patient who applied to our clinic due to complaints of sudden respiratory distress, rapid fatigue and cough as a result of dust chlorine exposure, and was diagnosed with alveolitis, hospitalized and followed up.

Keywords: Hypersensitivity pneumonia, dust chlorine exposure, alveolitis

INTRODUCTION

Hypersensitivity pneumonia of the lung, also called "extrinsic allergic alveolitis" or "hypersensitivity pneumonitis", is a condition in which the lung tissue becomes inflamed for reasons other than microbial causes. There may be many different reasons. Among the most common reasons were bird feeding, agricultural works and air conditioners. There are acute, subacute or chronic (slowly progressing) forms. Acute and subacute forms may recur, while the chronic form progresses and causes permanent and irreversible damage such as fibrosis and emphysema. Bird proteins, mammalian proteins, fungi, bacterial proteins and small molecular weight chemicals are generally blamed for the formation of the disease. Sometimes the causative agent may not be identified.

In this case, we aimed to present a patient who applied to our clinic due to complaints of sudden respiratory distress, rapid fatigue and cough as a result of dust chlorine exposure, and was diagnosed with alveolitis, hospitalized and followed up.

CASE

A 47-year-old male patient was admitted to our clinic with complaints of sudden respiratory distress, fatigue and cough. There was no known history of additional disease. He had a history of 16 pack-year cigarette smoking dating back to 10 years ago. He had no history of alcohol use. He had no history of tuberculosis or contact. He was working as a pool chemical worker in hotel services. The patient had been exposed to chlorine before, and the last time he had a history of heavy dust chlorine use. There was no history of chemical exposure other than chlorine. The lung tomography showed that he was in the upper lobes of both lungs. There were peribronchial focal ground-glass-shaped density increases. Septal thickenings were observed in the lower lobes. Diffuse central ground-glass-shaped density increases were observed in both lungs, and a peripheral mass-like consolidation area was observed in the anterior upper lobe of the right lung. The findings were compatible with alveolitis. On examination, breathing sounds, gross oxygen saturation, temperature was 36.5°C, blood samples were within normal limits. Pulmonary Function Test result was FEV1: 86% FVC: 81% FEV1/FVC: 84 (Figure 1).

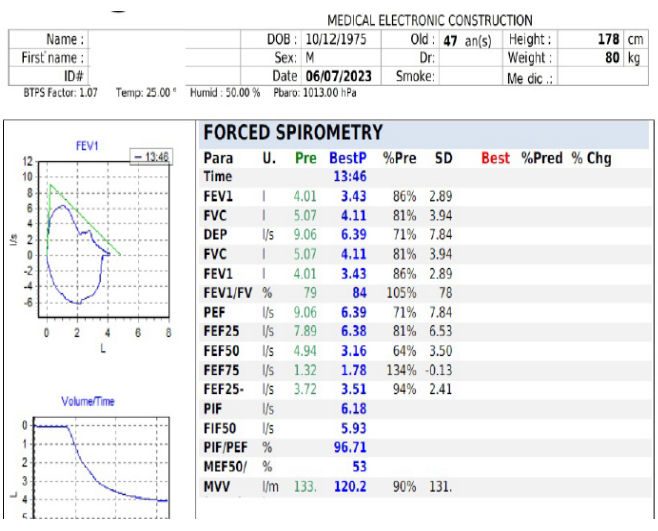

Figure 1. Pulmonary function test result.

During the hospitalization period, the patient was given 1x80 mg of prednol and bronchodilator treatment for 4 days. On the 5th day, 40 mg of prednol was given. Prednol 16 mg 20 tablets 1x1 was started for the next day and he was discharged. Tomography image comparisons at first arrival and 1 month later were seen at Figure 2 and Figure 3.

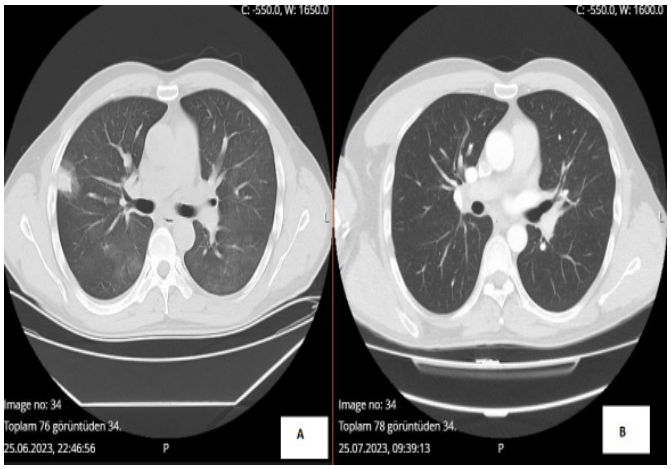

Figure 2. A: Peripheral mass in the anterior upper lobe of the right lung. Scattered consolidation area fibroatelectatic changes in both lungs. B: After using corticosteroids for one month, a considerable response was seen

