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C-reactive Protein Level, Admission to Intensive Care Unit, and High American Society of Anesthesiologists Score Affect Early and Late Postoperative Mortality in Geriatric Patients with Hip Fracture

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Purpose: The main purpose of this study is to evaluate prognostic factors that affected the patients' early (<30 days) and late (six months, one year, and overall) postoperative mortality following hip fracture surgery.
Materials and Methods: This retrospective study included 515 patients older than 75 years old with surgically treated osteoporotic hip fracture. The demographic data, American Society of Anesthesiologists (ASA) classification, type of anesthesia, duration of hospital stay, and history of intensive care unit (ICU) stay were collected. An analysis of laboratory values was also performed to determine their relationship with mortality. The primary outcome was survival, determined as the time from the surgery to death or the end of the study. The patients were divided into four groups according to survival time: at the first month, six months, first year, and overall survival. An analysis of demographic and laboratory values was performed to determine their validity as prognostic factors for each group.
Results: Postoperative C-reactive protein (CRP) level showed an independent association with a poor survival at the first month. ASA classification, admission to the ICU, and preoperative CRP levels showed an independent association with a poor survival for the first six months. Preoperative CRP level showed an independent association with a poor survival for the first year. ASA classification, admission to the ICU, and the preoperative CRP levels showed an independent association with a poor overall survival.
Conclusion: CRP level, a high ASA classification, and postoperative ICU admission were related to poorer overall survival rate following hip fracture surgery in the elderly.

Key Words: Hip fractures, Mortality, Elderly, Geriatric fracture, Cause of death

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INTRODUCTION

Hip fractures, which are one of the most common osteoporotic fractures in elderly patients, are an important health problem in society with the increase in life expectancy over time[1,2]. Mortality rates reaching up to 36% in the first year following a hip fracture have been reported[3,4]. In the treatment of hip fractures the main purpose is to provide rapid mobilization of patients and prevent possible complications.

Many studies evaluating the prognostic factors affecting mortality after a hip fracture have reported different results. Some of these include advanced age, male sex, delayed surgery, dementia, anemia, malnutrition, type of surgery, and comorbidities[4-7]. While some of these parameters are demographic factors, some are values obtained from laboratory tests.

The main purpose of this study is to evaluate prognostic factors related to mortality after a hip fracture, including timing of the surgery, sex, preoperative comorbidities, type of anesthesia used, and type of surgery that affected the patients' early (<30 days) and late (six months, one year, and overall) postoperative mortality.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Haseki Education and Research Hospital (No. 2020-221) and it was conducted in accordance with the standards of the Declaration of Helsinki. The written informed consent was obtained from all patients. A retrospective investigation of patients with hip fractures, including femoral neck and intertrochanteric femur fractures, who were admitted to Haseki Education and Research Hospital between January 2012 and October 2019 was conducted. Assessment of patient survivorship was based on the National Population Registry, which was checked for all patients in October 2020.

The inclusion criteria were as follows: patients older than 75 years, low-energy (osteoporotic) hip fractures, acute fractures (within 14 days), complete blood counts-laboratory values on admission and available demographics and medical records.

Exclusion criteria included history of malignancy or pathological femoral fractures, subtrochanteric fractures, neglected fractures (more than four weeks), abnormal laboratory results (due to infection or malignancy), and incomplete information on the registries. An evaluation of patients with abnormal laboratory values was performed by internal medicine and infectious diseases for possible diagnoses that could affect laboratory results, such as any infection (pneumonia, urinary tract infection, etc.). Patients with any additional diagnosis that could affect laboratory results were excluded from the study.

All patients were admitted and treated at a single level one trauma center. Treatment with an intramedullary nail or dynamic hip screw was administered according to the fracture pattern or the surgeon's preference in patients diagnosed with an intertrochanteric fracture, while treatment with hemiarthroplasty with or without cement was administered in patients with a femoral neck fracture. Surgery was performed as soon as possible on all patients under regional or general anesthesia upon completion of the preoperative preparations.

Information on demographics (age, sex, side of the fracture, and type of fracture), type of implant, operation time, American Society of Anesthesiologists (ASA) classification, time of surgery, type of anesthesia, duration of hospital stay, and history of intensive care unit (ICU) stay was collected. Preoperative ASA classification was determined by the anesthesiologists' preoperative evaluation. The patients were classified as low (ASA 1-2) or high (ASA 3-4). The ASA score and admission to ICU were used as an indicator of general health status and comorbidities in our study.

Laboratory values were also collected for analysis of their relationship with mortality. The erythrocyte sedimentation rate, red cell distribution width, mean corpuscular volume, hemoglobin (Hb) levels, albumin levels, white blood cell count, neutrophil count, lymphocyte count, platelet count, C-reactive protein (CRP) levels, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) were analyzed as prognostic factors. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, while the PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. Calculation of these values was performed both preoperatively and postoperatively. Laboratory values for the first admission to the hospital were used for preoperative evaluation in order to assess the long term health status of the patients. Postoperative day 2 values were used for postoperative evaluation.

The primary outcome was survival, determined as the time from the surgery to death or the end of the study. The patients were divided into four groups according to survival time: at the first month, six months, first year, and overall

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survival. An analysis of demographic and laboratory values was performed to determine their validity as prognostic factors for each group.

