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The Association of Macrophage Activation-Like Syndrome with Mortality in Elderly Patients with Sepsis

Sepsis Tanılı İleri Yaş Hastalarda Makrofaj Aktivasyon Benzeri Sendromun Mortalite ile İlişkisi

Şükriye Miray KILINÇER BOZGÜL[1](İD), Caner ACAR[1](İD), İlkçe AKGÜN KURTULMUŞ[1](İD), Özgür AYDIN[1](İD), Didem KOCA[1](İD), Güneş AK[2](İD), Fatma Feriha ÇİLLİ[3](İD), Devrim BOZKURT[1](İD)

[1] Department of Internal Diseases, Ege University Faculty of Medicine, İzmir, Türkiye
[2] Department of Clinical Biochemistry, Ege University Faculty of Medicine, İzmir, Türkiye
[3] Department of Medical Microbiology, Ege University Faculty of Medicine, İzmir, Türkiye

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ABSTRACT

Introduction: *Among the geriatric population, when compared to younger individuals, mortality is high. Macrophage activation-like syndrome (MALS) has been reported to be an independent immunological entity associated with mortality among sepsis patients in adults which represents the increased inflammation state. This study aimed to investigate the frequency of MALS in elderly sepsis patients and its association with intensive care unit (ICU) mortality.*

Materials and Methods: *This retrospective study included patients aged 65 years or older with sepsis between January 2013 and January 2022 in the ICU of the Internal Medicine Department of Ege University Hospital. MALS was diagnosed with a hemophagocytic syndrome score (H-score) of ≥151 and/or co-presence of hepatobiliary dysfunction (HBD) and disseminated intravascular coagulation (DIC). Clinical, demographic, and laboratory results were retrieved from the medical records. Factors affecting ICU mortality were investigated with binary logistic regression analysis.*

Results: *In our study of 194 patients, mortality was 46.4% and MALS frequency was 23.7%. Among non-survivors, MALS frequency was significantly higher than survivors; 32.2% and 16.3%, p= 0.010. The median H-score was 117 in non-survivors and 78.5 in survivors, p= 0.002. ICU mortality of elderly sepsis patients increased by approximately 25 times when MALS was present. Age was not identified as a risk factor for ICU mortality.*

Conclusion: *Among elderly sepsis patients, the frequency of MALS was found to be remarkably high in our single-center study. MALS may be one of the reasons for increased mortality in elderly sepsis patients.*

Key Words: *Sepsis; Macrophages; Mortality; Elderly; Critical care*

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ÖZ

Sepsis Tanılı İleri Yaş Hastalarda Makrofaj Aktivasyon Benzeri Sendromun Mortalite ile İlişkisi

Şükriye Miray KILINÇER BOZGÜL[1], Caner ACAR[1], İlkçe AKGÜN KURTULMUŞ[1], Özgür AYDIN[1], Didem KOCA[1], Güneş AK[2], Fatma Feriha ÇİLLİ[3], Devrim BOZKURT[1]

[1] Ege Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İzmir, Türkiye
[2] Ege Üniversitesi Tıp Fakültesi, Klinik Biyokimya Anabilim Dalı, İzmir, Türkiye
[3] Ege Üniversitesi Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı, İzmir, Türkiye

Giriş: *Geriatrik popülasyonda mortalite gençlere kıyasla daha yüksektir. Makrofaj aktivasyon benzeri sendromun (MALS) yetişkin sepsis hastalarında mortalite ile ilişkili bağımsız bir immünolojik antite olduğu ve artmış inflamasyon durumunu temsil ettiği bildirilmiştir. Bu çalışmanın amacı, yaşlı sepsis hastalarında MALS sıklığını ve bunun yoğun bakım ünitesi (YBÜ) mortalitesi ile ilişkisini araştırmaktır.*

