ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2023.55823
Nam Kem Med J 2023;11(3):219-225

Factors Associated with Mortality in Hospitalized Older Adults

Hospitalize Edilen Yaşlılarda Mortalite ile İlişkili Olan Faktörler

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ABSTRACT

Aim: This study aimed to evaluate mortality risk associated with readily accessible laboratory parameters and underlying conditions in hospitalized older adults.

Materials and Methods: This retrospective study included geriatric patients admitted for inpatient care to the internal medicine wards of two major university hospitals in two different regions of Turkey. Data related to the patients were collected by retrospective review of patient charts and electronic records. Survival data were obtained from the Death Reporting System of the Turkish Ministry of Health. Survival after admission at 30 days and 1 year was noted.

Results: The study included 1.465 hospitalized older adults with a median age of 74 years, of whom 51% were women. Of these patients, 115 (7.8%) died within 30 days and 382 (26.1%) died within 12 months. For 30-day mortality, independent risk factors appeared to be infectious diseases [odds ratio (OR) 2.109, p=0.006], receiving palliative support (OR 5.982, p=0.006), malignancy (OR 2.514, p=0.001), Charlson Comorbidity Index (CCI) (OR 1.219 per unit increase, p<0.001), MPV (OR 1.525 per unit increase, p<0.001), and CRP (OR 1.006 per unit increase, p<0.001). For 12-month mortality, independent risk factors were found to be infectious diseases (OR 1.978, p=0.01), palliative support (OR 6.506, p<0.001), malignancy (OR 2.654, p<0.001), CCI (OR 1.200 per unit increase, p<0.001), and CRP (OR 1.006 per unit increase, p<0.001).

Conclusion: The results of this study show that CCI, CRP, and NLR were associated with higher mortality both at 30 days and 12 months. A one-unit increase in MPV was an independent risk factor for 30-day mortality and increased the odds of mortality by 52.5%.

Keywords: Mortality, elderly, factors

ÖZ

Amaç: Çalışmamızda hospitalize edilen yaşlılarda kolay ulaşılabilir laboratuvar parametreleri ile mortalite açısından risk değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışma ülkemizin iki bölgesindeki iki büyük üniversitenin dahili servislerinde hospitalize edilen geriatrik hastalar arasında yapıldı. Bilgiler hasta dosyalarından ve elektronik kayıtlardan retrospektif olarak tarandı. Hastaların sağkalım bilgileri Türkiye Cumhuriyeti Sağlık Bakanlığı, Türkiye Halk Sağlığı Kurumu Ölüm Bildirim Sistemi'nden elde edildi. Hastaların 30 günlük ve 1 yıllık sağkalım bilgilerine ulaşıldı.

Bulgular: Bu çalışmaya dahil edilen 1,465 hastanın yaş ortancası 74 yıl idi ve %51'i kadındı. Hastaların 115'inin (%7,8) 30 gün ve 382'sinin (%26,1) 12 ay içeresinde öldüğü görüldü. Otuz günlük mortalite için enfeksiyon hastalıklarının 2,109 kat, palyatif destek alanların 5,982 kat, malignitenin 2,514 kat, Charlson Komorbidite İndeksi'nde (CCI) bir birimlik artışın 1,219 kat, MPV'deki bir birimlik artışın 1,525 kat, C-reaktif proteindeki (CRP) bir birimlik artışın 1,006 kat bağımsız risk faktörleri olduğu görüldü (sırasıyla p=0,006, p=0,006, p=0,001, p<0,001, p<0,001, p<0,001). On iki aylık mortalite için enfeksiyon hastalıklarının 1,978 kat, palyatif desteğin 6,506 kat, malignitenin 2,654 kat, CCI'deki bir birimlik artışın 1,200 kat, CRP'deki bir birimlik artışın 1,006 kat bağımsız risk faktörleri olduğu görüldü (sırasıyla p=0,010, p<0,001, p<0,001, p<0,001, p<0,001).