Statistical analysis was performed using the IBM SPSS Statistics (ver. 22.0; IBM Co., Armonk, NY, USA). Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used for evaluation of the study data. Kaplan–Meier survival analysis was used for evaluation of patient survival and the log-rank test was used for comparison of the survival curves. In addition, univariable Cox regression analysis was performed to determine potential prognostic factors. Elements with *P*-values (two-sided) $\leq$0.05 were included in the multivariable Cox proportional hazard model for identification of independent variables in a stepwise fashion. Variables with $P \leq 0.05$ or less in multivariable analysis were retained as independent risk factors. A $P<0.05$ was accepted as statistically significant. The receiver operating characteristic (ROC) curve was used to estimate the cutoff value of the delay to the day of surgery.

RESULTS

A total of 515 patients with an average age of 84.2±7.0 years (range, 75-103 years) were included. The study included 342 females (66.4%) and 173 males (33.6%). There were 318 patients (61.7%) diagnosed with intertrochanteric femoral fractures and 197 patients (38.3%) with femoral neck fractures. The right and left femur was involved in 263 patients (51.1%) and 252 patients (48.9%), respectively. Hemiarthroplasty was administered for treatment of all patients with femoral neck fractures. Of 318 patients with intertrochanteric femur fractures; hemiarthroplasty was administered for treatment of 36 patients, intramedullary nailing was administered for treatment of 195 patients, and a dynamic hip screw was administered for treatment of 87 patients. At the time of this study, 360 patients (69.9%) had died. Patient mortality rates at the first month, sixth month, and one year after surgery were 10.5% (n=54), 27.4% (n=141), and 35.7% (n=184) in all patients respectively. The overall survival was 10% according to the Kaplan–Meier survival analysis (Fig. 1). The mean survival was 19.5±21.1 months (range, 1 day to 96 months). Baseline demographic data are shown in Table 1.

1. Prognostic Factor Analyses in Patients at the First Month

Results of univariable analysis showed an association of the ASA classification (P=0.025), admission to the ICU

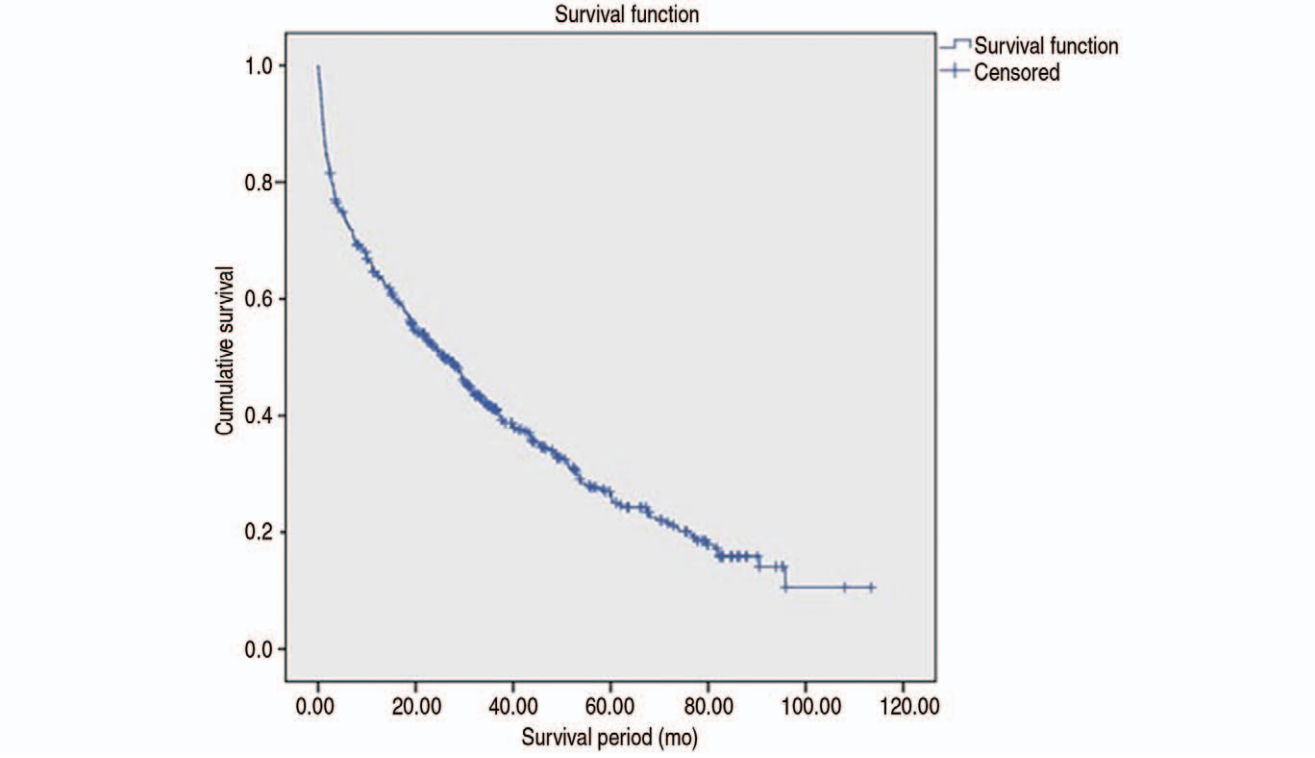

Fig. 1. Kaplan–Meier curve showing overall survival of the patients.

