Prognostic Nutritional Index Is a Better Predictor of Perioperative Adverse Outcomes in Patients With Femoral Fractures: a Retrospective Study

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Abstract

Background: Surgery is usually the best treatment for patients with femoral fractures. However, the incidence of perioperative adverse outcomes in such cases is quite high. Nutrition has a major influence on fracture healing, and malnutrition is associated with higher complication rates, higher mortality rates, and longer hospitalisation periods. In this study, we aimed to identify independent risk factors and assess the predictive value of the prognostic nutritional index (PNI) for perioperative adverse outcomes in patients with femoral fractures.

Methods: This retrospective observational study included 343 patients who underwent surgery for a single femur fracture at the Affiliated Hospital of Zunyi Medical University in 2018. Binary logistic regression analysis was applied to identify significant independent risk factors. The discriminatory ability of independent predictors was assessed using the receiver operating characteristic curve analysis, and DeLong's test was used to compare the area under the curve (AUC).

Results: In total, 159 patients (46.4%) had perioperative adverse outcomes. PNI (OR: 0.819, 95% CI: 0.754–0.889, $P < 0.001$), age (OR: 1.042, 95% CI: 1.020–1.066, $P < 0.001$), time to admission (OR: 1.404, 95% CI: 1.117–1.765, $P = 0.004$), hypertension (OR: 1.912, 95% CI: 1.049–3.488, $P = 0.034$), combined injures (OR: 2.739, 95% CI: 1.338–5.607, $P = 0.006$), and operation types (OR: 3.696, 95% CI: 1.913–7.138, $P < 0.001$) were independent factors for perioperative adverse outcomes. Based on the AUC (PNI: 0.772, 95% CI: 0.723–0.821, $P < 0.001$; age: 0.678, 95% CI: 0.622–0.734, $P < 0.001$; time to admission: 0.585, 95% CI: 0.525–0.646, $P = 0.006$), the PNI had the optimal discrimination ability, indicating its superiority over other independent predictors (age vs. PNI, $P = 0.002$; time to admission vs. PNI, $P < 0.001$).

Conclusions: This study showed that the PNI was a better and effective independent predictor of perioperative adverse outcomes in patients with femoral fractures. Our findings suggest that nutritional assessment at admission and appropriate intervention strategies are necessary for patients with femoral fractures.

Background

Globally, the number of individuals sustaining fractures is increasing, particularly among the elderly population (1, 2). Clinically, femoral fractures are one of the most commonly encountered fracture types and are associated with higher rates of complications, profound decreases in the quality of life, and increases in morbidity, mortality, and economic costs (2–4). Femoral fractures are generally classified according to the site of fracture as proximal, shaft, or distal femoral fractures. The incidence of proximal femoral fractures, classified as hip fractures, is the highest and is likely to continue increasing in the future owing to the rapid ageing of the population and associated occurrence of osteoporosis (5–7). Patients with hip fractures are at a considerable risk of premature death (8). Femoral shaft fractures, which are predominantly noted in young people with healthy bones (9), are caused mostly by road traffic accidents (being crushed or run over) or falling from a great height (9). Distal femoral fractures are rare injuries, accounting for approximately 2% of all femoral injuries (10), and often develop as a result of vehicular trauma or sports activities with varus or valgus impact at the knee (10).

Surgery is usually the best treatment, and it is often performed for patients with femoral fractures. However, the incidence of perioperative adverse outcomes is quite high, including lower limb vein thrombus or pulmonary embolism, pneumonia, incision disunion or infection, acute exacerbation of underlying chronic diseases, transfer to the intensive care unit (ICU), and even death. Age, trauma, stress, surgery, anaemia, bleeding, infection, pain, activity limitation, and a bedridden state are commonly considered to be the causes. Such patients can be at risk of protein catabolism and malnutrition. Nutrition has a major influence on fracture healing, and fracture healing impairment has been observed in the malnourished and undernourished population (2, 11, 12). Protein-depleted patients with a hip fracture have shown higher complication rates and longer hospitalisation periods (11). Notably, Hughes et al. showed that nutritional improvement led to increased muscle mass in the leg and greater bone mineral density in the fractured callus in protein-malnourished rats with femoral fractures (2). Nevertheless, only a few studies have investigated the impact of nutrition on adverse outcomes in patients with femoral fractures, specifically during the perioperative stage.