Materyal ve Metod: *Bu retrospektif çalışmaya, Ocak 2013 ile Ocak 2022 tarihleri arasında Ege Üniversitesi Hastanesi İç Hastalıkları Anabilim Dalı YBÜ'de sepsis tanısıyla yatan, 65 yaş ve üzeri hastalar dahil edilmiştir. MALS tanısı hemofagositik sendrom skorunun (H-score) ≥151 olması ve/veya hepatobiliyer disfonksiyon (HBD) ve dissemine intravasküler koagülasyon (DIK) birlikteliği ile konmuştur. Hastaların klinik, demografik ve laboratuvar sonuçları tıbbi kayıtlardan elde edilmiştir. YBÜ mortalitesini etkileyen faktörler lojistik regresyon analizi ile araştırılmıştır.*

Bulgular: *Yüz doksan dört hastanın dahil edildiği araştırmamızda mortalite %46.4 ve MALS sıklığı %23.7 idi. Ölen hastalar arasında MALS sıklığı sağ kalanlara göre anlamlı derecede yüksekti (%32.2 ve %16.3, p= 0.010). Medyan H-score ölenlerde 117 iken sağ kalanlarda 78.5 idi (p= 0.002). MALS varlığında, ileri yaş sepsis hastalarının YBÜ mortalitesinin yaklaşık 25 kat arttığı saptandı. Yaş, YBÜ mortalitesi için bir risk faktörü olarak saptanmadı.*

Sonuç: *Tek merkezli çalışmamızda, yaşlı sepsis hastaları arasında MALS sıklığının oldukça yüksek olduğu görülmüştür. MALS, yaşlı sepsis hastalarında artmış mortalitenin nedenlerinden biri olabilir.*

Anahtar Kelimeler: *Sepsis; Makrofaj; Mortalite; Yaşlı; Yoğun bakım*

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. Compared to younger patients, sepsis incidence and mortality are increased in the elderly[2]. With increasing age, immune system changes result in chronic hyperstimulation and dysregulated systemic response to infection[3] which also increases the risk of secondary infections and hospital-acquired infections.

Hemophagocytic syndrome (HS), also known as hemophagocytic lymphohistiocytosis (HLH), is a rare but life-threatening condition that develops as a result of over-activation of the immune response during inflammatory processes[4]. Primary HS is mostly due to genetic causes and occurs in childhood, whereas secondary HS occurs in adults and during the course of infection, malignancy, or autoimmune diseases[5]. Patients are frequently followed up in intensive care units (ICU) and mortality has been reported between 40-80%[6-8]. Macrophage activation syndrome (MAS) is another name for secondary HS that occurs in the presence of underlying rheumatologic disease[9,10]. One of the diagnostic criteria for HS is the presence of hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver[11]. However, it is difficult to perform such invasive procedures in critically ill patients. The Hellenic Sepsis Study Group classified patients who met the Sepsis-3 criteria and had a positive H-score or the co-presence of hepatobiliary dysfunction (HBD) and disseminated intravascular coagulation (DIC) as patients with macrophage activation-like syndrome (MALS). They reported the presence of MALS as an independent life-threatening entity in sepsis[12]. In the current literature, data about MALS in critically ill patients with sepsis are limited and to our best knowledge MALS in elderly sepsis patients has not been reported.

In this study, we aimed to determine the frequency of MALS and whether MALS influences sepsis-related mortality.

MATERIALS and METHODS

Study Participants and Data Acquisition

This study was performed retrospectively on patients followed up in the Ege University Faculty of Medicine Department of Internal Medicine Intensive Care Unit (ICU) between January 2013 and January 2022. The study was approved by the Ege University Ethics Committee with the reference number 23-4T/10 and adhered to the principles of the Declaration of Helsinki. Patients 65 years of age or above with sepsis were included after obtaining written informed consent. Patients with a history of advanced-stage malignancy, those on palliative care, and individuals who died within a period shorter than 24 hours were excluded from the study. The flowchart depicting patient inclusion is presented in supplementary Figure 1. The medical history, demographics, comorbidities, and routine laboratory parameters of the patients during ICU admission were collected from the medical files. The Sepsis-3 criteria were used to define sepsis[1]. Comorbidity was assessed using the Charlson Comorbidity Index (CCI)[13]. The Hellenic Sepsis Study Group report was used to define MALS[12]. The KDIGO criteria, which represent the international definition of acute kidney injury (AKI), were employed for the detection of AKI at any stage[14]. The H-score was calculated based on the findings from Fardet et al.'s study[15] at the time of MALS diagnosis; at admission or during follow-up. The sequential organ failure assessment (SOFA) score was calculated. Bacteremia was defined as the isolation of pathogenic bacteria in the blood culture. A specific organ was considered to be the source of sepsis if there were suspected, clinically documented signs observed during diagnostic imaging without microbiological documentation or if there was a microbiologically documented infection. In a blood non-immunocompromised host, a single positive culture for gram-positive rods, coagulase-negative staphylococci (CNS), or *Candida* at a site other than blood was considered to be a contaminant. The following standard definitions