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Received: 14.04.2023 **Accepted:** 31.05.2023

Sonuç: CCI'deki, CRP değerindeki, NLO'daki artışın hem 30 günlük mortalite hem de 12 aylık mortalite riskini artırdığı görülmüştür. MPV'deki bir birimlik artışın 30 günlük mortalite için bağımsız risk faktörü olup %52,5 olasılıkla mortaliteyi artırdığı görülmüştür.

Anahtar Kelimeler: Mortalite, yaşlı, faktör

INTRODUCTION

The older population is steadily growing worldwide. The rate of adults aged 60 years and older in the population is currently approximately 11% and is expected to reach 22% by 2050[1]. This is associated with an increase in hospital admissions among older adults. However, hospitalized older patients face potential loss of functionality[2], prolonged hospital stay, referral to an assisted living facility or nursing home because of increased care needs[3], and excessive health care costs. Therefore, early detection of patients at high risk and rapid initiation of appropriate treatment may shorten hospital stays and prevent indirect losses.

Studies on hospitalization in older adults have generally focused on geriatric syndromes such as cognitive function, falls, functionality, and incontinence[4]. These studies have shown that physical condition and cognitive function are the most important factors at the time of hospital admission[5]. However, there are few studies examining the association between laboratory parameters and mortality. The prognostic value of these parameters may facilitate patient selection, especially in centers with high potential patient volume but limited capacity. Therefore, this study aimed to evaluate mortality risk associated with readily accessible laboratory parameters and underlying conditions in a large patient cohort.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

This retrospective study included geriatric patients admitted for inpatient care to the internal medicine wards of two major university hospitals in two different regions of Turkey between January 1, 2018 and December 31, 2019.

Patients admitted for hematologic diseases such as leukemia, myelodysplastic syndrome, myelofibrosis, or myeloproliferative disease, those admitted due to trauma or towards other than internal medicine, and those admitted to receive chemotherapy were not included. In addition, patients for whom complete blood count was not performed at the time of admission were excluded from the study.

Data related to the patients' demographic characteristics, underlying conditions, reason for admission (kidney disease, electrolyte imbalance, infection diseases, endocrine diseases, delirium, malnutrition, gastrointestinal bleeding, liver disease, palliative support, general follow-up and examination) and complete blood count values at admission were collected with retrospective review of patient charts and electronic records. The diagnoses of the patients were obtained from the International Statistical Classification of Diseases and Related Health Problems codes and the anamnesis in the files. Their values of white blood cell (WBC), neutrophil, lymphocyte, and platelet (PLT) counts, hemoglobin (Hb) level, mean thrombocyte volume (MPV), and neutrophil to lymphocyte ratio (NLR) were recorded. Complete blood count was measured with an automated cell counter (Sysmex XN-1000). NLR was calculated by dividing the neutrophil count by the lymphocyte count from the same blood sample obtained at admission.

The patients' underlying conditions were evaluated using the Charlson Comorbidity Index (CCI), which is a practical and widely used method for predicting mortality. The CCI was first described in the literature in 1987[6] and was modified in 1992[7].

Survival data were obtained from the Death Reporting System of the Turkish Ministry of Health, General Directorate of Public Health using the patients' citizenship numbers. Survival after admission at 30 days and 1 year was noted.

The study was conducted after obtaining ethical approval from İzmir Tınaztepe University Ethics Committee (decision no: 13, dated: 20/04/2021).

Statistical Analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences statistics version 21.0 package program. Descriptive statistics were presented as median (minimum-maximum) or number and percent distribution. Comparisons between surviving and non-surviving patients were made using the chi-square and Mann-Whitney U tests. A multivariate logistic regression model was created with infectious disease, palliative care, diabetes mellitus (DM), coronary artery disease (CAD), presence of malignancy, CCI, MPV, and C-reactive protein (CRP) value, which were found to be statistically significant among 30-day mortality categorical and time variables. A multivariate logistic regression model was created with the presence of infectious disease, palliative care, DM, CAD, malignancy and CCI, and CRP value, which were found to be statistically significant among the 30-day mortality categorical and time variables (Model: Backward: LR. Entry: 0.05 and Removal: 0.10).