The prognostic nutritional index (PNI), initially proposed by Buzby et al. (13), is a comprehensive index for evaluating the preoperative nutritional status of surgical patients (14, 15) and for predicting the risk of postoperative complications (14–17). Currently, a low PNI, as a proxy of subpar perioperative nutritional status, is reported to be a significant predictor of poor postoperative outcomes and increased mortality in various malignancies (16, 17). However, no studies on PNI have focused on perioperative adverse outcomes in patients undergoing surgery for femoral fractures. Therefore, in this retrospective study, we aimed to determine the independent risk factors and evaluate the predictive value of the PNI for perioperative adverse outcomes in patients with femoral fractures.

Methods

Data source

The data for this retrospective observational study were extracted from the Hospital Information System (HIS; TianJian Technology Co., Ltd., Beijing, China) and Anesthesia Information Management System (AIMS; Medical System Technology Co., Ltd., Suzhou, Jiangsu, China). The HIS and the AIMS, which maintain a complete record of healthcare services, are electronic medical record management systems for hospitals in China.

Patients

A retrospective review was performed using data from a database of 446 patients who underwent surgery for a single femur fracture during hospitalisation between January 2018 and December 2018 at the Affiliated Hospital of Zunyi Medical University. The case definition of femur fracture was based on specific diagnosis codes from the International Classification of Diseases, Tenth Revision (ICD-10, S72).

These codes were listed as the primary diagnosis on the electronic inpatient healthcare claim submitted to the HIS. The exclusion criteria were as follows: 1) reoperation or multi-location operations (n = 44); 2) incomplete data (n = 27); 3) systemic wasting diseases (such as tuberculosis, tumours, and hyperthyroidism; n = 19); 4) age < 18 years (n = 4); 5) thromboembolism history (n = 4); 6) chronic renal failure, chronic hepatic dysfunction, and serious heart disease (n = 4); and 7) pregnancy (n = 1). Finally, a total of 343 patients was identified after applying all exclusion criteria; of these, 257 (75.0%) had a proximal fracture, 79 (23.0%) had a shaft fracture, and 7 (2.0%) had a distal fracture.

Study endpoint

The occurrence of perioperative adverse outcomes was assessed as the study endpoint. Perioperative complications, such as lower limb vein thrombus (ICD-10, I80.301), pulmonary embolism (ICD-10, I26), hospital-acquired pneumonia (ICD-10, J12-18), incision disunion (ICD-10, T81.406 or T81.009), bedsores (ICD-10, L89), and transfer to ICU and death (ICD-10, R99), were defined as perioperative adverse outcomes.

Variables

The following various potential influencing factors were investigated: 1) demographic characteristics, including sex, age, and weight; chronic diseases; combined injuries; aetiology; time to admission; and fracture site. Time to admission was graded as 1 (within 24 hours), 2 (2–3 days), 3 (4–7 days), 4 (8–21 days), or 5 (> 22 days); 2) operation and anaesthesia records, including the American Society of Anesthesiologists (ASA) grade, surgeons (eight chief surgeons with at least 20 years of surgical experience [surgeons A, B, C, D, E, F, G, and H] participated in this study), operation types, anaesthesia methods, postoperative analgesic methods, duration of anaesthesia and surgery, the ratio of blood transfusion, intraoperative blood loss, and intraoperative crystal and colloidal liquid infusion volumes; and 3) laboratory results at admission, including albumin (ALB), prealbumin (PAb), globulin (GLB), and haemoglobin (HB) levels; lymphocyte (LYM) and neutrophil (NEUT) counts; and PNI. PNI was calculated using the following formula: $10 \times$ ALB (g/dL) $+ 0.005 \times$ LYM count (per mm^3) (14, 16) (Table 1).