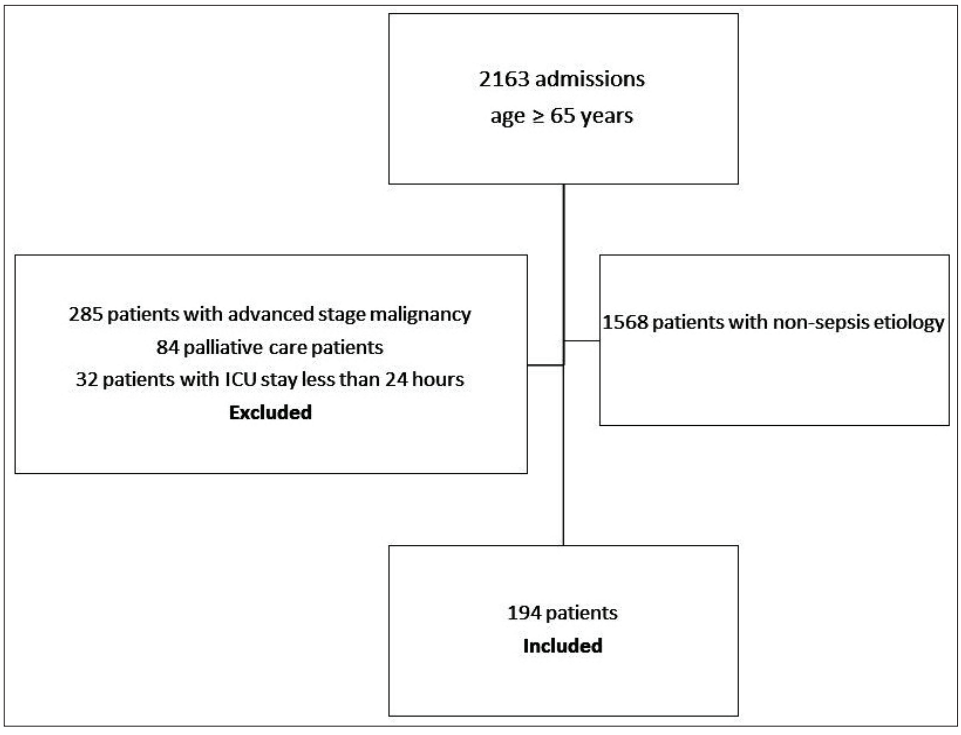

Figure 1. Flowchart of patient inclusion.

were used: multiple drug resistant (MDR) referred to a species of bacteria resistant to at least one agent in three or more antimicrobial categories, while extensively drug resistant (XDR) denoted a species of bacteria resistant to all antimicrobial agents except in two or fewer antimicrobial categories[16]. The primary outcome of the study was ICU mortality.

Statistics

Descriptive statistics were presented as medians (M), interquartile range (IQR), and means ± standard deviation, depending on the normality distribution of the variables, whereas categorical variables were expressed as numbers (n) and percentages (%). The normality of the continuous variables was assessed using the Shapiro-Wilk test and Q-Q plots. The independent samples t-test and Mann-Whitney U test were used for comparisons between survivors and non-survivors. Pearson's Chi-square and Fisher's exact tests were used for the comparison of categorical variables. Factors predicting ICU mortality were investigated with binary logistic regression analysis. The IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) program was used for all statistical analyses, and a p-value of <0.05 was determined statistically significant.

