ORIGINAL RESEARCH

Early Postoperative Hypoalbuminaemia as a Risk Factor for Postoperative Pneumonia Following Hip Fracture Surgery

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Purpose: Postoperative pneumonia is a common and devastating complication of hip fracture surgery in older individuals. This study aimed to determine the relationship between early postoperative hypoalbuminaemia and pneumonia after hip fracture surgery.

Patients and Methods: In this retrospective cohort study conducted at one centre, we reviewed the medical records of 1155 consecutive patients (>60 years) who underwent hip fracture surgery. Multivariate logistic regression analysis was performed to identify the independent risk factors for postoperative pneumonia. After determining the cut-off value for postoperative serum albumin, the patients were divided into two groups according to the minimum serum albumin level recorded during the first two post-operative days: group A included patients with a minimum serum album level less than 3.0 g/dL and group B included patients with a minimum serum album level of at least 3.0 g/dL. The prevalence of postoperative pneumonia was analysed using inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) analyses.

Results: The incidence of postoperative pneumonia following hip fracture surgery was 5.1% (n=59). Age, cardiovascular disease, and early postoperative hypoalbuminaemia during the first two postoperative days were independent risk factors for postoperative pneumonia. Early postoperative hypoalbuminaemia was associated with postoperative pneumonia development in the PSM and IPTW analyses (P = 0.016 and <0.001, respectively).

Conclusion: This study demonstrated that early postoperative hypoalbuminaemia is an independent risk factor for the development of postoperative pneumonia in patients undergoing hip fracture surgery.

Keywords: osteoporosis, osteoporotic fracture, albumin, complication

Introduction

As human life expectancy and the size of the aging population have increased, so too has the number of individuals vulnerable to hip fractures.[1] Postoperative adverse complications are commonly associated with hip fracture surgeries, with a one-year mortality rate of 18%.[2–10]

Postoperative pneumonia is one of the most frequent and devastating complications after hip fracture surgery.[11,12] Postoperative pneumonia is associated with an increased surgical mortality rate and prolonged length of hospital stay and its reported incidence ranged between 49% in patients with hip fractures.[13–17]

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Preoperative hypoalbuminaemia has been established as an independent predictor for postoperative complications and mortality after hip fracture surgery.[13,17,18] However, given that the clinical importance of a perioperative decrease in serum albumin levels or early postoperative hypoalbuminaemia on postoperative morbidities has been emphasized, it is important to concentrate on perioperative or early postoperative changes in serum albumin levels and their relationship with postoperative outcomes.[19–24]

Several reports demonstrated the relationship between perioperative changes in serum albumin and the development of postoperative pneumonia in patients with gastric, colorectal, and lung cancers.[19,21,22,24] However, scant studies investigated the risk factors of postoperative pneumonia in patients undergoing hip fracture surgery, and the relationship between early postoperative hypoalbuminaemia and postoperative pneumonia has never been delineated.[25,26] Therefore, the purpose of this study was to investigate the incidence of postoperative pneumonia and identify risk factors associated with the development of this condition in patients who underwent hip fracture surgery.

Patients and Methods
Study Population
This study was approved by the institutional review board of Korea University Medical Centre. A retrospective review was performed based on the medical records of 1228 patients who were aged >60 years and underwent surgery for hip fractures, including intertrochanteric and femoral neck fractures, at our hospital between January 1, 2010, and October 31, 2019. A single orthopaedic surgeon at our institution operated upon all patients via total joint arthroplasty or bipolar hemiarthroplasty for femoral neck fractures and via osteosynthesis using dynamic hip screws or intramedullary nail insertion for intertrochanteric fractures of the proximal femur. The exclusion criteria included patients who (1) who had pathological or periprosthetic fractures, (2) had X-ray and/or computed tomography-confirmed preoperative pneumonia and (3) had incomplete data or their data could not be obtained. Finally, a total of 1155 patients who underwent hip fracture surgery comprised the final study cohort (Figure 1). All patients were divided into two groups: group A included patients with a minimum serum albumin level less than 3.0 g/dL during the first two postoperative days and group B included patients with a minimum postoperative serum albumin level of at least 3.0 g/dL.