Table 1. Demographic Data of the Patients with Hip Fracture Aged More than 75 Years

Variable	Value	
Age (yr)	84.2±7.0 (75-103)	
Sex, female/male	342/173	
Side, right/left	263/252	
Fracture type, Int/FN	318/197	
Treatment method, IMN/HA/DHS	195/233/87	
Mortality		
First month	54 (10.5)	
Six months	141 (27.4)	
First year	184 (35.7)	
Overall	360 (69.9)	
Survive (mo)	19.5±21.1 (0.1-96)	
Preoperative hospital stay (day)	5.8±3.5 (1-20)	
Hospital stay (day)	12.3±8.4 (2-108)	
Operation time (min)	109.3±40.1 (28-420)	
History of intensive care	176 (34.2)	
Type of anesthesia, G/R	78/437	
ASA score		
1	98 (19.0)	
2	191 (37.1)	
3	120 (23.3)	
4	106 (20.6)	
	Preoperative	Postoperative
C-reactive protein (mg/dL)	73.1±53.2 (0-302)	132±79 (1-323)
Erythrocyte sedimentation rate (0-25)	50.6±33.1 (0-124)	19.3±34.4 (0-93)
Red cell distribution width	15.3±4.5 (11-92)	15.5±4.6 (9-96)
Mean corpuscular volume	87.1±9.4 (14-124)	87.5±7.2 (17-110)
Hemoglobin (g/dL)	10.6±1.9 (6-16)	9.6±1.6 (6-13)
Albumin (g/dL)	3.6±1.1 (2-6)	2.9±0.6 (1.8-4.9)
White blood cell count (10^3/L)	10.5±3.6 (3.2-29.8)	12.1±4.3 (3.4-34.5)
Neutrophil count (10^3/L)	7.4±3.4 (1-24)	9.8±4.1 (0.6-29)
Lymphocyte count (10^3/L)	1.8±2.0 (0.2-18)	1.2±1.1 (0.1-13)
Platelet (10^3/L)	247±104 (52-843)	284±114 (25-752)
Neutrophil/lymphocyte	7.1±6.5 (0.1-62)	10.1±7.7 (0.2-75)
Platelet/lymphocyte ratio	216±122 (0.2-1,500)	290±233 (10-3,200)

Values are presented as mean±standard deviation (range), number only, or number (%).
Int: intertrochanteric fracture, FN: femoral neck, IMN: intramedullary nailing, HA: hemiarthroplasty, DHS: dynamic hip screw, G: general, R: regional, ASA: American Society of Anesthesiologists.

(*P*=0.003), postoperative CRP level (*P*=0.012), and preoperative NLR (*P*=0.007) with a worse survival at the first month. Results of multivariable analysis showed an independent association of the postoperative CRP level (hazard ratio [HR], 1.005; 95% confidence interval [CI], 1.001-1.010; *P*=0.014) with a poor survival at the first month (Table 2). Results of ROC analysis showed that the area under the curve for the model including the postoperative CRP value was 0.683 (95% CI, 586-780), and the sensitivity and specificity of the age level for identifying high-risk patients for mortality were 65.2% and 63.5%, respectively, with an optimum diagnostic cutoff value of 148 mg/dL (Fig. 2).

2. Prognostic Factor Analyses in Patients at the First Six Months

Results of univariable analysis showed an association of the ASA classification (*P*=0.021), admission to the ICU (*P*=0.016), preoperative CRP levels (*P*<0.001), and preoperative NLR (*P*=0.017) with a worse survival at the first six months. Results of multivariable analysis showed an association of the ASA classification (HR, 1.515; 95% CI, 1.011-2.270; *P*=0.044), admission to the ICU (HR, 1.923; 95% CI, 1.137-3.252; *P*=0.015), and preoperative CRP levels (HR, 1.005; 95% CI, 1.002-1.007; *P*=0.001)

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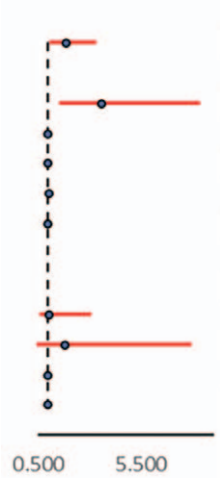
Table 2. Univariable and Multivariable Cox Regression Analysis for Patients Who Died in the First Month after Surgery

Factors		HR (95% CI)	*P*-value
Univariable Cox regression analysis			
ASA score	1-2	Reference	Reference
	3-4	1.859 (1.081-3.230)	0.025*
Intensive care	No	Reference	Reference
	Yes	3.571 (1.528-8.345)	0.003*
C-reactive protein	Preop	0.999 (0.999-1.001)	0.121
	Postop	1.005 (1.001-1.009)	0.012*
Neutrophil/lymphocyte ratio	Preop	1.032 (1.009-1.056)	0.007*
	Postop	0.998 (0.962-1.035)	0.896
Multivariable Cox regression analysis			
ASA score	Low	Reference	Reference
	High	1.035 (0.592-3.099)	0.472
Intensive care		1.805 (0.411-7.922)	0.434
C-reactive protein	Postop	1.005 (1.001-1.010)	0.014†
Neutrophil/lymphocyte ratio	Preop	0.950 (0.861-1.048)	0.304



HR: hazard ratio, CI: confidence interval, ASA: American Society of Anesthesiologists, Preop: preoperative, Postop: postoperative.
* These *P* values were less than 0.05 (univariable analysis). † These *P* values were less than 0.05 (multivariable analysis).