RESULTS

A total of 5200 patients hospitalized between January 2013 and January 2023 in the internal medicine ICU were retrospectively reviewed. Out of this cohort, 194 patients, who were admitted with sepsis and were aged 65 years or older, were included in the study. About 104 (53.6%) were male and 90 (46.4%) were females. The median age of the included patients was 74 years, and the median hospital stay was eight days. The in-hospital mortality rate was 46.4%. Hypertension (HT) was the most common comorbidity, observed in 63.4% of the patients. The median CCI was five. The median H-score was 96 (80.8) and MALS was present in 23.7% of the patients. 65.5% of the patients had AKI and 22.7% developed AKI requiring hemodialysis. The median SOFA score on ICU admission was seven (4). The urinary tract was the most common source of infection (24.7%). Bacteremia was present in 32% of the patients. The most common microorganism was extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* (11.9%). Among them; 45.8% were multidrug-resistant and 18.6% extensively-drug resistant. The clinical, demographic, and laboratory characteristics of the study population are summarized in Table 1.

There was no significant difference between survivors and non-survivors in terms of age. The most common comorbidity was HT both survivors and non-survivors. No significant difference was present in terms of comorbidities and CCI. SOFA score was significantly higher in non-survivors ($p= 0.005$). Septic shock was present in 60% of non-survivors and 46.6% of survivors ($p= 0.063$). Among the survivors, 66.3% of patients had AKI, and 20.2% of patients received hemodialysis. Among non-survivors, 64.4% of patients had AKI, and 25.6% of patients received hemodialysis ($p= 0.781$, $p= 0.374$, respectively). Bacteremia was significantly higher in non-survivors, $p= 0.005$. MDR and XDR were similar between survivors and non-survivors. MALS frequency was significantly higher in non-survivors, $p= 0.01$. On ICU admission mean albumin was 3.1 ± 0.5 in survivors and 2.7 ± 0.6 in non-survivors ($p< 0.001$). The median lactate and serum ferritin levels were significantly higher and hemoglobin (Hb) was significantly lower in patients who expired ($p= 0.038$, $p< 0.001$, $p= 0.007$, respectively). Although the maximum CRP level was higher in survivors, it was not significant statistically. Minimum albumin was significantly lower in non-survivors. The median H-score was 78.5 (62) in survivors and 117 (102.8) in non-survivors ($p= 0.002$). Results are summarized in Table 2. The predictors of mortality were examined in binary logistic regression analysis. The results showed that the presence of MALS increased mortality 25-fold ($p= 0.018$). Results are summarized in Table 3.

Table 1. Clinical, demographic, and laboratory characteristics of the studied population

