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C-reactive protein is an independent predictor for 1-year mortality in elderly patients undergoing hip fracture surgery

A retrospective analysis

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Abstract

Numerous factors are associated with mortality after hip fracture surgery in elderly patients. The aim of this study was to investigate whether preoperative C-reactive protein (CRP) was an independent risk factor for 1-year mortality after hip fracture surgery in the elderly. The electronic medical records of 772 elderly patients (age ≥ 65 years) undergoing hip fracture surgery from May 2003 to November 2011 were reviewed retrospectively. The patients comprised a high CRP group (>10.0 mg/dL) and low CRP group (≤10.0 mg/dL), based upon preoperative CRP levels. The overall 1-year mortality was 14.1%; the value was significantly higher in the high CRP group than in the low CRP group (31.8% vs 12.5%; $P < 0.001$). On binary logistic regression, body mass index (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.88–0.99; $P = 0.025$), history of malignancy (OR, 2.59; 95% CI, 1.47–4.57; $P = 0.001$), American Society of Anesthesiologists physical status (ASA PS) class 3–4 (OR, 1.96; 95% CI, 1.25–3.07; $P = 0.003$), preoperative albumin (OR, 0.39; 95% CI, 0.25–0.61; $P < 0.001$), preoperative CRP > 10.0 mg/dL (OR, 2.04; 95% CI, 1.09–3.80; $P = 0.025$), postoperative intensive care unit (ICU) admission (OR, 2.29; 95% CI, 1.15–4.59; $P = 0.019$), and creatinine on the second postoperative day (OR, 1.20; 95% CI, 1.00–1.45; $P = 0.048$) were independent predictors of 1-year mortality after hip surgery. Male gender and low preoperative hemoglobin were associated with in-hospital mortality, whereas delayed surgery and femoral neck fracture were related to the 6-month mortality. Low preoperative albumin and low body mass index predicted the 6-month and 1-year mortality. An increased preoperative CRP level, particularly >10.0 mg/dL, was associated with the 1-year mortality after hip fracture surgery in the elderly. In addition, a history of malignancy, high ASA PS score, and postoperative ICU admission were related to mortality after hip fracture.

Abbreviations: ASA PS = American Society of Anesthesiologists' physical status, BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, ICU = intensive care unit, OR = odds ratio, POD = postoperative day.

Keywords: C-reactive protein, hip fracture surgery, 1-year mortality

1. Introduction

Hip fractures remain one of the most common causes of morbidity and mortality among the elderly. The recently reported 1-year mortality after hip fracture surgery ranges from 19% to 33%.[1–3] A variety of factors are associated with mortality after hip surgery. These include old age, male gender, high American Society of Anesthesiologists physical status (ASA PS) score, poor preoperative walking capacity, poor activities of daily living, poor mental state, low body mass index (BMI), anemia, malnutrition, high serum creatinine level, pre-existing medical conditions, postoperative ambulation level, surgery type, and delayed surgery.[4–10]

C-reactive protein (CRP) is a serum biomarker of acute phase reaction and its elevation is associated with bacterial infection, inflammation, and trauma.[11,12] Although CRP is nonspecific systemic marker of inflammation, elevated serum CRP has been known to be independent predictor for high mortality and poor clinical outcome in elderly patients with vascular diseases including coronary heart disease, stroke, aneurysmal subarachnoid hemorrhage, and atherosclerosis.[13–16] However, it is unclear whether preoperative CRP level can play a role as a predictor of postoperative mortality in elderly patients undergoing hip fracture surgery.

The aim of this study was to investigate whether preoperative CRP was an independent risk factor for 1-year mortality after hip

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fracture surgery in the elderly. In addition, we sought to identify other perioperative risk factors associated with 1-year mortality after the surgery.

2. Materials and methods

2.1. Ethics statement

After approval by the Institutional Review Board, we retrospectively analyzed the data on adults ≥65 years of age who underwent hip fracture surgery following trauma at Seoul National University Bundang Hospital between May 2003 and November 2011.

2.2. Exclusion criteria

Patients with pathological fractures were excluded. Patients with overt or suspected bacterial infection from the time of hospital admission until 2 days after surgery were excluded because co-existing infection significantly affects the serum CRP level. For patients undergoing bilateral hip surgery during the study period, only data associated with the first hip surgery were included in the analysis.