Table 1
Comparison between patients with and without adverse outcomes

Variables	**No adverse outcomes** **(n = 184)**	**Adverse outcomes** **(n = 159)**	***P*-values**
Male/Female, n (%)	88 (55.7)/96 (51.9)	70 (44.3)/89 (48.1)	0.481
Left/Right femur, n (%)	94 (54.7)/90 (52.6)	78 (45.3)/81 (47.4)	0.708
Age, years, mean (range)	60 (43.25–71)	70 (60–81)	**< 0.001**
Weight, kg, mean (range)	55 (50–62)	55 (50–60)	0.259
Hypertension, n (%)	85 (37.9)	74 (62.2)	**< 0.001**
Diabetes, n (%)	141 (45)	18 (60)	0.117
Combined injuries, n (%)	112 (43.1)	47 (56.6)	**0.031**
Aetiology, n (%)			0.968
Sprain or tumble	142 (77.2)	123 (77.4)	
RTA, falls, or assaults	42 (22.8)	36 (22.6)	
Fracture site, n (%)			0.493
Proximal femoral fracture	140 (76.1)	117 (73.6)	
Femoral shaft fracture	39 (21.2)	40 (25.2)	
Distal femoral fracture	5 (2.7)	2 (1.3)	
Time to admission, n (%)			**0.002**
1: Within 24 hours	127 (69.0)	81 (50.9)	
2: 2–3 days	17 (9.2)	24 (15.1)	
3: 4–7 days	14 (7.6)	19 (11.9)	
4: 8–21 days	12 (6.5)	26 (16.4)	
5: ≥ 22 days	14 (7.6)	9 (5.7)	
ASA, n (%)			**< 0.001**
[illegible]	4 (2.2)	2 (1.3)	
[illegible]	157 (85.3)	106 (66.7)	
[illegible]	23 (12.5)	50 (31.4)	

Variables	No adverse outcomes (n = 184)	Adverse outcomes (n = 159)	*P*-values
□	0 (0)	1 (0.6)	
Surgeons, n (%)			0.161
Surgeon A	28 (15.2)	22 (13.8)	
Surgeon B	38 (20.7)	21 (13.2)	
Surgeon C	22 (12.0)	18 (11.3)	
Surgeon D	27 (14.7)	22 (13.8)	
Surgeon E	31 (16.8)	32 (20.1)	
Surgeon F	13 (7.1)	17 (10.7)	
Surgeon G	18 (9.8)	11 (6.9)	
Surgeon H	7 (3.8)	16 (10.1)	
Operation types, n (%)			**0.014**
(Hemi/total) Hip replacement	73 (39.7)	43 (27.0)	
Internal fixation	111 (60.3)	116 (73.0)	
Anaesthesia methods, n (%)			0.445
General anaesthesia	47 (25.5)	35 (22.0)	
Non-General anaesthesia	137 (74.5)	124 (78.0)	
Post-analgesic methods, n (%)			0.315
NO	9 (4.9)	4 (2.5)	
PCIA	123 (66.8)	101 (63.5)	
PCEA	52 (28.3)	54 (34.0)	
Duration of anaesthesia, min, mean (range)	180 (140, 225)	180 (149, 230)	0.323
Duration of surgery, min, mean (range)	111 (80, 153.5)	110 (80, 155)	0.914
Blood transfusion, n (%)	72 (36.9)	87 (58.8)	**< 0.001**
Intra-blood loss, $\times 10^2$ mL, mean (range)	2 (1, 3)	2 (1,3)	**0.052**
Intra-crystal liquids $\times 10^2$ mL, mean (range) (×102)	8.5 (6, 11)	7.5 (6, 11)	0.662

Variables	No adverse outcomes (n = 184)	Adverse outcomes (n = 159)	*P*-values
Intra-colloidal liquids ×10^2 mL, mean (range)	5 (5, 7.5)	5 (5, 10)	0.983
ALB, g/L, mean ± SD	38 ± 3.91	34.48 ± 4.34	**< 0.001**
PAb, mg/L, mean (range)	191 (154–229.5)	158 (126, 194)	**< 0.001**
GLB, g/L, mean (range)	27.15 (23.35, 29.95)	27.70 (24.90, 30.80)	0.110
HB, g/L, mean ± SD	120.02 ± 18.96	108.24 ± 20.99	**< 0.001**
LYM, × 10^9/L, mean (range)	1.30 (0.98, 1.68)	1.12 (0.87, 1.50)	**0.004**
NEUT, × 10^9/L, mean (range)	5.52 (4.31, 7.16)	4.97 (3.92, 6.43)	**0.035**
PNI, mean ± SD	44.54 ± 5.05	39.30 ± 4.99	**< 0.001**

Note: Bold text represents confounding factors with *P* < 0.10.