RESULTS

The study included 1.465 hospitalized older adults with a median age of 74 years (range: 60-99), of whom 747 (51.0%) were women. Of these patients, 115 (7.8%) died within 30 days and 382 (26.1%) died within 12 months. Reasons for hospital admission compared according to 30-day and 12-month mortality are presented in Table 1. Both 30-day and 12-month mortality rates were significantly higher among patients hospitalized due to infectious diseases, delirium, malnutrition, and palliative support, and significantly lower in patients admitted for endocrine diseases.

Comparisons of underlying conditions and admission laboratory values according to 30-day and 12-month mortality are presented in Table 2. The 30-day mortality rate was significantly lower in patients with hypertension, DM, and CAD and significantly higher in patients with malignancy. Malignancy, chronic kidney disease, Alzheimer's disease, and chronic liver disease were significantly more common among patients who died within 12 months, while hypertension and DM were significantly less common. Patients who died within 30 days had significantly lower Hb, lymphocyte and PLT counts, and PLT/MPV and significantly higher WBC and neutrophil counts, NLR, MPV, and CRP level. Hb, lymphocyte, WBC, and neutrophil counts, NLR, and CRP levels were also significantly higher among patients who died within 12 months.

Reasons for hospital admission, underlying conditions, and admission laboratory values that were statistically significant in comparisons based on 30-day and 12-month mortality were further evaluated in logistic regression analysis (Table 3). Admission for infectious diseases or palliative support and the presence of malignancy were identified as independent risk factors for both 30-day and 12-month mortality (~6-6.5 times higher odds in patients hospitalized for palliative support, ~2.5 times higher odds for malignancy, and ~2 times higher odds for infectious disease). The presence of DM was associated with significantly lower risk of mortality at both time points (~65% lower), while the presence of CAD was associated with lower odds of mortality only in the first 30 days (~50% lower). A one-unit increase in CCI corresponded to 20% higher odds of both 30-day and 12-month mortality. A one-unit increase in MPV was associated with 52.5% higher odds of 30-day mortality. A one-unit increase in CRP was associated with a small but statistically significant 0.6% increase in the odds of 30-day and 12-month mortality (Table 3).

DISCUSSION

NLR is a systemic marker of inflammation that can be easily obtained from CBC and serves as an indicator of the balance between the natural and acquired immune systems. High NLR has been shown to be associated with mortality in oncology patients[8], including those with lung[9], ovarian[10], and breast[11] cancer, in patients with sepsis and bacteremia[12-14], and after cardiovascular disease, acute coronary syndrome, and stroke[15-17]. Kim et al.[18] reported that high NLR was associated with mortality in patients with ST-elevated myocardial infarction before undergoing primary percutaneous angioplasty. In their study of patients presenting to the emergency department, Hwang et al.[13] found that high NLR was an independent risk factor in patients with sepsis and septic shock. High NLR was also associated with stroke severity in patients diagnosed with acute ischemic stroke[15]. A possible reason for this may be that inflammatory factors released by neutrophils cause vascular degeneration, whereas lymphocytes are believed to have an anti-atherosclerotic role.

Table 1. Causes of hospitalization according to 30-day and 12-month mortality

	Mortality					
	30-day		p	12-month		p
	Yes (n=115)	No (n=1350)		Yes (n=382)	No (n=1083)	
Kidney disease, electrolyte imbalance	48 (41.7)	460 (34.1)	0.097	175 (45.8)	333 (30.7)	<0.001
Infection diseases	33 (28.7)	204 (15.1)	**<0.001**	**101 (26.4)**	**136 (12.6)**	**<0.001**
Endocrine diseases	15 (13.0)	374 (27.7)	**<0.001**	**71 (18.6)**	**318 (29.4)**	**<0.001**
Delirium	8 (7.0)	45 (3.3)	**0.046**	**23 (6.0)**	**30 (2.8)**	**0.003**
Malnutrition	20 (17.4)	90 (6.7)	**<0.001**	**58 (15.2)**	**52 (4.8)**	**<0.001**
GIS bleeding	3 (2.6)	58 (4.3)	0.383	16 (4.2)	45 (4.2)	0.978
Liver disease	9 (7.8)	71 (5.3)	0.245	33 (8.6)	47 (4.3)	0.001
Palliative support	10 (8.7)	13 (1.0)	**<0.001**	**15 (3.9)**	**8 (0.7)**	**<0.001**
General follow-up and examination	45 (39.1)	474 (35.1)	0.387	**134 (35.1)**	**385 (35.5)**	**0.869**