Data Collection
Demographic Characteristics
Baseline characteristics of patients and perioperative laboratory, clinical, and radiologic data were acquired from the computerised databases of our institution (Electronic Medical Record System and Picture Archiving Communication System). Baseline characteristics of each patient were collected, including age, sex, period from injury date to operation date, medication history including antiplatelets and anticoagulants, and comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease.

Perioperative Laboratory Findings and Clinical Data
Serum haemoglobin (Hb) and haematocrit (Hct) levels of patients were measured preoperatively and daily for 1 week postoperatively. The minimum Hb level observed during the first postoperative week was recorded. Estimated blood loss was calculated from the change in Hct level and the patient's estimated blood volume. The patient's blood volume was calculated according to Nadler's formula, and the total red blood cell (RBC) loss was calculated according to the Gross formula.[27,28] According to the Gross formula, we calculated the total RBC loss during the first postoperative week. Since the Gross formula presents total blood loss in milliliters of RBCs, we converted this to milliliters of blood using the average of the preoperative and final Hct values.

Preoperative platelet counts and serum creatinine levels were also recorded. Patients' preoperative serum albumin levels were recorded and the minimum value observed during the first two postoperative days was recorded. The postoperative transfusion rate was recorded. The restrictive transfusion guidelines of our institution were followed: one unit of packed RBCs (derived from 400 mL of whole blood) was administered to patients with Hb levels of 6.0–6.9 g/dL, whereas two units of packed RBCs were administered to those with Hb levels of 5.0–5.9 g/dL. Transfusions were performed immediately after patients developed symptoms of anaemia and hypovolemia, including hypotension, tachycardia, tachypnoea, and dizziness. Intraoperative factors, including the type of surgical procedure (osteosynthesis or arthroplasty), duration of anaesthesia, and volume of fluid administered intraoperatively, were assessed using the intraoperative anaesthesia records.
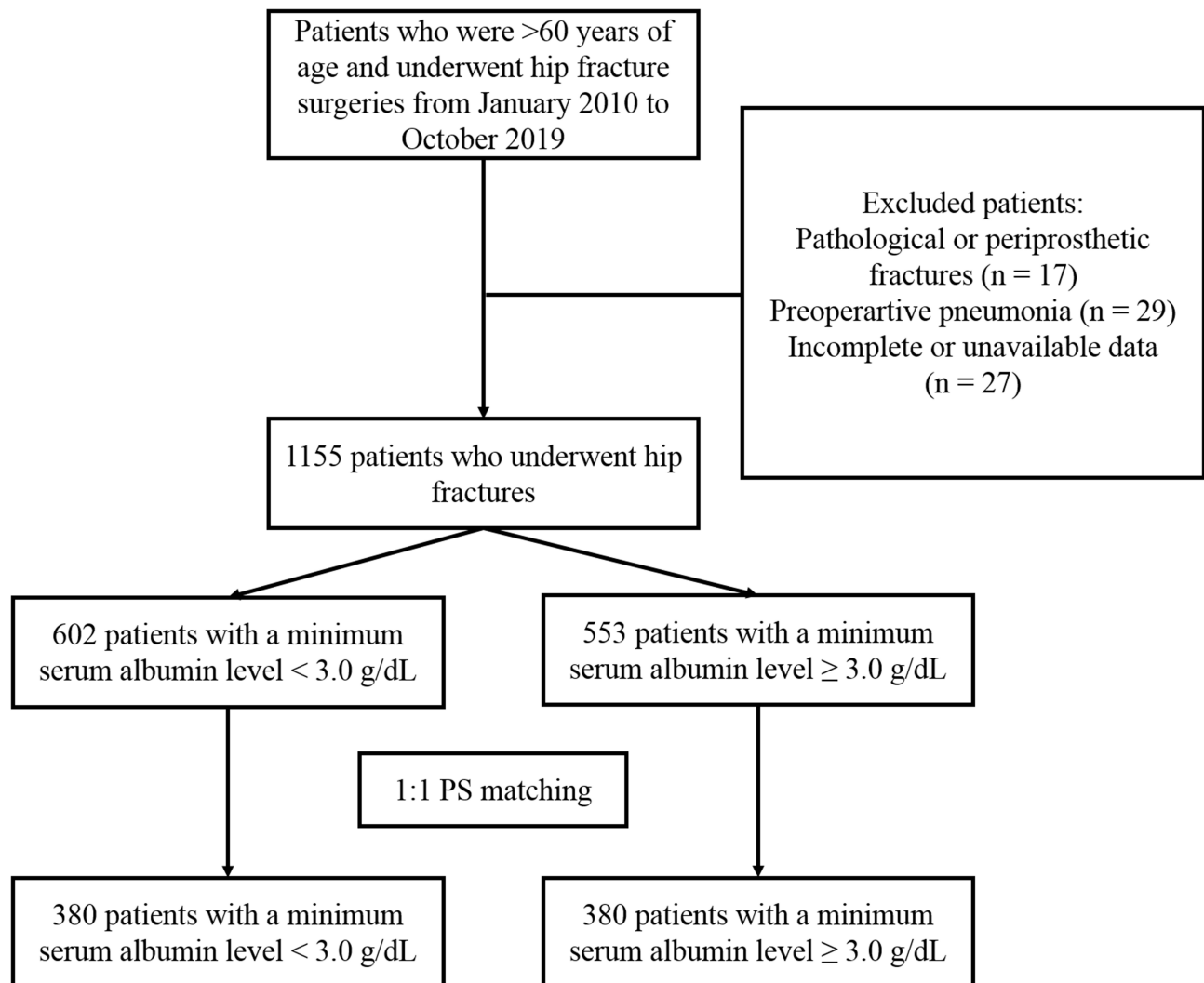
Patients who were >60 years of
age and underwent hip fracture
surgeries from January 2010 to
October 2019