2.3. Data collection

The electronic medical records of the patients were reviewed, including (1) preoperative (demographic data, co-existing disease, ASA PS classification, preoperative walking ability using the Koval classification,[17] and lab findings); (2) intraoperative (time to surgery from hospital admission, surgery length, fracture site, and anesthetic technique); and (3) postoperative (admission to surgical intensive care unit [ICU] and lab findings) factors. Laboratory parameters measured on the second postoperative day included hemoglobin, creatinine, albumin, and CRP. Based on a previous study,[18] patients were divided into the low CRP group (≤10 mg/dL) and the high CRP group (>10.0 mg/dL).

2.4. Outcomes

The primary outcome was the 1-year mortality after hip fracture surgery. Mortality data were obtained from the national population database center, which provides data for research purposes.

2.5. Statistical analyses

For the analyses, SPSS ver. 20 (SPSS, Chicago, IL) was used. The chi-square test or Fisher's exact test where the cell size was small was used to analyze categorical variables. Student's *t*-test was used for continuous variables. Laboratory parameters were compared using repeated measures Analysis of variance (ANOVA), followed by Student's *t* test to compare laboratory data at each time point. To detect a difference in the cumulative survival rate between 2 different preoperative CRP levels, the Kaplan–Meier curves and log-rank test were used. To identify independent factors predicting the 1-year mortality after hip fracture surgery, only variables with *P*-values < 0.15 in the *t*-test or chi-square test were subjected to binary logistic regression with the forward stepwise conditional method. Collinearity (Pearson's correlation coefficient >0.7) between variables was tested before modeling, and if present, only 1 variable was entered into the binary logistic regression test. For example, there was a collinearity between preoperative and postoperative creatinine levels (Pearson's correlation coefficient: 0.878). Therefore, only the postoperative creatinine level was used for the statistical analysis. We considered results to be statistically significant when the *P*-value was < 0.05.

3. Results

There were 905 patients in total. We excluded 135 patients (72 for missing data, 32 with pathological fractures, 16 with operations due to contralateral femur fractures during the study period, and 15 with overt or suspected infections from the time of hospital admission until 2 days after surgery). The final study cohort comprised 772 patients.

Based upon the preoperative CRP level, 706 and 66 patients were divided into the low and high CRP group, respectively (Table 1). The proportions of males, postoperative creatinine,

Table 1

The comparisons of preoperative, intraoperative, and postoperative variables based upon the preoperative C-reactive protein level.

	Preoperative CRP level (mg/dL)		
	≤10.0 (n = 706)	>10.0 (n = 66)	*P*
Preoperative factors			
Age, y	79.3 (7.2)	80.7 (8.0)	0.156
Male gender	167 (23.7%)	25 (37.9%)	0.016
Body mass index, kg/m^2	21.6 (3.7)	21.7 (3.8)	0.773
Koval grade			0.390
1–2	450 (63.7%)	38 (57.6%)	
3–7	256 (36.3%)	28 (42.4%)	
ASA PS class			0.855
1–2	463 (65.6%)	42 (63.6%)	
3–4	243 (34.4%)	24 (36.4%)	
Co-morbidity			
Diabetes	212 (30.0%)	27 (40.9%)	0.091
Hypertension	464 (65.7%)	42 (63.6%)	0.837
Neurologic	236 (33.4%)	25 (37.9%)	0.552
Cardiac	113 (16.0%)	13 (19.7%)	0.547
Pulmonary	37 (5.2%)	4 (6.1%)	0.772
Hepatic	33 (4.7%)	1 (1.5%)	0.350
Renal	50 (7.1%)	9 (13.6%)	0.094
Malignancy	69 (9.8%)	12 (18.2%)	0.055
Laboratory findings			
Hemoglobin, g/dL	11.8 (2.0)	10.7 (1.4)	<0.001
Albumin, g/dL	3.7 (0.5)	3.2 (0.4)	<0.001
Creatinine, mg/dL	1.0 (0.7)	1.5 (1.8)	0.051
C-reactive protein, mg/dL	2.4 (2.5)	14.9 (4.6)	<0.001
Intraoperative factors			
Time to surgery, days	5.1 (5.8)	5.7 (5.2)	0.452
Fracture site			0.010
Neck	337 (47.7%)	20 (30.3%)	
Intertrochanteric	369 (52.3%)	46 (69.7%)	
Operation site			1.000
Right	354 (50.1%)	33 (50.0%)	
Left	352 (49.9%)	33 (50.0%)	
Anesthetic technique			0.165
Regional	616 (87.3%)	62 (93.9%)	
General	90 (12.7%)	4 (6.1%)	
Operation time, min	87.2 (32.6)	83.5 (23.4)	0.233
Postoperative factors			
ICU admission	42 (5.9%)	6 (9.1%)	0.457
Laboratory findings on POD 2			
Hemoglobin, g/dL	10.0 (1.4)	9.9 (1.7)	0.965
Albumin, g/dL	3.0 (0.3)	2.9 (0.3)	0.001
Creatinine, mg/dL	1.0 (0.8)	1.4 (1.6)	0.038
C-reactive protein, mg/dL	13.1 (6.5)	17.9 (6.6)	<0.001
Clinical outcomes			
Postoperative delirium	91 (12.9%)	18 (27.3%)	0.002
Hospital stay, days	26.7 (26.1)	31.6 (30.3)	0.149
One-year mortality	88 (12.5%)	21 (31.8%)	<0.001