GIS: Gastrointestinal, Kidney disease and electrolyte imbalances: Acute kidney failure, chronic kidney disease, hyponatremia, hypernatremia, uremia, hypervolemia; Infectious diseases: Pneumonia, diabetic foot infection, decubitus ulcer infection, urinary tract infection; Endocrine diseases: Hyperglycemia, hypoglycemia, hypothyroidism, hyperthyroidism, pituitary insufficiency, osteoporosis

Table 2. Comparison of systemic diseases and admission laboratory values according to 30-day and 12-month mortality

	Mortality					
	30-day		p	12-month		p
Comorbidity	Yes (n=115)	No (n=1350)		Yes (n=382)	No (n=1083)	
HT	60 (52.2)	860 (63.7)	**0.014**	211 (55.2)	709 (65.5)	**<0.001**
DM	35 (30.4)	639 (47.3)	**<0.001**	140 (36.6)	534 (49.3)	**<0.001**
CAD	15 (13.0)	326 (24.1)	**0.007**	75 (19.6)	266 (24.6)	0.050
CHF	21 (18.3)	191 (14.1)	0.229	64 (16.8)	148 (13.7)	0.140
Depression	6 (5.2)	40 (3.0)	0.183	15 (3.9)	31 (2.9)	0.305
CRF	34 (29.6)	431 (31.9)	0.602	142 (37.2)	323 (29.8)	**0.008**
RA	2 (1.7)	20 (1.5)	0.526	4 (1.0)	18 (1.7)	0.396
Nephrotic syndrome	1 (0.9)	15 (1.1)	0.638	4 (1.0)	12 (1.1)	0.591
Nephritic syndrome	-	7 (0.5)	0.564	1 (0.3)	6 (0.6)	0.418
Other CTD	1 (0.9)	11 (0.8)	0.627	4 (1.0)	8 (0.7)	0.565
Chronic liver disease	10 (8.7)	81 (6.0)	0.250	33 (8.6)	58 (5.4)	**0.022**
CVE	7 (6.1)	101 (7.5)	0.583	36 (9.4)	72 (6.6)	0.074
Parkinson's disease	2 (1.7)	32 (2.4)	0.493	9 (2.4)	25 (2.3)	0.958
Alzheimer's disease	4 (3.5)	63 (4.7)	0.383	30 (7.9)	37 (3.4)	**<0.001**
COPD	15 (13.0)	139 (10.3)	0.218	46 (12.0)	108 (10.0)	0.257
Malignancy	50 (43.5)	178 (13.2)	**<0.001**	124 (32.5)	104 (9.6)	**<0.001**
Decompensated CHF	4 (3.5)	16 (1.2)	0.065	9 (2.4)	11 (1.0)	0.051
Hyperthyroidism	4 (3.5)	36 (2.7)	0.385	6 (1.6)	34 (3.1)	0.106
Hypothyroidism	10 (8.7)	104 (7.7)	0.703	24 (6.3)	90 (8.3)	0.203
Osteoporosis	6 (5.2)	62 (4.6)	0.447	19 (5.0)	49 (4.5)	0.720
CCI	6 (4-8)	5 (3-6)	**<0.001**	5 (3.7-7)	4 (3-6)	**<0.001**
Laboratory values						
Hb	10.8 (9.3-12.5)	11.7 (9.8-13.5)	**0.002**	10.5 (9.1-12.3)	12.1 (10.1-13.8)	**<0.001**
WBC count	9.55 (6.87-13.99)	8.23 (6.43-10.66)	**0.001**	8.88 (6.72-12.34)	8.11 (6.83-10.47)	**<0.001**
Neutrophil count	7.24 (4.65-11.51)	5.56 (4.02-7.95)	**<0.001**	6.6 (4.58-9.71)	5.11 (3.83-7.79)	**<0.001**
Lymphocyte count	1.06 (0.72-1.46)	1.42 (9.30-2.04)	**<0.001**	1.11 (0.74-1.54)	1.51 (0.99-2.13)	**<0.001**
NLR	7.7 (4.0-12.9)	3.7 (2.3-6.8)	**<0.001**	5.5 (3.5-10.4)	3.5 (2.1-6.4)	**<0.001**
PLT count	228 (155-290)	240 (183-300)	**0.020**	232 (157-317)	240 (187-298)	0.100
MPV	10.6 (9.9-11.7)	10.3 (9.6-11.0)	**0.001**	10.3 (9.7-11.2)	10.3 (9.7-11.1)	0.674
PLT/MPV	20.2 (13.0-26.8)	23.0 (17.1-30.1)	**0.003**	22.2 (14.8-30.7)	23.1 (17.5-29.7)	0.227
CRP	64 (34-128)	18 (4.9-62)	**<0.001**	48 (22-101)	14 (4-53)	**<0.001**