Excluded patients:
Pathological or periprosthetic
fractures (n = 17)
Preoperartive pneumonia (n = 29)
Incomplete or unavailable data
(n = 27)

1155 patients who underwent hip
fractures

602 patients with a minimum
serum albumin level < 3.0 g/dL

553 patients with a minimum
serum albumin level ≥ 3.0 g/dL

1:1 PS matching

380 patients with a minimum
serum albumin level < 3.0 g/dL

380 patients with a minimum
serum albumin level ≥ 3.0 g/dL

Figure 1 Flowchart illustrating the selection of the patients for this study.

Definition of Postoperative Pneumonia

The primary study outcome was the incidence of postoperative pneumonia during hospitalisation. Patients with postoperative pneumonia were defined as those who did not present with preoperative pneumonia and exhibited new infiltrations on the postoperative chest X-ray and/or computed tomography images. Patients were diagnosed with postoperative pneumonia when one of more of the following criteria were met: (1) presence of new and/or progressive and persistent respiratory symptoms, including coughing and purulent secretions; (2) presence of fever (body temperature >38.0°C) or hypothermia (body temperature <36.0°C); (3) physical examination showing lung consolidation and/or moist rale; (4) lab tests indicating leukocytosis (white cell count $>10 \times 10^9$/L) or leukopenia (white cell count $<4 \times 10^9$/L); and (5) pathogen isolation from blood or sputum cultures.[29–31]