Data are expressed as mean (SD) or number (%).

ASA PS = American Society of Anesthesiologists' physical status, CRP = C-reactive protein, ICU = intensive care unit, POD = postoperative day.

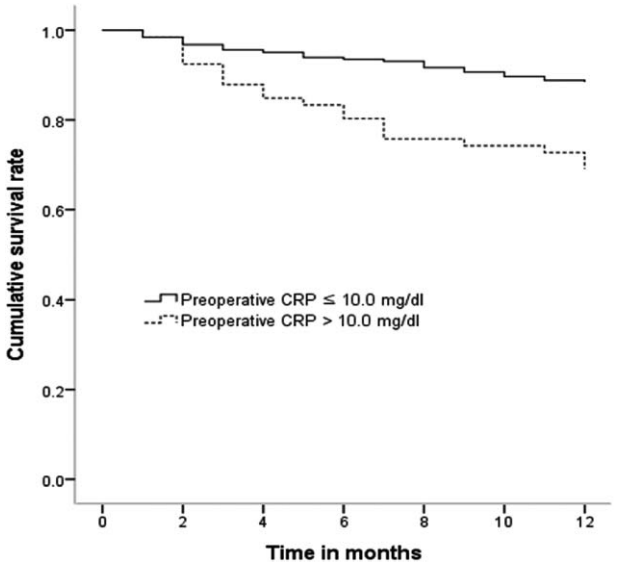

Figure 1. Mortality rate based upon preoperative C-reactive protein (CRP) levels for 1-year after hip surgery. There is a significant increase in mortality in patients with preoperative CRP >10.0 mg/dL ($P < 0.001$ in the log-rank test). CRP = C-reactive protein.

and incidence of delirium were lower in the low CRP group than in the high CRP group. Preoperative and postoperative hemoglobin and albumin levels were higher in the low CRP group compared to the high CRP group. The 1-year mortality was significantly lower in the low CRP group than the high CRP group ($P < 0.001$, Fig. 1).

The 1-year mortality rate was 14.1%. Males had a higher mortality rate than females (Table 2). Deceased patients had a higher ASA PS class and incidences of chronic renal disease, malignancy, and postoperative ICU admission than surviving patients. The preoperative hemoglobin and albumin levels were lower, whereas the preoperative CRP and creatinine levels were significantly higher in deceased patients. The postoperative creatinine level was higher in patients with 1-year mortality. On binary logistic regression (Table 3), BMI (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.88–0.99; $P = 0.025$), history of malignancy (OR, 2.59; 95% CI, 1.47–4.57; $P = 0.001$), ASA PS class 3–4 (OR, 1.96; 95% CI, 1.25–3.07; $P = 0.003$), preoperative albumin (OR, 0.39; 95% CI, 0.25–0.61; $P < 0.001$), preoperative CRP> 10 mg/dL (OR, 2.04; 95% CI, 1.09–3.80; $P = 0.025$), postoperative ICU admission (OR, 2.29; 95% CI, 1.15–4.59; $P = 0.019$), and creatinine level on postoperative day 2 (OR, 1.20; 95% CI, 1.00–1.45; $P = 0.048$) were independent predictors of 1-year mortality after hip surgery.