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Chronic heart failure, CRF: Chronic renal failure, RA: Rheumatoid arthritis, CTD: Connective tissue disease, CVE: Cerebrovascular event, COPD: Chronic obstructive pulmonary disease, CCI: Charlson Comorbidity Index, Hb: Hemoglobin, WBC: White blood cell, NLR: Neutrophil to lymphocyte ratio, PLT: Platelet, MPV: Mean platelet volume, CRP: C-reactive protein

Table 3. Independent risk factors for 30-day and 12-month mortality according to logistic regression analysis

	30-day mortality	p	12-month mortality	p
	Multivariate OR (95% CI)		Multivariate OR (95% CI)	
Infectious diseases (yes or no)	2.109 (1.241-3.584)	**0.006**	1.978 (1.174-3.332)	**0.010**
Palliative support (yes or no)	5.982 (2.229-16.050)	**<0.001**	6.506 (2.482-17.054)	**<0.001**
DM (yes or no)	0.434 (0.266-0.708)	**0.001**	0.462 (0.288-0.742)	**0.001**
CAD (yes or no)	0.496 (0.268-0.915)	**0.025**		
Malignancy (yes or no)	2.514 (1.451-4.356)	**0.001**	2.654 (1.568-4.493)	**<0.001**
CCI (1-unit increase)	1.219 (1.117-1.353)	**<0.001**	1.200 (1.093-1.317)	**<0.001**
MPV (1-unit increase)	1.525 (1.294-1.798)	**<0.001**		
CRP (1-unit increase)	1.006 (1.003-1.009)	**<0.001**	1.006 (1.004-1.009)	**<0.001**

OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus, CAD: Coronary artery disease, CCI: Charlson Comorbidity Index, MPV: Mean platelet volume, CRP: C-reactive protein

In our study, we observed that high NLR was associated with higher mortality in hospitalized older adults at 1 and 12 months. Although the exact relationship between NLR and mortality among hospitalized patients is not clear, possible mechanisms include systemic inflammation caused by acute disease. NLR may also increase mortality due to underlying sepsis or bacteremia. Another possible cause is chronic inflammation, which naturally increases with age[16]. However, more studies are needed to elucidate the relationship between NLR and mortality in hospitalized older patients.