Statistical Analysis

All data were presented as means with standard deviations for continuous variables or percentages for categorical variables. Baseline characteristics and perioperative data were compared between the two groups using the Student's *t*-test and Fisher's exact test as appropriate. Multiple logistic regression analyses were performed to identify predictors of postoperative pneumonia and evaluate the impact of albumin level on the development of postoperative pneumonia. The model was adjusted for all covariates with a P value <0.1 in the univariate analysis. After confirming the significant relationship between early postoperative albumin level and the development of postoperative pneumonia, the cut-off value for postoperative albumin was determined based on the Youden index according to the receiver operating characteristic (ROC)

curve. To reduce the effect of confounding factors between the two groups, we performed propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). Propensity score was estimated using multiple logistic regression analysis with early postoperative hypoalbuminaemia as the dependent variable. All parameters presented in Table 1 except postoperative transfusion rate, length of stay, estimated blood loss, and minimum Hb level during the first postoperative week

was used to determine the PS. After adjustment by PSM and IPTW, the balance between the two groups was assessed using the standardised mean difference. The association of early postoperative hypoalbuminaemia on postoperative pneumonia was evaluated using conditional logistic regression analysis or weighted logistic regression analysis. All P values <0.05 were deemed statistically significant. R software version 3.4.2 and Statistical Product and Service Solutions (SPSS) software version

Table I Univariate and Multivariate Regression Analyses of Risk Factors for Postoperative Pneumonia

Variables	Univariate			Multivariate		
	Pneumonia (n=59)	Non-pneumonia (n=1096)	P-value	OR	95% CI	P-value
Demographic characteristics						
Sex (male/female)	21 (35.6)/38 (64.4)	295 (26.9)/801 (73.1)	0.145			
Age (years)	83.08 ± 7.30	77.90 ± 10.05	<0.001	1.062	(1.022, 1.103)	0.002
BMI (kg/m^2)	22.32 ± 3.43	22.57 ± 3.63	0.673			
Period between injury and operation date (days)	3.92 ± 4.39	3.72 ± 3.14	0.643			
HTN	46 (78.0)	748 (68.2)	0.117			
DM	21 (35.6)	388 (35.4)	0.976			
COPD	4 (6.8)	54 (4.9)	0.526			
CKD	10 (16.9)	140 (12.8)	0.353			
Cardiovascular disease	17 (28.8)	170 (15.5)	0.007	2.03	(1.118, 3.688)	0.02
Cerebrovascular disease	11 (18.6)	230 (21.0)	0.666			
Medication history						
Antiplatelets	20 (33.9)	371 (33.9)	0.994			
Anticoagulants	6 (10.2)	66 (6.0)	0.199			
Type of surgery			0.385			
Osteosynthesis	33 (55.9)	675 (61.6)				
Arthroplasty	26 (44.1)	421 (38.4)				
Laboratory findings						
Preoperative Hb (g/dL)	11.62 ± 1.57	11.59 ± 1.60	0.856			
Preoperative Hct (%)	34.90 ± 4.69	34.67 ± 4.69	0.721			
Preoperative Plt (×10^9/L)	216.31 ± 98.02	204.57 ± 73.31	0.369			
Preoperative Cr (mg/dL)	0.96 ± 0.32	0.96 ± 0.77	0.953			
Albumin (g/dL)						
Preoperative	3.59 ± 0.45	3.71 ± 0.43	0.04	1.012	(0.514, 1.994)	0.972
<3.0 during the first two postoperative days	45 (76.3)	557 (50.8)	<0.001	2.428	(1.261, 4.676)	0.008
EBL during the first postoperative week (mL)	941.96 ± 434.69	893.41 ± 373.88	0.336			
Minimum Hb during the first postoperative week (g/dL)	8.63 ± 1.18	8.54 ± 1.21	0.611			
Volume of fluid administered intraoperatively (mL)	701.69 ± 409.79	614.69 ± 420.60	0.121			
Anaesthesia time (minutes)	121.44 ± 31.12	121.00 ± 34.20	0.924			
Length of stay (days)	17.25 ± 9.93	15.77 ± 11.18	0.319			
Postoperative transfusion rate (%)	3 (5.1)	73 (6.7)	0.634			

Note: Data are presented as mean ± standard deviation or number (%)
Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; Hb, haemoglobin; Hct, haematocrit; Plt, platelet count; Cr, creatinine; EBL, estimated blood loss.