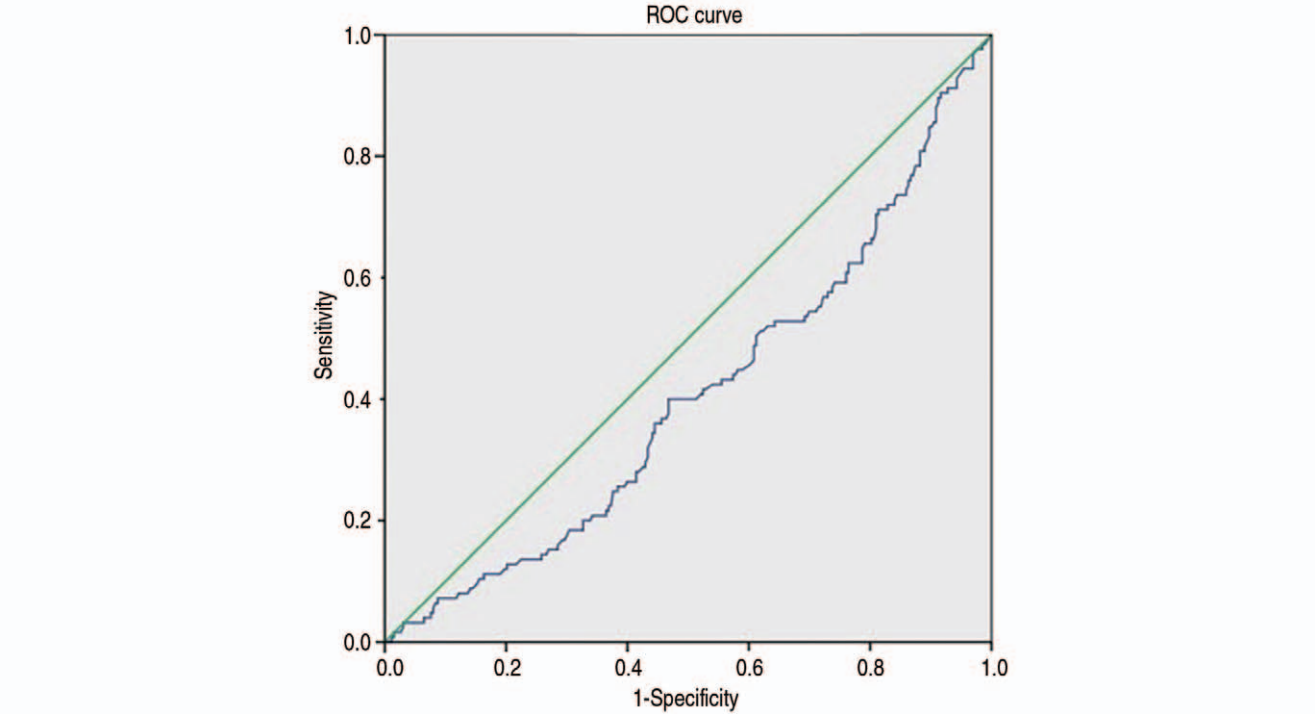


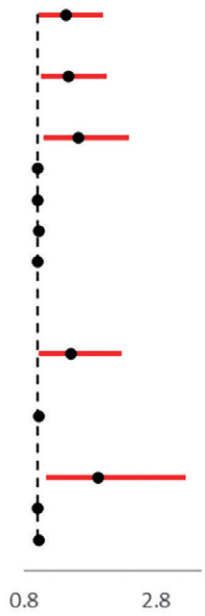
Fig. 2. The receiver operating characteristic (ROC) curve of C-reactive protein level for mortality for the first month following hip fracture surgery.

with a poor survival at the first six months (Table 3).

Results of ROC analysis showed that the area under the curve for the model including the preoperative CRP value was 0.632 (95% CI, 567-697), and the sensitivity and specificity of the age level for identifying high-risk patients for mortality were 59.8% and 62.6%, respectively, with an optimum diagnostic cutoff value of 75.2 mg/dL (Fig. 3).