Abbreviations: RTA, road traffic accidents; ASA, American Society of Anesthesiologists; Post-, postoperative; PCIA, patient-controlled intravenous analgesia; PCEA, patient-controlled epidural analgesia; Intra-, intraoperative; ALB, albumin; SD, standard deviation; PAb, prealbumin; GLB, globulin; HB, haemoglobin; LYM, lymphocyte counts; NEUT, neutrophil counts; PNI, prognostic nutritional index.

Statistical analysis

Continuous data are presented as mean with standard deviation or median (interquartile range) according to statistical distribution (assumption of normality assessed using the Kolmogorov-Smirnov test). Categorical parameters are presented as frequencies and associated percentages. A Student's t-test was used to analyse continuous variables with normal distribution, and a Mann-Whitney U test was used to analyse continuous variables with non-normal distribution and ordinal variables (ASA, surgical grades, and time to admission). A chi-squared or Fisher's exact test was employed to analyse categorical variables. In these analyses, variables with unadjusted *P* < 0.10 were identified as confounding factors and were included in multivariate regression analyses to determine independent predictors of perioperative adverse outcomes. The results are expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). The discriminatory ability of independent predictors was assessed using the receiver operating characteristic (ROC) curve analysis. Optimal cut-off values were obtained using the Youden index, and DeLong's test was used to compare the area under the curve (AUC) with MedCalc statistical software version 19.3.1 (MedCalc Software Ltd., Ostend, Belgium). A *P value of* < 0.05 was considered statistically significant. All tests were two-sided. All statistical analyses were conducted using Statistical Package for Social Sciences version 17.0 (IBM SPSS Statistics for Windows, Corp., Armonk, NY, USA).

Results

Patients

A total of 159 (46.4%) patients underwent surgery for femoral fractures with perioperative adverse outcomes. Of these patients, 123 (35.9%) had lower limb vein thrombus, 68 (19.8%) had hospital-acquired pneumonia, 6 (1.7%) were transferred to postoperative ICU, 4 (1.2%) had pulmonary embolism, 3 (0.9%) died during hospitalisation, 2 (0.6%) had incision disunion, and 7 (2.0%) had other adverse outcomes, including renal and liver function impairment, acute heart failure, acute cerebral infarction, and stress gastroenteritis (Table 1).

Confounding and independent factors

As shown in Table 1, age; hypertension; combined injuries; time to admission; ASA classification; operative types; the ratio of blood transfusion; intraoperative blood loss; ALB, PAb, and HB levels; LYM counts; NEUT counts; and PNI were associated with adverse outcomes (all P values < 0.10). All the above confounding factors, except ALB levels (which showed collinearity with PNI), were included in multivariate regression analyses to determine independent predictors. As shown in Table 2, PNI (OR: 0.819, 95% CI: 0.754–0.889, $P < 0.001$), age (OR: 1.042, 95% CI: 1.020–1.066, $P < 0.001$), time to admission (OR: 1.404, 95% CI: 1.117–1.765, P = 0.004), hypertension (OR: 1.912, 95% CI: 1.049–3.488, $P = 0.034$), combined injures (OR: 2.739, 95% CI: 1.338–5.607, $P = 0.006$), and operation types (OR: 3.696, 95% CI: 1.913–7.138, $P < 0.001$) were identified as independent factors for perioperative adverse outcomes.

Table 2
Multivariate regression analyses of confounding factors

Confounding factors	**OR (95%CI)**	***P*-values**
PNI (per 1)	0.819 (0.754, 0.889)	**< 0.001**
Age (per 1 year)	1.042 (1.020, 1.066)	**< 0.001**
Time to admission (per 1)	1.404 (1.117, 1.765)	**0.004**
Hypertension (ref: no)	1.912 (1.049, 3.488)	**0.034**
Combined injuries (ref: no)	2.739 (1.338, 5.607)	**0.006**
Operation types (ref: hip replacement)	3.696 (1.913, 7.138)	**< 0.001**
ASA (per [illegible])	1.357 (0.706, 2.606)	0.360
Blood transfusion (ref: no)	1.414 (0.737, 2.715)	0.297
Intra-blood loss (per 1×10^2 mL)	1.110 (0.950, 1.296)	0.188
PAb (per 1 mg/L)	1.002 (0.996, 1.009)	0.421
HB (per 1 g/L)	1.014 (0.995, 1.033)	0.157
LYM (per 1×10^9/L)	1.760 (0.896, 3.459)	0.101
NEUT (per 1×10^9/L)	1.053 (0.951, 1.165)	0.319

Note: The ALB level was not included in the model and showed significant collinearity with PNI. Bold fonts represent independent factors with $P < 0.05$.