Characteristics	Value (n= 194)	Characteristics	Value (n= 194)
Age, years	74 (12)	H-score	96 (80.8)
Length of hospital stay, days	8 (8)	MALS, present (%)	46 (23.7)
In-hospital mortality, present (%)	90 (46.4)	AKI, present (%)	127 (65.5)
Gender, female (%)	90 (46.4)	Acute Hemodialysis, present (%)	44 (22.7)
DM, present (%)	72 (37.1)	Septic shock, present (%)	102 (52.8)
HT, present (%)	123 (63.4)	SOFA score	7 (4)
HF, present (%)	41 (21.1)	Source of infection, n (%)	
CVD, present (%)	48 (24.7)	Respiratory system	45 (23.2)
COPD, present (%)	28 (14.4)	Urinary tract	48 (24.7)
CKD, present (%)	34 (17.5)	Hepatobiliary tract	14 (7.2)
On dialysis, present (%)	27 (14)	Skin-soft tissue	16(8.2)
CVA, present (%)	11 (5.9)	Abdomen	18 (9.3)
Dementia, present (%)	26 (13.9)	Catheter and bloodstream	19 (9.8)
Malignancy, present (%)	27 (13.9)	Endocarditis	4 (2.1)
Charlson-comorbidity index	5 (2)	Septic arthritis	5 (2.6)
Urea (mg/dL)	105 (91.3)	Multiple sources	13 (6.7)
Creatinine (mg/dL)	2.9 (3.2)	Others	12 (6.1)
ALT (U/L)	30 (44)	Bacteremia, present(%)	62 (32)
Albumin (g/L)	2.9 (0.9)	MDR, present (%)	54 (45.8)
CRP (mg/L)	194 (194.8)	XDR; present (%)	22 (18.6)
Procalcitonin (µg/L)	5.5 (22.1)	Microorganisms, n (%)	
Ferritin (µg/L)	801.5 (2096.8)	ESBL producing Enterobacteriaceae	23 (11.9)
LDH (U/L)	301 (156.8)	*Staphylococcus aureus*	12 (4.6)
Troponin (ng/L)	60 (96.5)	*Acinetobacter baumannii*	10 (5.2)
NT-proBNP (ng/L)	5943 (23541.8)	*Candida* spp.	10 (4.1)
Lactate (mmoL/L)	2.3 (2)	*Klebsiella* spp.	9 (4.1)
Fibrinogen (mg/dL)	430 (356.8)	CoNS	8(3.1)
Neutrophils (x10^3/µL)	10.0 (11.9)	*Enterococcus* spp.	7 (3.6)
Hb (g/dL)	10.3 (3.1)	Others	9 (4.6)
Platelet (x10^3/µL)	167.5 (169.0)	Polymicrobial	14 (7.2)

Descriptive statistics were presented as median (IQR) in continuous variables and number (%) in categorical variables. DM: Diabetes mellitus, HT: Hypertension, HF: Heart failure, CVD: Cardiovascular disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, CVA: Cerebrovascular accident, CRP: C-reactive protein, LDH: Lactate dehydrogenase, NT-proBNP: N-terminal pro-brain natriuretic peptide, NLR: Neutrophil- to- lymphocyte ratio, Hb: Hemoglobin, H-score: Reactive hemophagocytic syndrome diagnostic score, MALS: Macrophage activation like syndrome, AKI: Acute kidney injury, SOFA: Sequential organ failure assessment, MDR: Multidrug-resistant, XDR: Extensively-drug resistant, ESBL: Extended-spectrum β lactamase, CoNS: Coagulase-negative staphylococci.

Table 2. Comparison of clinical, demographic, and laboratory characteristics of the patients based on ICU mortality

Characteristics	Survivors (n= 104)	Non-survivors (n= 90)	p
Length of hospital stay, days	10 (11)	7 (8)	<0.001
Age, years	74 (13)	73 (11)	0.472
DM, present (%)	41 (39.4)	31 (34.4)	0.474
HT, present (%)	67 (64.4)	56 (62.2)	0.751
HF, present (%)	24 (23.1)	17 (18.9)	0.476
CVD, present (%)	24 (23.1)	24 (26.7)	0.563
COPD, present (%)	12 (11.5)	16 (17.8)	0.217
CKD, present (%)	16 (15.4)	18 (20)	0.399
On dialysis, present (%)	15 (14.6)	12 (13.3)	0.806
CVA, present (%)	5 (5)	6 (6.9)	0.582
Dementia, present (%)	14 (14)	12 (13.8)	0.967
Malignancy, present (%)	12 (11.5)	15 (16.7)	0.303
Charlson-comorbidity index	5 (2)	5 (2)	0.665
SOFA score	7 (3)	8 (5.8)	**0.005**
H-score	78.5 (62)	117 (102.8)	**0.002**
Septic shock, present (%)	48 (46.6)	54 (60)	0.063
AKI, present (%)	69 (66.3)	58 (64.4)	0.781
Acute Hemodialysis, present (%)	21 (20.2)	23 (25.6)	0.374
Bacteremia, present (%)	25 (26.6)	37 (47.4)	**0.005**
MDR, present (%)	26 (44.8)	28 (46.7)	0.841
XDR, present (%)	7 (12.1)	15 (25)	0.071
MALS, present (%)	17 (16.3)	29 (32.2)	**0.010**
Albumin (g/L)	3.1 ± 0.5	2.7 ± 0.6	**<0.001**
Hb (g/dL)	11 (3.2)	9.6 (2.4)	**0.007**
Lactate (mmoL/L)	2 (1.7)	2.4 (2.1)	**0.038**
Ferritin (µg/L)	599 (746.3)	1716.5 (4361.5)	**<0.001**
Maximum CRP (mg/L)	233.3 ± 120.3	265.1 ± 121.5	0.074
Minimum albumin (g/L)	2.6 (0.8)	2.2 (0.8)	**<0.001**