Table 3. Univariable and Multivariable Cox Regression Analysis for Patients Who Died in the First Six Months after Surgery

Factors		HR (95% CI)	*P*-value
Univariable Cox regression analysis			
Sex	Female	Reference	Reference
	Male	1.426 (1.018-1.996)	0.039*
ASA score	1-2	Reference	Reference
	3-4	1.468 (1.054-2.045)	0.021*
Intensive care	No	Reference	Reference
	Yes	1.615 (1.093-2.387)	0.016*
C-reactive protein	Preop	1.005 (1.002-1.007)	<0.001*
	Postop	1.004 (1.001-1.007)	0.07
Neutrophil/lymphocyte ratio	Preop	1.024 (1.004-1.044)	0.017*
	Postop	1.010 (0.990-1.030)	0.330
Multivariable Cox regression analysis			
ASA score	Low	Reference	Reference
	High	1.515 (1.011-2.270)	0.044†
Sex	Female	Reference	Reference
	Male	1.016 (0.995-1.037)	0.161
Intensive care	No	Reference	Reference
	Yes	1.923 (1.137-3.252)	0.015†
C-reactive protein	Preop	1.005 (1.002-1.007)	0.001†
Neutrophil/lymphocyte ratio	Preop	1.016 (0.995-1.037)	0.147



HR: hazard ratio, CI: confidence interval, ASA: American Society of Anesthesiologists, Preop: preoperative, Postop: postoperative.
* These *P* values were less than 0.05 (univariable analysis). † These *P* values were less than 0.05 (multivariable analysis).

3. Prognostic Factor Analyses in Patients at the First Year

Results of univariable analysis and multivariable analysis showed an independent association of the preoperative CRP level (HR, 1.004; 95% CI, 1.002-1.006; *P*=0.001) with a poor survival at the first year (Table 4).

Results of ROC analysis showed that the area under the curve for the model including the preoperative CRP value was 0.613 (95% CI, 555-672), and the sensitivity and specificity of the age level for identifying high-risk patients for mortality were 55.4% and 63.5%, respectively, with an optimum diagnostic cutoff value of 75.2 mg/dL (Fig. 4).

4. Prognostic Factor Analyses for All Patients

Results of univariable analysis showed an association of the ASA classification (*P*=0.002), admission to the ICU (*P*=0.002), sex (*P*=0.005), and preoperative CRP levels (*P*<0.001) with a worse overall survival. Results of multivariable analysis showed an independent association of the ASA classification (HR, 1.299; 95% CI, 1.011-1.668; *P*=0.041), admission to the ICU (HR, 1.595; 95% CI, 1.202-2.118; *P*=0.001), and the preoperative CRP levels (HR, 1.004; 95% CI, 1.002-1.006; *P*<0.001) with a poor overall survival (Table 5).

Results of ROC analysis showed that the area under the curve for the model including the preoperative CRP value was 0.596 (95% CI, 535-656), and the sensitivity and specificity of the age level for identifying high-risk patients for mortality were 57% and 56.8%, respectively, with an optimum diagnostic cutoff value of 54.75 mg/dL (Fig. 5). The patients were also classified into two groups according to the optimum diagnostic cutoff value of CRP as lower than 54.75 mg/dL and higher than 54.75 mg/dL as we found in the results of ROC analysis. We then compared the overall survival of these two groups of patients. It was found that patients with preoperative CRP value above 54.75 mg/dL had significantly poorer survival than the group with a preoperative CRP value below 54.75 mg/dL (*P*=0.002) (Fig. 6).

DISCUSSION

This study reports that the CRP level, postoperative admission to the ICU, and an ASA classification ≥3 showed an association with poor survival in patients with hip fractures

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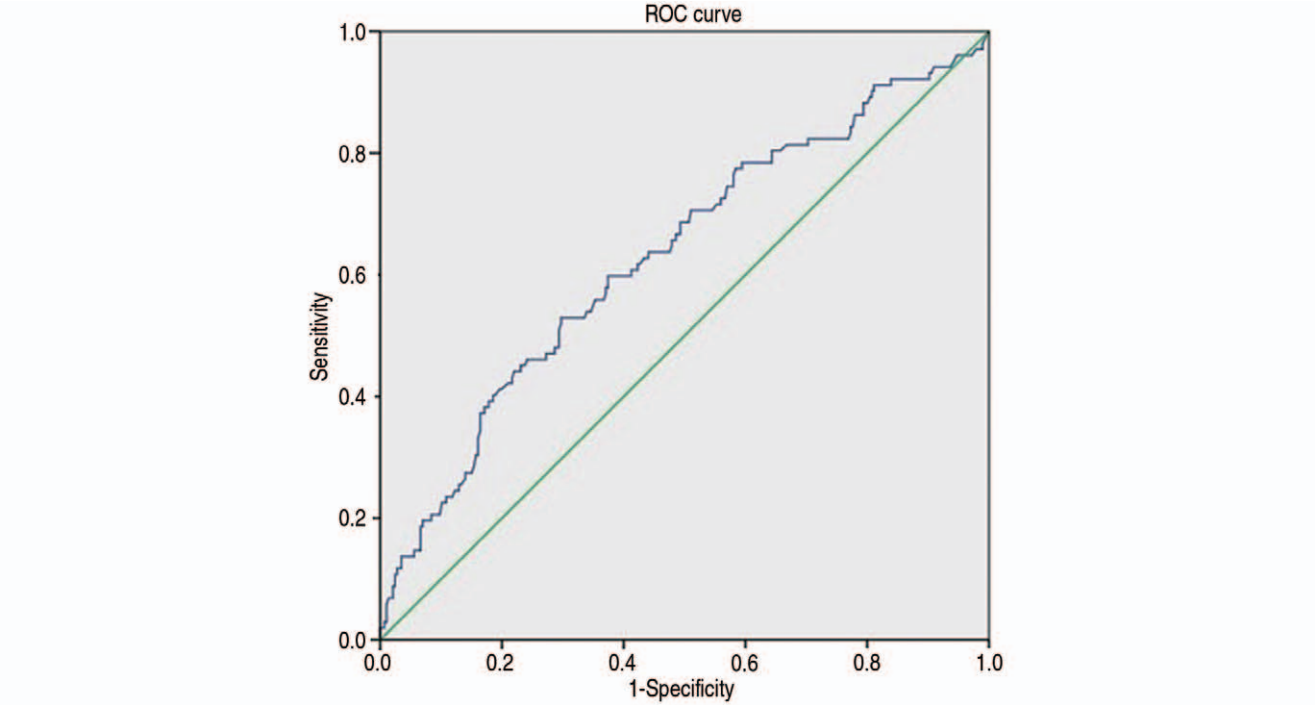
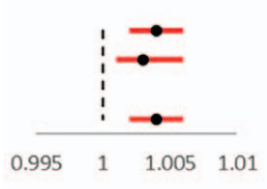