Abbreviations: PNI, prognostic nutritional index; ASA, American Society of Anesthesiologists; Intra-, intraoperative; PAb, prealbumin; HB, haemoglobin; LYM, lymphocyte counts; NEUT, neutrophil counts

AUC and optimal cut-off values of PNI, age, time to admission, and ALB

Predictive values of independent factors (PNI, age, and time to admission) were assessed using the ROC curve analysis. Based on the AUC (PNI: 0.772, 95% CI: 0.723–0.821, $P < 0.001$; age: 0.678, 95% CI: 0.622–0.734, $P < 0.001$; time to admission: 0.585, 95% CI: 0.525–0.646, $P = 0.006$), the PNI had the most optimal discrimination ability and was superior to other independent predictors (age vs. PNI, $P = 0.002$; time to admission vs. PNI, $P < 0.001$). Because the ALB level is one main measure included in the PNI, there might be a relationship between ALB and adverse outcomes. However, the PNI was still a better predictor ($P = 0.038$) than the ALB level (0.736, 95% CI: 0.683–0.790, $P < 0.001$). The optimal cut-off values of PNI, age, time to admission, and ALB were 42.425, 55.5 years, 2 days, and 36.35 g/L, respectively (Table 3).

Table 3
Comparison of the AUC for PNI, age, time to admission, and ALB

	AUC (95%CI)	Sensitivity	Specificity	*P*	$Youden_{max}$	Threshold	*P**
PNI	0.772 (0.723, 0.821)	0.696	0.730	**< 0.001**	0.425	42.425	
Age	0.678 (0.622, 0.734)	0.799	0.451	**< 0.001**	0.250	55.5 years	**0.002**
Time to admission	0.585 (0.525, 0.646)	0.491	0.690	**0.006**	0.181	2 days	**< 0.001**
ALB	0.736 (0.683, 0.790)	0.679	0.714	**< 0.001**	0.384	36.35 g/L	**0.038**

Note: Bold fonts represent statistical significance, $P < 0.05$; $P^* < 0.05$ *vs.* PNI.

Abbreviations: AUC, area under the curve; PNI, prognostic nutritional index; ALB: albumin; CI, confidence interval.

Discussion

This study found that PNI, age, time to admission, hypertension, combined injuries, and operation types were independent factors for perioperative adverse outcomes in patients with femoral fractures, and PNI was a better independent predictor than age and time to admission. Our findings suggest that preoperative nutritional status cannot be underestimated and that interventions should be considered for patients with femoral fractures, where necessary.

The PNI uses the combined effects of hypoalbuminemia and lymphocytopenia to assess the immunologic and nutritional aspects of surgical patients (13, 17), and it is a pre-treatment nutritional risk stratification tool (18). Accumulating evidence indicates that approximately 20–40% of the patients show an acute, prolonged, and profound decrease in serum albumin levels after surgery (17), and this is even more serious in patients with femoral fractures; lower serum albumin levels and total lymphocyte counts are important risk factors for predicting the 1-year mortality of elderly patients with intertrochanteric fractures (19). Consistently, in this study, multivariate regression analysis showed that the nutritional status at admission was negatively correlated with perioperative adverse outcomes in patients with femoral fractures. Although age ($P < 0.001$), time to admission ($P = 0.004$), hypertension ($P = 0.034$), combined injures ($P = 0.006$), and operative types ($P < 0.001$) were also independent predictors, they are factors that are not necessarily controllable. Notably, the ROC curve analysis showed that PNI could provide more accurate prediction than other independent predictors in this study, including age and time to admission. Because the ALB level is one main measure included in the PNI (in addition to lymphocyte concentration), the ALB level might also be associated with adverse outcomes. Nevertheless, the PNI was superior to ALB in predicting perioperative adverse outcomes in patients with femoral fractures (P = 0.038). Collectively, PNI was a better and regulatable predictor of perioperative adverse outcomes. Therefore, nutritional assessment at admission and appropriate intervention strategies are necessary for patients with femoral fractures.