22.0 (IBM Corporation, Armonk, NY, USA) were used to handle and analyse the data.

Results

The incidence of pneumonia during hospitalisation among patients who underwent hip fracture surgeries was 5.1% (n = 59 out of 1155 patients). Multivariate regression analysis showed that age (odds ratio [OR], 1.062; 95% confidence interval [CI], 1.022–1.103; P = 0.002) and cardiovascular disease (OR, 2.03; 95% CI, 1.118–3.688; P = 0.02) were determined to be independent risk factors for postoperative pneumonia (Table 1). Further, early postoperative rather than preoperative hypoalbuminemia was determined as an independent risk factor for postoperative pneumonia (OR, 2.428; 95% CI, 1.261, 4.676; P = 0.008) (Table 1).

The optimal cut-off value of the minimal albumin level during the first two postoperative days that predicts postoperative pneumonia was determined to be 3.0 g/dL (area under the ROC curve, 0.701). The demographic data and perioperative findings of patients with and without postoperative hypoalbuminaemia are summarised in Table 2. There were significant intergroup differences in sex, age, and preoperative Hb, Hct, and albumin levels. In addition, patients in group A were more likely to have lower minimum Hb levels during the first postoperative week and a higher postoperative transfusion rate.

After adjustment by PSM and IPTW to reduce the effect of confounding factors other than early postoperative hypoalbuminemia, the two groups were found to be well balanced without any significant difference (Supplement S1). The association between postoperative pneumonia and early postoperative hypoalbuminaemia is summarised in Table 3. Even after PSM and IPTW analyses, the incidence of postoperative pneumonia was significantly associated with early postoperative hypoalbuminaemia during the first two postoperative days (P = 0.016 and <0.001, respectively).

Discussion

The principal finding of this study is that early postoperative hypoalbuminaemia (minimum serum albumin level less than 3.0 g/dL during the first two postoperative days) was a significant predictor for postoperative pneumonia following hip fracture surgery even after PSM and IPTW analyses.

Pneumonia is one of the most devastating postoperative complications after general surgical procedures and is associated with a 3-fold increase in mortality.[25,32] The incidence of postoperative pneumonia following hip fracture surgery is approximately 5%.[25,26] Although little is known regarding risk factors for pneumonia after hip fracture surgery, several potential risk factors have been suggested, including sex, age, chronic obstructive pulmonary disease, low body mass index, anaemia, congestive heart failure, functional status, and surgery type.[25,26] Recently, preoperative hypoalbuminaemia is reported to be associated with postoperative pneumonia following hip fracture surgery.[17,26]

Serum albumin level is used to assess protein-energy malnutrition in patients with hip fractures.[33] Preoperative hypoalbuminaemia has been proven to be a significant risk factor for perioperative morbidity in patients undergoing orthopaedic surgery.[13,17,18,33–36] However, if we concentrate only on preoperative albumin levels, we may not identify perioperative or early postoperative changes in albumin levels and their association with postoperative outcomes. A relationship between a postoperative decrease in serum albumin levels and adverse perioperative outcomes has been demonstrated in patients undergoing non-orthopaedic surgery.[19,21,22,24] A postoperative decrease in serum albumin levels during the first three postoperative days is a significant predictor for short-term complications following gastric cancer resection.[22] Moreover, an early postoperative decrease in serum albumin levels was determined to be a risk factor for infectious complications including pneumonia in patients undergoing laparoscopic surgery for colorectal cancer.[24] In addition, a reduction in serum albumin levels on postoperative day one was determined to be a predictor of postoperative pulmonary complications after thoracoscopic anatomical resection in patients with lung cancer.[21] To the best of our knowledge, no studies have investigated the role of early postoperative hypoalbuminaemia in predicting postoperative pneumonia in patients undergoing hip fracture surgery. In this study, clinical and laboratory findings were evaluated to determine independent risk factors for postoperative pneumonia in patients undergoing hip fracture surgery. Multivariate analysis revealed that age, cardiovascular disease and early postoperative hypoalbuminaemia during the first two postoperative days were independent risk factors for postoperative pneumonia. Even after reducing the influence of possible confounding factors by PSM and IPTW analyses, early postoperative hypoalbuminaemia was found to be an independent risk factor for postoperative pneumonia.