Regarding postoperative complications, delirium was seen in 109 (14.1%) patients. Patients with postoperative delirium had higher mortality than those without 1 year (33.0 vs 11.0%; $P < 0.001$) postoperatively. The preoperative mean CRP (4.8 ± 5.7) vs (3.2 ± 4.2) mg/dL; $P = 0.008$) and postoperative mean CRP (15.2 ± 7.4) vs (13.2 ± 6.5) mg/dL; $P = 0.003$) were significantly higher in patients with delirium compared to those without.

4. Discussion

The binary logistic regression analysis revealed that low BMI and preoperative low serum albumin level, preoperative CRP > 10 mg/dL, history of malignancy, high ASA PS grade, postoperative ICU admission, and high postoperative creatinine level were predominant risk factors for 1-year mortality after hip surgery in the elderly.

The CRP level is associated with the severity and clinical outcome of vascular disorders, such as coronary artery disease, stroke, atherosclerosis, and vasospasm after aneurysmal subarachnoid hemorrhage.[13–15] However, previous studies investigating the change in CRP after hip fracture surgery did not focus on the relationship between the CRP level and postoperative mortality.[12,19] Beloosesky et al[20] found no association between the pre- and postoperative CRP levels and the 6-month mortality

Table 2

The comparisons of preoperative, intraoperative, and postoperative variables after hip surgery.

	One-year mortality		
	Yes (n = 109)	No (n = 663)	*P*
Preoperative factors			
Age, y	80.2 (8.0)	79.3 (7.1)	0.265
Male gender	36 (33.0%)	156 (23.5%)	0.045
Body mass index, kg/m^2	20.9 (4.0)	21.7 (3.6)	0.048
Koval grade			0.002
1–2	54 (49.5%)	434 (65.5%)	
3–7	55 (50.5%)	229 (34.5%)	
ASA PS class			<0.001
1–2	50 (45.9%)	455 (68.6%)	
3–4	59 (54.1%)	208 (31.4%)	
Comorbidity			
Diabetes	37 (33.9%)	202 (30.5%)	0.538
Hypertension	69 (63.3%)	437 (65.9%)	0.673
Neurologic	37 (33.9%)	224 (33.8%)	1.000
Cardiac	18 (16.5%)	72 (10.9%)	0.123
Pulmonary	10 (9.2%)	31 (4.7%)	0.087
Hepatic	7 (6.4%)	27 (4.1%)	0.392
Renal	17 (15.6%)	42 (6.3%)	0.001
Malignancy	24 (22.0%)	57 (8.6%)	<0.001
Laboratory findings			
Hemoglobin, g/dL	11.0 (1.8)	11.8 (2.0)	<0.001
Albumin, g/dL	3.4 (0.5)	3.7 (0.5)	<0.001
Creatinine, mg/dL	1.4 (1.1)	1.0 (0.8)	<0.001
C-reactive protein, mg/dL	5.4 (5.8)	3.1 (4.1)	<0.001
C-reactive protein level, mg/dL			<0.001
≤ 10.0	88 (80.7%)	618 (93.2%)	
> 10.0	21 (19.3%)	45 (6.8%)	
Intraoperative factors			
Time to surgery, days	6.1 (5.2)	5.0 (5.8)	0.062
Fracture site			0.101
Neck	42 (38.5%)	315 (47.5%)	
Intertrochanteric	67 (61.5%)	348 (52.5%)	
Operation site			0.658
Right	52 (47.7%)	335 (50.5%)	
Left	57 (52.3%)	328 (49.5%)	
Anesthetic technique			0.481
Regional	93 (85.3%)	585 (88.2%)	
general	16 (14.7%)	78 (11.8%)	
Operation time, min	84.7 (26.8)	87.3 (32.7)	0.434
Postoperative factors			
ICU admission	16 (14.7%)	32 (4.8%)	<0.001
Laboratory findings on POD 2			
Hemoglobin, g/dL	10.1 (1.5)	9.9 (1.4)	0.454
Albumin, g/dL	2.9 (0.3)	3.0 (0.3)	0.010
Creatinine, mg/dL	1.4 (1.1)	1.0 (0.9)	<0.001
C-reactive protein, mg/dL	14.1 (7.4)	13.4 (6.6)	0.313

Data are expressed as mean (SD) or number (%).
ASA PS = American Society of Anesthesiologists' physical status, ICU = intensive care unit, POD = postoperative day.

Table 3

Parameters associated with 1-year mortality rate on binary logistic regression.