PLTs are involved in a wide range of pathophysiological processes, such as hemostasis, thrombosis, coagulation, vascular constriction and repair, atherosclerosis, host defense, and tumor growth and metastasis[17]. PLT size is expressed as MPV, a parameter that serves as an indicator of PLT function. Higher PLT volume is associated with PLT reactivation, reduced bleeding time, increased PLT aggregation, and higher risk of thrombosis[18]. The PLTs found in circulating blood differ in size. Large PLTs are more active and release more GPIIb-IIIa and P-selectin. In addition, the proteins on the surface of these PLTs have higher activation, aggregation, and endothelial binding capacities[19,20]. Epidemiological studies have shown that MPV is associated with obesity[21], hyperlipidemia[22], diabetes[23], hypertension[24], and arterial thickening[25]. In metabolic syndrome, adipose tissue releases cytokines such as tumor necrosis factor-alpha and interleukin-6, and adinopectins such as adiponectin and leptin. These proinflammatory cytokines cause a chronic increase in PLT number[26-28]. Low MPV can also increase the number of PLTs and eventually lead to metabolic syndrome[29]. High MPV levels have been associated with myocardial infarction[30], stroke[31], and peripheral vascular disease[32,33]. A study of 25,923 patients in Norway showed that high MPV increased the risk of venous thrombosis in the absence of surgery, trauma, immobilization, and malignancy. In addition, high MPV has been shown to increase the risk of ischemic stroke and subsequent death[34]. In a Copenhagen study involving 39,531 people, the prevalence of myocardial infarction was found to be higher in those with high MPV[35-37]. In our study, we determined that MPV was an independent risk factor for 30-day mortality in hospitalized older patients, with a one-unit increase in MPV associated with a 50% higher risk of death. In addition to thrombopoietin, inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor-alpha are among the factors that stimulate thrombopoiesis[38]. Therefore, MPV is thought to increase in severe inflammation. Although the relationship between MPV and increased mortality is also unclear, several mechanisms have been proposed. The first is that large PLTs contain larger prothrombotic material such as thromboxane A2 and alpha granules, thus leading to PLT activation, adhesion, and vascular proliferation[39,40]. At the same time, large PLTs have larger glycoprotein Ib and IIb/IIIa adhesion receptors, which may require more cleavage to achieve antiplatelet treatment response[41].

Studies demonstrating the effect of comorbidity on mortality are contradictory. Among epidemiological studies conducted in different European countries, some have shown that mortality increases with comorbidity[42,43]. However, other studies have indicated that comorbidity has no effect on mortality[44-46]. Frenkel et al.[47] reported that CCI was a good predictor of post-discharge mortality in older patients hospitalized for acute causes. Studies on patients followed up after hip surgery in China also showed that CCI was an indicator of long-term mortality[48]. A one-unit increase in CCI corresponded to 20% higher odds of both 30-day and 12-month mortality.

In our study, it was shown that the presence of anemia increased mortality. It has been shown in the literature that anemia increases mortality[49]. In addition, we determined that a one-unit increase in CRP was associated with slightly mortality risk at 30 days and 1 year. Similar results have been observed in studies with older people in the general population[50,51] and hospitalized older patients[46].

Long-term hyperglycemia is known to increase reactive oxygen release, lead to cellular damage and electrolyte imbalance, and impair immune functions[52]. However, there are publications in the literature showing that the presence of diabetes does not increase mortality[53,54]. In contrast, other reports indicate that mortality is higher in diabetic patients with pneumonia[55]. In our study, the presence of diabetes was actually associated with lower mortality. However, the diabetic patients in our study were not asked about the treatment they received and whether their diabetes was effectively managed.

Study Limitations

The strength of our study is that it was conducted with a very large patient cohort from two major university hospitals in two major cities. However, one of the limitations of our study is that biomarkers that might affect mortality, such as albumin, were not investigated. A second limitation is that the study was retrospective. In addition, we evaluated the association between mortality and NLR, but this ratio was affected by systemic diseases and the use of drugs such as steroids. We did not determine parameters such as steroid use. Finally, we did not evaluate the severity of disease in the patients.

CONCLUSION

In conclusion, the results of this study showed that CCI, CRP, and NLR were associated with higher mortality both at 30 days and 12 months. A one-unit increase in MPV was associated with 52.5% higher odds of 30-day mortality. Our study provides preliminary results that may guide further investigations on this subject.

Ethics

Ethics Committee Approval: The study was conducted after obtaining ethical approval from İzmir Tınaztepe University Ethics Committee (decision no: 13, dated: 20/04/2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.K., Design: S.Ş., F.Ş.A., Data Collection or Processing: P.T.T., Z.K.Ö., F.Ş.A., Analysis or Interpretation: P.T.T., S.Ş., Ö.K., M.Ü., Z.K.Ö., F.Ş.A., Literature Search: P.T.T., Ö.K., Writing: P.T.T., S.Ş., Ö.K., M.Ü., Z.K.Ö., F.Ş.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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