Table 2 Demographic and Perioperative Characteristics of Patients According to Minimum Serum Albumin Level During the First Two Postoperative Days

Variable	Total (N=1155)	Minimum Albumin During the First Two Postoperative Days (g/dL)		P-value	Standardised Difference
		<3.0 (n=602)	≥3.0 (n=553)		
Demographic characteristics					
Sex (male/female)	316 (27.4)/839 (72.6)	129 (21.4)/473 (78.6)	187 (33.8)/336 (66.2)	<0.001	0.631
Age (years)	78.16 ± 9.99	80.77 ± 7.99	75.33 ± 11.13	<0.001	0.058
BMI (kg/m^2)	22.73 ± 18.95	22.55 ± 24.44	22.93 ± 10.02	0.740	0.001
Period between injury and operation date (days)	3.73 ± 3.22	3.83 ± 3.07	3.61 ± 3.37	0.259	0.021
HTN	794 (68.7)	418 (69.4)	376 (68.0)	0.597	0.067
DM	409 (35.4)	205 (34.1)	204 (36.9)	0.314	0.124
COPD	58 (5.0)	36 (6.0)	22 (4.0)	0.120	0.423
CKD	150 (13.0)	84 (14.0)	66 (11.9)	0.308	0.179
Cardiovascular disease	187 (16.2)	99 (16.4)	88 (15.9)	0.806	0.039
Cerebrovascular disease	241 (20.9)	139 (23.1)	102 (18.4)	0.052	0.283
Medication history					
Antiplatelets	391 (33.9)	210 (34.9)	181 (32.7)	0.440	0.096
Anticoagulants	72 (6.2)	43 (7.1)	29 (5.2)	0.182	0.326
Type of surgery				0.544	0.073
Osteosynthesis	708 (61.3)	364 (60.5)	344 (62.2)		
Arthroplasty	447 (38.7)	238 (39.5)	209 (37.8)		
Laboratory findings					
Preoperative Hb (g/dL)	11.59 ± 1.60	11.22 ± 1.52	11.99 ± 1.59	<0.001	0.317
Preoperative Hct (%)	34.68 ± 4.69	33.67 ± 4.48	35.78 ± 4.67	<0.001	0.101
Preoperative Plt (×10^9/L)	205.17 ± 74.76	206.64 ± 79.61	203.57 ± 69.15	0.483	0.001
Preoperative Cr (mg/dL)	0.96 ± 0.75	0.93 ± 0.57	1.00 ± 00.91	0.150	0.112
Preoperative albumin (g/dL)	3.70 ± 0.43	3.54 ± 0.42	3.88 ± 0.38	<0.001	2.135
EBL during the first postoperative week (mL)	895.89 ± 377.16	894.13 ± 376.81	897.81 ± 377.88	0.868	<0.001
Minimum Hb during the first postoperative week (g/dL)	8.55 ± 1.20	8.18 ± 1.03	8.96 ± 1.25	<0.001	0.594
Volume of fluid administered intraoperatively (mL)	619.14 ± 420.31	632.24 ± 425.97	604.88 ± 413.98	0.269	<0.001
Anaesthesia time (minutes)	121.03 ± 34.04	122.44 ± 36.96	119.48 ± 30.51	0.137	0.003
Length of stay (days)	15.85 ± 11.12	16.31 ± 9.41	15.35 ± 12.72	0.146	0.008
Postoperative transfusion rate (%)	76 (6.6)	55 (9.1)	21 (3.8)	<0.001	0.892

Note: Data are presented as mean ± standard deviation or number (%).
Abbreviations: BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; Hb, haemoglobin; Hct, haematocrit; Plt, platelet count; Cr, creatinine; EBL, estimated blood loss.