Descriptive statistics were presented as median (IQR) or mean ± for continuous variables according to normality, and number (%) for categorical variables.
DM: Diabetes mellitus, HT: Hypertension, HF: Heart failure, CVD: Cardiovascular disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, CVA: Cerebrovascular accident, SOFA: Sequential organ failure assessment, H-score: Reactive hemophagocytic syndrome diagnostic score, AKI: Acute kidney injury, MDR: Multidrug-resistant, XDR: Extensively-drug resistant, MALS: Macrophage activation like syndrome, Hb: Hemoglobin, CRP: C-reactive protein.

Table 3. Binary logistic regression analysis of mortality predictors

	β	SE	Wald Statistics	p	Exp (β)	95% CI for exp (β)	
						Lower	Upper
Constant	9.737	4.111	5.610	0.018			
MALS							
Not present	Reference						
Present	3.248	1.374	5.589	**0.018**	25.741	1.742	380.291
SOFA score	-0.179	0.174	1.059	0.303	0.836	0.595	1.176
Albumin	-1.621	1.109	2.136	0.144	0.198	0.022	1.738
Lactate	0.157	0.278	0.322	0.571	1.170	0.679	2.016
Ferritin	0.000	0.000	0.003	0.959	1.000	1.000	1.000
H-score	0.000	0.012	0.000	0.997	1.000	0.977	1.023
Minimum albumin	-1.761	0.940	3.512	0.061	0.172	0.027	1.084

MALS: Macrophage activation-like syndrome, SOFA: Sequential organ failure assessment, H-score: Reactive hemophagocytic syndrome diagnostic score, Method: Enter, SE: Standard error, CI: Confidence interval.

DISCUSSION

In our single-center retrospective cohort study, we observed a mortality rate of 46.4% among all patients. MALS was present in 23.7% of the patients and MALS frequency was significantly higher among non-survivors. ICU mortality of elderly sepsis patients increased by about 25 times when MALS was present.

The clinical and demographic profiles of the patients are comparable with current findings. As sepsis predominantly affects the older population[17-19], in the present study, the median age was 74 years. Nasa et al. reported mortality rates of 60.7% among sepsis patients aged 60-80 years and 78.9% among those classified as very old (>80 years)[18]. Other studies have also reported high mortality rates, such as 48% and 77%[20,21]. In our study, no difference was observed in terms of age among survivors and non-survivors. Some studies reported no association between age and death, on the other hand, age was reported as an independent risk factor for mortality in different studies[18,22-25]. Mortality in elderly sepsis has also been attributed to comorbidities. Chronic lung disease, chronic kidney disease, and chronic heart failure were associated with high mortality[26,27]. In the current study, no difference was found between survivors and non-survivors in terms of comorbidities and CCI. Diagnosis of sepsis in the elderly population can be challenging due to atypical presentations which may influence the therapeutic approach[28]. Data on time to treatment could not be accessed in the present study and, therefore, could not be the research subject of this study. The reason that age is associated with mortality appears to be multifactorial.

An increase in the SOFA score of two points or more is associated with an in-hospital mortality rate of greater than 10%[1]. In elderly sepsis patients, the SOFA score was also associated with mortality[20,29,30]. Additionally, in elderly and very elderly sepsis patients, SOFA score at ICU admission was found to be an independent predictor of ICU mortality[31]. Our results align with the existing literature, showing that non-survivors tend to have a higher SOFA score upon ICU admission.