	One-year mortality*		
	OR	95% CI	*P*
Body mass index, kg/m^2	0.93	0.88–0.99	0.025
History of malignancy	2.59	1.47–4.57	0.001
ASA PS class 3–4: 1–2	1.96	1.25–3.07	0.003
Preoperative albumin, g/dL	0.39	0.25–0.61	<0.001
Preoperative CRP, mg/dL >10.0: ≤10.0	2.04	1.09–3.80	0.025
Postoperative ICU admission	2.29	1.15–4.59	0.019
Creatinine on POD 2, mg/dL	1.20	1.00–1.45	0.048

ASA PS = American Society of Anesthesiologists' physical status, CI = confidence interval, CRP = C-reactive protein, ICU = intensive care unit, OR = odds ratio, POD = postoperative day.

* After adjusting gender, Koval grade, chronic cardiac, renal and pulmonary diseases, preoperative hemoglobin level, the time to surgery, and postoperative albumin and creatinine levels. Nagelkerke R2 statistic was 0.181 in step 7. Hosmer and Lemeshow goodness of fit test was not significant at 5% (P = 0.433 in step 7).

in hip-fracture surgery geriatric patients. However, their sample size was too small to determine the association between the CRP level and mortality after hip surgery. In our study, the preoperative CRP level was significantly higher in the patients who died compared to the survivors and was an independent risk factor for mortality after hip fracture surgery in elderly patients. CRP is associated with infection, inflammation, and trauma.[11,13,19] Elevated CRP correlates with the severity of injury following major trauma.[9] This suggests that the severity of systemic inflammation due to the initial hip injury may affect mortality.

Considering the time course of the CRP in elderly patients undergoing hip fracture surgery, the CRP level tends to be elevated postoperatively and peaks on the second postoperative day.[21] Postoperative CRP is a sensitive marker for detecting postoperative complications, especially delirium, in elderly patients undergoing hip fracture surgery.[20,21–25] In agreement with previous studies, our results showed that patients with postoperative delirium had higher pre- and postoperative CRP levels than did those without. Delirium *per se* is associated with an increased risk of death in elderly patients with hip fractures.[26,27] Other clinical investigations closely linked postoperative delirium to persistent functional and cognitive deterioration, increased morbidity and mortality, longer hospital stays, and increased health-care costs.[28,29]

Numerous risk factors associated with mortality after hip surgery in the elderly have been reported, including age, gender, ASA PS class, preoperative walking capacity, dementia, BMI, preoperative albumin and hemoglobin levels, serum creatinine, co-morbidity, postoperative ambulation level, surgery type, and delayed surgery.[3–10] We found that a high preoperative CRP level, history of malignancy, high ASA PS grade, and postoperative ICU admission were predominant risk factors for the 1-year mortality after hip surgery in geriatric patients. A history of malignancy and high ASA PS score are well-known predictors of postoperative mortality in elderly patients with hip fractures.[3,6] In our study, postoperative ICU admission due to an intraoperative event, worsening medical comorbidity, and pre-existing severe organ dysfunction were significant predictors of the mortality in elderly patients undergoing hip fracture surgery. A recent study likewise reported that ICU admission was an important factor associated with the in-hospital mortality in geriatric patients with hip fractures.[30]

This study has some limitations. First, it was conducted retrospectively in a single center, which weakens the generalizability of the results. It is difficult to discriminate whether an increase in CRP is caused by infection or systemic inflammation without infection in hip-fracture patients. In this study, patients with overt or suspected bacterial infections in the period from hospital admission to least 2 days postoperatively were excluded, to rule out the influence of infection on the CRP level. Second, although the total number of subjects was large, the patients with high C-reactive protein level still did not make a large enough sample size. Further larger studies are required to confirm these results. The direct cause of death was not determined in this study, limiting our ability to explain the reason for the association between a high preoperative CRP level and postoperative mortality in elderly patients with hip fractures. Preoperative factors, such as nursing home residence and daily living activities, were not investigated in this study. A previous study demonstrated that nursing home/facility residence and poor daily living activities strongly predicted the mortality after hip fracture surgery in geriatric patients.[8]

In conclusion, a high preoperative CRP level, especially >10 mg/dL, was associated with increased 1-year mortality after hip fracture surgery in elderly patients. In addition to a high preoperative CRP, a history of malignancy, high ASA PS score, and postoperative ICU admission were related to mortality after hip fracture surgery in the elderly.

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