The reduction in albumin levels after surgical trauma can be attributed to intra- and postoperative blood loss, perioperative haemodilution, and generalised inflammation.[37–40] Moreover, postoperative hypoalbuminaemia may result from increased capillary permeability into the interstitial space.[37,38,40] Albumin protects the endothelial glycocalyx and maintains endothelial barrier function.[41–43] Disruption of the endothelial glycocalyx has been demonstrated following surgical trauma or severe injury.[44–46] Consequently, a vicious cycle of postoperative damage to the endothelial glycocalyx and hypoalbuminaemia may contribute to transcapillary albumin leakage and interstitial oedema in patients undergoing hip fracture surgery.

Hypoalbuminaemia may predispose patients to infection and other postoperative complications by promoting granuloma formation and reducing collagen synthesis, thus inhibiting the innate immune response.[18,33,47] These highlight that the immune dysfunction in the postoperative period, expressed as early postoperative hypoalbuminemia, may have contributed to the development of postoperative pneumonia.

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Table 3 Comparison of the Incidence of Pneumonia According to Minimum Serum Albumin Level During the First Two Postoperative Days

Outcome	Minimum Albumin During the First Two Postoperative Days (g/dL)	Crude			IPTW*		PSM*		
		Event/N	OR (95% CI)	P-value	OR (95% CI)	P-value	Event/N	OR (95% CI)	P-value
Pneumonia	<3.0	45/602	3.110 (1.688, 5.732)	<0.001[a]	3.053 (1.958, 4.760)	<0.001[b]	19/223	3.111 (1.237, 7.825)	0.016[c]
	≥3.0	14/553					7/223		

Notes: *The propensity score was calculated using a multiple logistic regression model that included all variables presented in Table 1 excluding postoperative transfusion rate, length of stay, estimated blood loss, and minimum Hb during the first postoperative week. [a]p-value by simple logistic regression. [b]p-value by weighted logistic regression. [c]p-value by conditional logistic regression
Abbreviations: IPTW, inverse probability of treatment weighting; PSM, propensity score matching

Recognising risk factors for postoperative complications is important for optimising perioperative patient care and predicting prognosis after surgery. This study is the first to demonstrate an association between early postoperative hypoalbuminaemia and the development of pneumonia after hip fracture surgery in older individuals. Therefore, monitoring serum albumin levels to detect early postoperative hypoalbuminaemia may aid in the early detection and prevention of postoperative pneumonia and patients with early postoperative hypoalbuminemia may benefit from more intense postoperative observation.

Several limitations of the current study should be noted. First, this was a retrospective observational analysis conducted at a single institution, which entails inherent limitations. Although we used PSM and IPTW analyses to adjust for the effects of confounding factors and reduce bias, confounding factors and unknown bias could not be entirely excluded. Second, we were unable to elucidate the mechanisms underlying the effect of early postoperative hypoalbuminaemia on postoperative pneumonia. Additionally, the causal relationship between early postoperative hypoalbuminaemia and pneumonia and the protective effect of albumin administration on prevention of postoperative pneumonia were not determined because this was an observational study. Therefore, large-scale multicentre prospective studies are needed to determine the causal relationship between the two conditions and to verify the protective effect of albumin administration.

Conclusion

This study suggests that early postoperative hypoalbuminaemia is an independent risk factor for the development of postoperative pneumonia in patients undergoing hip fracture surgery.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Institutional Board Review of Korea University Medical Centre (2020AN0081). This study was conducted in accordance with the Declaration of Helsinki. The consent was waived due to the retrospective nature of the study. We confirm that the privacy of the participants was saved, and the data were anonymized and maintained with confidentiality.

Disclosure

The authors report no conflicts of interest in this work.

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