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Multiple preoperative biomarkers are associated with incidence of surgical site infection following surgeries of ankle fractures

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Abstract
The aim of the study was to investigate the epidemiologic characteristics of surgical site infection (SSI) following surgeries of ankle fractures. This was a retrospective study. Patients who underwent surgeries for ankle fractures in our hospital between January 2016 and June 2019 were included. Inpatient medical records were inquired for data collection, including demographics, comorbidities, injury-related data, laboratory biomarkers, and confirmation of the SSI cases. Univariate analyses and multivariate logistic regression analyses were used to identify the independent risk factors. Among the 1532 patients, 45 had a postoperative SSI, indicating the incidence rate of 2.9%. About 18% of SSIs were identified after discharge. Twenty percent of SSIs were caused by mixed bacteria, and 39% were caused by drug-resistant bacteria. In the final multivariate model, 7 factors including 5 biomarkers were identified to be independently associated with SSI: gender (male vs female, OR, 2.69; 95% CI, 1.33-4.76), perioperative blood transfusion (OR. 3.02; 95% CI, 1.30-7.04), albumin <35 g/L (OR, 2.87; 95% CI, 1.31-6.31), lower high-density lipoprotein cholesterol (HDL-C) (OR, 2.34; 95% CI, 1.19-4.60), haemoglobin (OR, 2.16; 95% CI, 1.03-4.67), elevated alanine aminotransferase (OR, 2.09; 95% CI, 1.10-3.95) and neutrophile/lymphocyte rate (NLR, OR, 3.45; 95% CI, 1.33-6.74). These epidemiologic data on SSI may help counsel patients about the risk of SSI, individualised assessment of the risk factors, and accordingly the risk stratification.

KEYWORDS
ankle fracture, biomarker, epidemiology, surgical site infection

1 | INTRODUCTION

Ankle fracture is a most common fracture in department of emergency and orthopaedics, representing 7.6% of all adult fractures,[1] with an incidence of 37 to 108 per 100 000 person-years.[2-4] Because of its special anatomic features, most of ankle fractures involve the articular surface and 50% to 80% of them require surgical interventions.[1,4] However, even promptly surgically treated, a certain proportion of patients would be compromised by the unfavourable outcome, and surgical site infection (SSI) was an important cause.[5] It was reported that 24.1%

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of the unplanned readmissions were related to SSI.[6] In addition, SSI significantly prolonged the hospitalisation stay by 6 to 12 days and increased the medical care costs.[7] Therefore, understanding of epidemiologic characteristics about SSI especially identification of the related risk factors is of importance in individualised assessment of infection risk and accordingly the targeted prevention.

By far, numerous factors associated with SSI following surgeries of ankle fractures have been identified, which involved demographics, injury, comorbidities, surgery, and the postoperative management. However, very few studies focused on the preoperative biomarkers. One major reason for this phenomenon might be the great variability of biomarkers, especially after the trauma.[8] In fact, the role of these biomarkers in predicting postoperative complications including SSI was underestimated. Hypoalbuminemia was a well-known serum marker that is related to numerous postoperative complications.[9] Hyperglycaemia was demonstrated to be independently associated with postoperative 31-day SSI, even in a subgroup of orthopaedic trauma patients without a history of diabetes.[10] In recent years, neutrophil-to-lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have been increasingly emphasised and were showed to be predictive for mortality,[11] infectious events,[12] knee osteoarthritis severity,[13] and deep venous thrombosis.[14]

Review of the literature showed very few data about biomarkers with postoperative SSI following orthopaedic surgeries. As a simple and inexpensive measurement, biomarkers should be further explored, especially their predictive value in the postoperative complications. In this study, our aim was to evaluate the incidence of SSI following surgeries of ankle fractures and identify the associated risk factors. We hypothesise that some preoperative biomarkers are independently associated with the postoperative SSI.

Key Messages

- the overall incidence of SSI following surgery of ankle fracture was 2.9% within postoperative 1 year
- drug-resistant bacteria and mixed bacteria causative SSI remain an issue, taking 30% and 19.5% of all SSIs, and should be more emphasised
- multiple preoperative biomarkers were identified to be associated with SSI, and their role in SSI requires further research

2 | METHODS

The method of this study was performed in accordance with the STROCSS (Strengthening the Reporting of Cohort Studies in Surgery) guidelines. It was designed as a retrospective study and approved by the ethics committee of the 3rd Hospital of Hebei Medical University, which waived the requirement for informed consent because of the anonymous nature of the data.