The conservative therapy of traditional Chinese orthopaedics is easily accepted by patients (particularly the elderly population) in China, especially in minority nationality regions (Guizhou is a multi-ethnic province of China). Some patients might choose conservative treatment using Chinese medicine in Chinese medical clinics or at home before a surgical operation. Therefore, it is reasonable that some patients were admitted to the hospital after sustaining the fracture for > 22 days in this study. Although traditional Chinese medicine has a long history and has curative effects on fracture rehabilitation, our findings suggest that early admission after trauma (within 2 days) for surgical treatment is beneficial to patients with femoral fractures, especially elderly patients.

Hypertension is closely related to vascular endothelial cell injury and is often accompanied by dyslipidaemia, and both vascular endothelial cell injury and dyslipidaemia are associated with the formation of venous thrombus. In this study, we observed that thrombus accounted for 77.4% (123/159) of perioperative adverse outcomes. This finding suggests that hypertension is an independent risk factor for perioperative adverse outcomes.

Operation types were classified into only two primary categories in this study: hemi/total hip replacement and internal fixation (mainly consisting of intramedullary nailing, cannulated-screw, and plate-screw internal fixation). The former is primarily performed in elderly patients with proximal femoral fractures, and the latter is performed commonly in younger or non-hip fracture patients. There are differences in incision, operating time, degree of ache, blood loss, and hospital stay among patients treated by different surgical methods. This present study comprehensively evaluated the above-mentioned surgery-related factors using univariate and multivariate analyses. The results indicated that the number of patients with femoral fractures who underwent internal fixation was 3.7 times as many as that of patients with femoral fractures who underwent hemi/total-hip replacement. The possible reasons were more severe pain, bleeding, inflammation, activity limitation, and a longer bedridden period in internal fixation-treated patients than in hemi/total-hip replacement patients.

There are several limitations of this study. First, the body mass index (BMI) was not evaluated in this study. The BMI is an indicator for the assessment of nutritional status and a good predictor of morbidity and mortality (20); however, the height values were not documented in this study, mainly because patients with femoral fractures were unable to stand up to provide an accurate height measurement. Second, the lipid profile was not measured in most enrolled patients. Further studies are needed to evaluate the lipid profile (total cholesterol, triglycerides, and lipoprotein levels) because the lipid profile is associated with the risk of venous thrombus (21–23). Third, the duration that a patient is bedridden is closely associated with lower limb vein thrombus, hypostatic pneumonia, and bedsores, and it was not assessed in this retrospective study. Fourth, we did not observe the long-term complications and mortality. Further studies are needed to evaluate the aforementioned issues and explore the effects of preoperative nutritional treatment on perioperative adverse outcomes in patients with femoral fractures.

Conclusions

In conclusion, this study showed that age, hypertension, combined injuries, and internal fixation were independent risk factors for perioperative adverse outcomes in patients with femoral fractures, and earlier admission to hospital for treatment and improved preoperative nutrition were associated with a significant decrease in the incidence of perioperative adverse outcomes. Notably, the PNI was a better and regulatable independent predictor of outcomes. Our findings suggest that preoperative nutritional interventions should be considered for patients with femoral fractures.

List Of Abbreviations

AIMS, Anesthesia Information System

ALB, albumin

ASA, American Society of Anesthesiologists

AUC, area under the curve

BMI, body mass index

CI, confidence interval

GLB, globulin

HB, haemoglobin

HIS, Hospital Information System

ICD-10, International Classification of Diseases, Tenth Revision

ICU, intensive care unit

LYM, lymphocyte

NEUT, neutrophil

OR, odds ratio

PAb, prealbumin

PNI, prognostic nutritional index

ROC, receiver operating characteristic

Declarations

Ethics approval and consent to participate

This retrospective study (reference number: KLL-2020-022) was approved by the Research Ethics Committee of Affiliated Hospital of Zunyi Medical University. The need for informed consent was waived due to the anonymous nature of the data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MH and QF designed and oversaw the study, prepared the statistical analysis plan, conducted the data analysis, and wrote the manuscript; YZ, DL, XL, SX, JP, and ZZ contributed to the design; ZZ revised the paper and had primary responsibility for the final content. All authors read and approved the final manuscript.