MALS was initially defined by the Hellenic Sepsis Study Group[12] in sepsis patients and identified as a condition associated with increased mortality due to the hyper-inflammatory response of the host[32]. Sepsis, systemic inflammatory response syndrome (SIRS), HS, and MAS share similar findings of inflammation[33] and

are difficult to distinguish. In the presence of HS/MAS, especially in the ICU, mortality rates are significantly higher, and any delay in diagnosis and treatment further exacerbates this risk. H-score, which is a score for the diagnosis of reactive HS, was also used in the diagnosis of MALS[12]. In the current study, the frequency of MALS was 23.7%, which is remarkably higher than the Hellenic Sepsis Study Group findings. The reason for such a high frequency of MALS may be related to the age group of the patients. However, we did not have the chance to make a comparison since no study was found in the literature specifically focusing on this age group. The median H-score was 96 (80.8) and non-survivors had significantly higher H-scores at ICU admission. Additionally, we found that the presence of MALS increased in-hospital mortality by a factor of 25.

The incidence of bacteremia is on the rise, particularly in very elderly patients, and it has been reported as a predictor of mortality in both the short and long term[34-36]. We found that bacteremia was present in 32% of patients, and among non-survivors, the frequency of bacteremia was significantly higher. However, it's important to note that patient-related factors, including the presence of MALS, should also be taken into consideration.

In elderly sepsis patients, the respiratory system and genitourinary system are reported to be the most common source of infection with gram-negative bacteria[18,31,24]. Our findings are in line with the current literature, with a primary focus on urinary tract infections (24.7%) and respiratory system infections (23.2%). ESBL-producing *Enterobacteriaceae* (11.9%) were identified as the most common infectious agents. In our study, there was no significant difference between survivors and non-survivors in terms of the sepsis focus and infectious agent. The possible reason could be the small number of patients in the subgroups.

Among laboratory results, the non-surviving group had higher levels of lactate and serum ferritin levels. Serum ferritin levels in HS patients have been identified as a prognostic factor in different studies including HS and MALS patients[12,37]. Among sepsis patients, ferritin level above 4420 ng/mL was reported to be a reliable cut-off to diagnose MALS[12]. For HS, lower cut-off values have also been reported. Machowicz et al.[38] recommended evaluating sepsis patients with no history of transfusion or iron metabolism defects for HS when the serum ferritin level exceeds 2000 ng/mL. It appears that different cut-off limits for ferritin should be considered when investigating MALS in sepsis patients. In addition, hemoglobin and platelet counts were significantly lower among non-survivors. Cytopenias, which are one of the diagnostic criteria of HS[11], may indicate the onset of MALS. Consequently, patients should be closely monitored and their treatment should be evaluated for possible modifications.

Limitations

This study had several limitations. Firstly, it was a single-center retrospective study. Secondly, the evaluation of treatment modifications was not conducted. Thirdly, we used 65 as the age cut-off, but we did not compare the results with younger adults. Lastly, our study did not include long-term outcomes.

CONCLUSION

In conclusion, our study demonstrated an elevated mortality rate among elderly sepsis patients with MALS. These initial findings warrant further investigation to gain a deeper understanding of the association between MALS and mortality in this patient population. Prospective trials involving a larger number of participants from various types of ICUs, including those where rapid resuscitation is essential, should be conducted.

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ETHICS COMMITTEE APPROVAL

This study was approved by the Ege University Ethics Committee (Decision no: 23-4T/10, Date: 12.04.2023).

CONFLICT of INTEREST

The authors have no relevant financial or non-financial interests to disclose.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: ŞMKB, CA, DB

Analysis/Interpretation: ŞMKB, CA, İAK, ÖA, DK

Data Collection or Processing: CA, İAK, ÖA, DK

Writing: ŞMKB, CA, İAK, ÖA, DK

Review and Correction: GA, FFÇ, DB

Final Approval: ŞMKB, GA, FFÇ, DB

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Address for Correspondence/Yazışma Adresi

Dr. Şükriye Miray KILINÇER BOZGÜL

Department of Internal Diseases,
Ege University Faculty of Medicine,
İzmir, Türkiye

E-posta: miraybozgul@gmail.com