Fig. 3. The receiver operating characteristic (ROC) curve of C-reactive protein level for mortality for six months following hip fracture surgery.

Table 4. Univariable and Multivariable Cox Regression Analysis for Patients Who Died in the First Year after Surgery

Factors		HR (95% CI)	*P*-value
Univariable Cox regression analysis			
C-reactive protein	Preop	1.004 (1.002-1.006)	0.001*
	Postop	1.003 (1.001-1.006)	0.061
Multivariable Cox regression analysis			
C-reactive protein	Preop	1.004 (1.002-1.006)	0.001†



HR: hazard ratio, CI: confidence interval, Preop: preoperative, Postop: postoperative.
* These *P* values were less than 0.05 (univariable analysis). † These *P* values were less than 0.05 (multivariable analysis)

older than 75 years old.

Most of the previous studies reported an overall one-year mortality rate between 14% and 37% in elderly patients with hip fractures[8-11]. The reported mortality rates of elderly patients with hip fractures were 19.5% in the study by Zaki et al.[12] and 25.0% in the study by Prodovic et al.[13]. The mortality rates of the patients in this study at six months and one year following surgery were 27.4% and 35.7%, respectively. While the overall sixth month mortality rate in our study was relatively higher than that reported in the literature, the one-year mortality rate was similar to that reported in the literature. The wide distribution of mortality rates reported in the literature may be related to the heterogeneity of patient populations (age, comorbidities, level of development of the country) in these studies and the differences in postoperative care and follow-up.

Postoperative admission to the ICU is strongly related to the patients' comorbidities and health status. An increase in the number of comorbid diseases and an insufficiency in the physiological compensation mechanisms may increase the need for postoperative admission to the ICU. Patients can also be admitted to the ICU for treatment of serious postoperative complications or unstable vital signs. Sofu et al.[9] and Giummarra et al.[14] reported a higher mortality rate for patients admitted to the ICU postoperatively. The results of the current study showed significantly higher mortality for

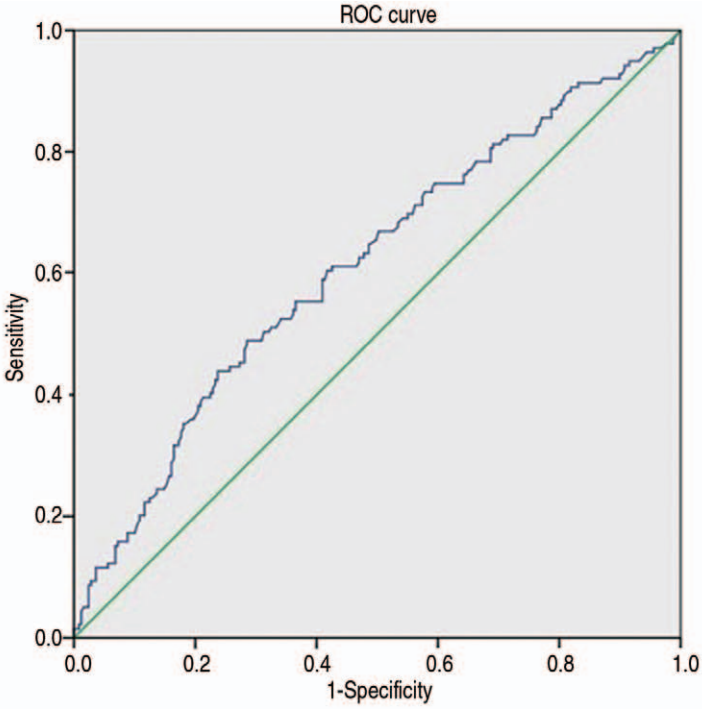


Fig. 4. The receiver operating characteristic (ROC) curve of C-reactive protein level for mortality for the first year following hip fracture surgery.