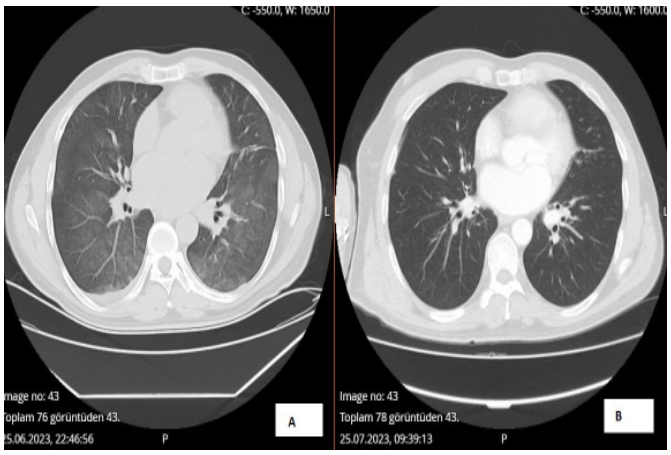

Figure 3. A: Widespread central ground glass pattern in both lungs. B: After using corticosteroids for one month, a considerable response was seen

DISCUSSION

The annual prevalence of hypersensitivity pneumonia is 1.6-2.7/100000. Its incidence varies according to age, profession and geographical region. It is seen at a rate of 1.3-12.9% in farmers, 3.7-10.4% in bird breeders, and 3.5-29% in mushroom workers. In our country, it has been detected in the third place after IPF and interstitial lung diseases due to collagen tissue diseases. Bird proteins, mammalian proteins, fungi, bacterial proteins and small molecular weight chemicals are generally blamed for the formation of the disease. Sometimes, the causative agent may not be identified. HP is seen in 80-95% of non-smokers.[1]

Chlorine is a green-yellow gas, heavier than air, with a characteristic odor. It is used in industry to make alkali and bleach, as a disinfectant, and as a whitening agent in the paper and textile industry. Although its irritating effects on the lungs occur throughout the entire airway due to its moderate water solubility, it is especially evident in the bronchioles and alveoli.[2-4]

Exposure to chlorine gas often occurs in the home environment, either from mixing household cleaning agents or, as in our case, during pool or spa maintenance. In a retrospective study on chlorine poisonings in a poison center, it was determined that 73% of the admissions were due to mixing cleaning products containing acid and hypochlorite bleach, 14% were related to swimming pools, and 7% were related to industrial exposure.[5] If the exposure time is long and ventilation is insufficient, the patient complains of eye and respiratory system irritation. In mild exposures, the main symptoms are nasal irritation, conjunctivitis, dry throat, cough and mild shortness of breath. In more severe exposures, as in our case, symptoms such as obvious shortness of breath, headache, cough, white-pink sputum production, chest pain, and vomiting are added. Since the odor threshold value is above the threshold value of respiratory irritation, the absence of odor does not indicate the absence of exposure. On physical examination, there is no exposure in the lungs. rales and rhonchi may be heard; In cases of heavy exposure, it may result in noncardiogenic pulmonary edema.[6,7] In the treatment of these patients, they generally respond to eye irrigation, oxygen, cough suppressants, bronchodilators, and, in cases where airway obstruction does not improve, steroid administration, as in our case.[7,8] There are studies reporting that sodium bicarbonate application by nebulization may be beneficial. Theoretically, sodium bicarbonate neutralizes the acid formed as a result of contact of chlorine with water.[5,7] It has been reported that permanent bronchial hyperreactivity and RADS develop after single exposure to high amounts of chlorine gas.[4]

RADS is a condition of bronchospasm that occurs within hours after a person who has no previous respiratory complaints is exposed to a respiratory irritant intensely.[9] It has been reported that permanent bronchial hyperreactivity and RADS develop after single exposure to high amounts of chlorine gas. The diagnosis of RADS is made if there is no previous respiratory complaint, the symptoms begin after a single accidental or incidental exposure, the respiratory irritant such as gas, smoke or vapor is in high concentration, the symptoms start within 24 hours after the exposure, and lasting at least 3 months, symptoms such as cough, shortness of breath, wheezing consistent with asthma, presence of nonspecific bronchial hyperresponsiveness, normal respiratory function tests or airway obstruction, and other respiratory symptoms It is diagnosed by ruling out diseases.[4,10,11] In our case, it was observed that he responded to steroid treatment and RADS did not develop.

CONCLUSION

As a result, although chlorine gas inhalation is frequently observed, it may cause mild effects on the respiratory tract, but may also cause the development of RADS in more severe exposures. The most important issue in treatment is to avoid exposure to the agent. Corticosteroids are indicated for the treatment of acute, subacute and chronic HP. Corticosteroids may also be useful in the treatment of severe or progressive chronic HP.

ETHICAL DECLARATIONS

Informed Consent: All patients signed and free and informed consent form

Reviewer Evaluation Process: Externally peer-reviewed.

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