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Figures

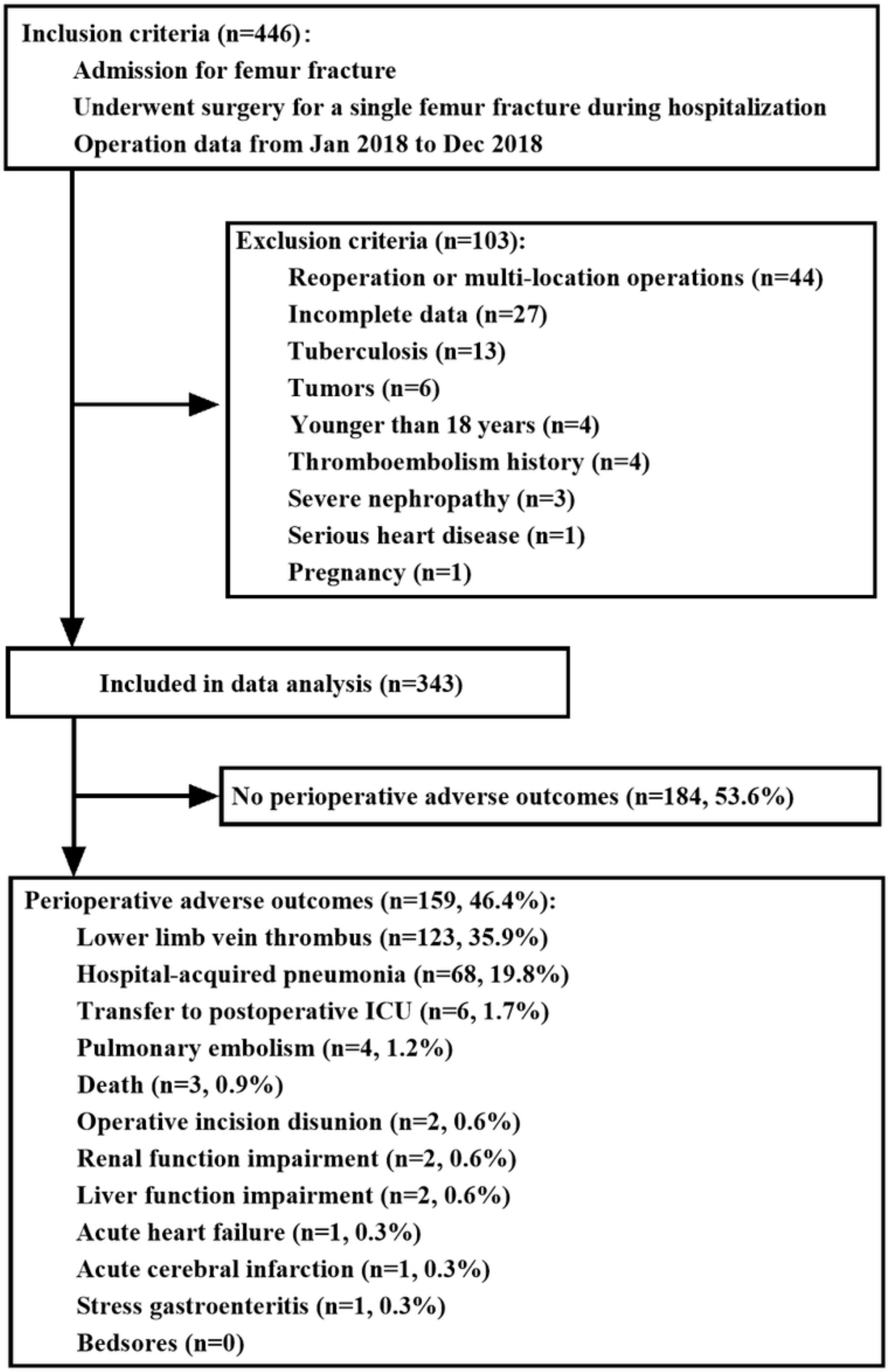

Figure 1

Flow chart of patient inclusion Abbreviations: ICU, intensive care unit.