Table 5. Univariable and Multivariable Cox Regression Analysis for Overall Mortality

Factors		HR (95% CI)	*P*-value
Univariate Cox regression analysis			
Sex	Female	Reference	Reference
	Male	1.369 (1.097-1.708)	0.005*
ASA score	1-2	Reference	Reference
	3-4	1.403 (1.136-1.734)	0.002*
Intensive care	No	Reference	Reference
	Yes	1.420 (1.132-1.782)	0.002*
C-reactive protein	Preop	1.004 (1.002-1.006)	<0.001*
	Postop	1.002 (1.000-1.004)	0.128
Multivariate Cox regression analysis			
ASA score	Low	Reference	Reference
	High	1.299 (1.011-1.668)	0.041†
Sex	Female	Reference	Reference
	Male	1.261 (0.974-1.631)	0.078
Intensive care	No	Reference	Reference
	Yes	1.595 (1.202-2.118)	0.001†
C-reactive protein	Preop	1.004 (1.002-1.006)	<0.001†

HR: hazard ratio, CI: confidence interval, ASA: American Society of Anesthesiologists, Preop: preoperative, Postop: postoperative.
* These *P* values were less than 0.05 (univariable analysis). † These *P* values were less than 0.05 (multivariable analysis).

patients who stayed in the ICU postoperatively. Not surprisingly, high mortality rates were observed for patients with poorer general health status and more comorbidities.

The ASA score has been confirmed as a total marker of

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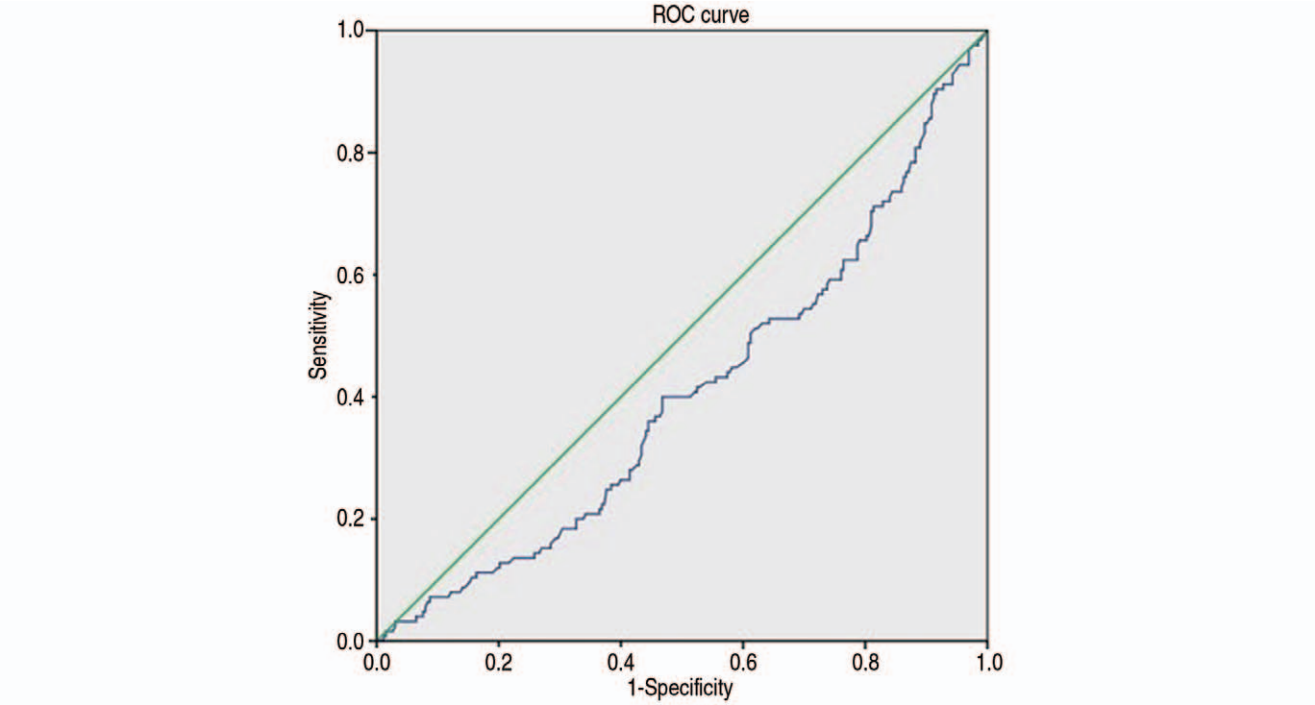

Fig. 5. The receiver operating characteristic (ROC) curve of C-reactive protein level for overall mortality following hip fracture surgery.

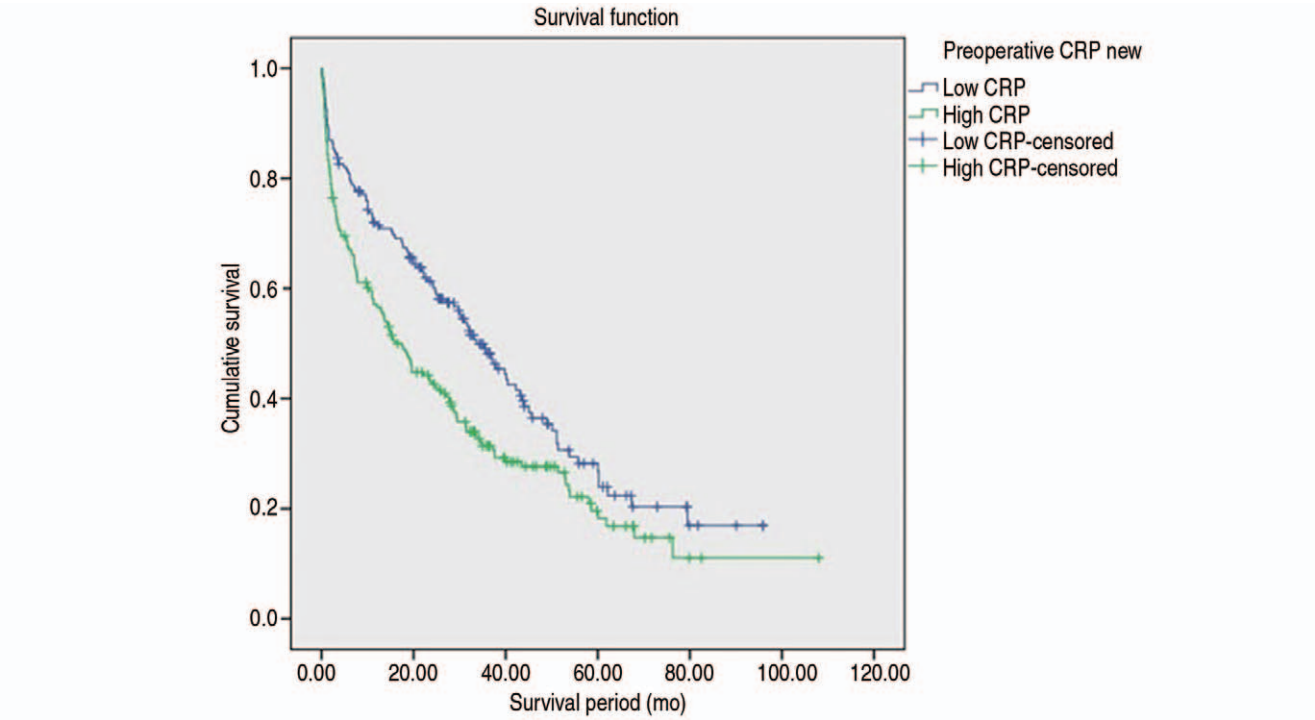

Fig. 6. Comparison of two survival curves of the patients following grouping the patients according to the preoperative C-reactive protein (CRP) cut off levels of 54.75 mg/dL.

comorbidities (medical conditions) and has been reported to show correlation with mortality rates for hip fracture[15]. In their prospective studies Paksima et al.[16] and Söderqvist et al.[17] reported a statistically increased risk of mortality

for geriatric patients with an ASA class ≥3 following a hip fracture. Similarly, many retrospective studies reported significantly higher mortality rates for elderly patients who were preoperatively classified as either ASA class 3 or 4 following a hip fracture[9,18,19]. An ASA status that was either 3 or 4 showed an association with a significantly higher risk of mortality in patients aged >75 years old following a hip fracture surgery, and this finding was consistent with those reported in the literature.

CRP, an acute phase serum biomarker, is elevated in the inflammatory response such as in infection and trauma[20]. CRP is also a prognostic factor in older patients for different pathologies such as atherosclerosis, vascular diseases, and cerebral hemorrhage[20,21]. In addition, it is studied both for changes after hip fracture and as a prognostic factor for survival following hip fracture surgery. Kim et al.[22] reported that the preoperative CRP level was a predominant risk factor for one-year mortality after hip fracture surgery in the elderly. Their study included a larger number of patients compared with our study; however, the minimum age for inclusion in their study was 65 years while it was 75 years in our study. On the contrary, Beloosesky et al.[23] reported no significant relationship between CRP levels and six-month mortality following hip fracture surgery in elderly patients. In the current study, we found that preoperative CRP levels showed an independent association with a poor survival at the sixth month and one year following hip fracture surgery. However, the postoperative CRP level was also found to show an association with a poorer survival rate at the first month following hip fracture surgery, in contrast to the preoperative CRP level. CRP level is elevated with inflammation and can indicate the severity of the trauma[22,24]. As a result of the current study, the severity of either the injury preoperatively or the advanced postoperative inflammatory response may be associated with higher mortality rate.

Our study has several limitations. First, this is a retrospective study. Multicentric, prospective studies including larger numbers of patients are needed to confirm our results. Second, the decision for admission to the ICU during the postoperative period was not a standardized choice. Multiple variables dictate this decision, including the behavior of the anesthesiologist. Third, the CRP level is normally elevated in infections and systemic inflammation in addition to trauma. Although patients with systemic infections at the time of hospitalization were excluded from the study, it is not possible to be certain that every patient in the study had no infection.

CONCLUSION

In conclusion, the CRP level showed an association with an increased first month, sixth month, and one year mortality after hip fracture surgery in elderly patients. In addition to the CRP level, a high ASA classification and postoperative ICU admission showed an association with a poorer overall survival rate following hip fracture surgery in the elderly.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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