3 | INCLUSION AND EXCLUSION CRITERIA

Between January 2016 and June 2019, patients who underwent surgeries of ankle fractures in our hospital were included. The relevant baseline characteristics were obtained by inquiring patient's hospitalisation medical records. Inclusion criteria were adult patients (18 years or older), surgical treatment for ankle fracture, and complete data available in medical records. Exclusion criteria were pathological (metastatic) or old fracture (> 3 weeks since occurrence), open fracture, concurrent fractures in other locations, and incomplete medical records.

4 | DIAGNOSIS OF SSI

SSI was diagnosed in consistency with the criteria proposed by Center for Disease Control (CDC),[15] as an infection that occurred within postoperative 1 year if implantation was in place. A deep SSI was classified if an infection met at least one of the following: involving deep soft tissue, muscle or fascia; wound discharge or dehiscence; visible abscess or gangrenosis that required surgical debridement or even hardware removal. Superficial SSI was defined as redness, swelling, hot, pain related to the surgical site, responsive well to antibiotic treatment, but not meeting the criteria for diagnosis of deep SSI.

SSI was determined based on the description of signs and symptoms from patients' index hospitalisation EMRs for ankle fracture surgery, bacteria culture results, and antibiotic sensitivity from microbiological records. We also inquired the rehospitalisation EMRs for potential SSI occurrence.

5 | DATA COLLECTION

Medical records, picture archiving and communication system (PACS), and operation reports were inquired for relevant data. The demographic data included age, gender, residence (urban or rural), body mass index (BMI), cigarette smoking, and alcohol consumption. The comorbidities included hypertension, diabetes, chronic heart disease, and previous history of any surgery, all of which were self-reported by patients. Injury-related data included fracture location (uni, bi-, or trimalleolar fracture), injury mechanism (low- or high-energy trauma), accompanied dislocation, and American Society of Anesthesiologists (ASA) classification. Low-energy injury was defined as an injury caused by a fall from a standing height, and others such as fall from a height and motor accidents were high-energy injury.

The biomarkers from preoperative laboratory tests included total protein (TP) level, albumin (ALB) level, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALT), sodium ions (Na+), total bilirubin (TBIL), indirect bilirubin (IBIL), direct bilirubin (DBIL), fasting blood glucose (FBG) level, preoperative red blood cell (RBC) count, white blood cell (WBC) count, neutrophile (NEUT) count, lymphocyte (LYM) count, neutrophile/lymphocyte rate (NLR), haemoglobin (HGB) level, haematocrit (HCT), platelet (PLT), platelet/lymphocyte rate (PLR), red blood cell distribution width (RDW), serum total cholesterol (TC) level, triglyceride (TG) level, low-density lipoprotein (LDL-C) level, high-density lipoprotein (HDL-C) level, very low-density lipoprotein (VLDL) level, lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBDH), uric acid (UA), urea, and D-dimer level. If patients had multiple laboratory tests before operation, laboratory tests closest to the operation were chosen for data analysis.

6 | STATISTICAL ANALYSIS

Continuous variables were expressed by mean and SD and were evaluated by Student's t test or Mann Whitney U test when appropriate. The categorical data were expressed as number and percentage (%) and were evaluated by chi-square or Fisher's exact test. As for NLR and PLR that no normal reference ranges have been established in the literature or guidelines, the relevant data were used to construct a receiver operating characteristic (ROC) curve to determine a cut-off value, at which the specificity plus sensitivity is the maximum and above which the risk of SSI was significantly increased. Area under the curve (AUC) was calculated, with $P < .05$ considered statistically significant.

Multivariate logistics regression model was used to identify the independent risk factors associated with SSI, using the stepwise backward elimination method. Variables with $P < .10$ were retained in the final model, and the correlation strength is indicated by odd ratio (OR) and 95% confidence interval (95% CI).The statistical test level was set as $P < .05$. Hosmer-Lemeshow (H-L) test was used to evaluate the fitness of the final model, and $P > .05$ represented the acceptable result. SPSS23.0 was used to perform all the tests (IBM, Armonk, New York).

7 | RESULTS

A total of 1532 patients with 1555 ankle fracture treated surgically were included for data analysis, consisting of 888 males and 644 females, with an average of 43.0 years (SD, 15.1; range, 18-95; median, 43.0). Unimalleolar fracture accounted for 45.8% (712/1555), followed by trimalleolar fractures (496, 31.9%) and bimalleolar fractures (347, 22.3%). There were 284 (18.3%) fractures that were accompanied by dislocation or subluxation. The total hospitalisation stay was 16.6 days in average (SD, 14.0; median, 14; range, 2-341).

Of the 1532 patients, 45 had a postoperative SSI and the incidence rate was 2.9%, with 0.8% (12/1532) for deep and 2.1% (33/1532) for superficial SSI. Thirty-seven (82.2%) cases were identified during the hospitalisation stay for ankle surgery, and 8 (17.8%) were identified after

TABLE 1 Frequency of causative bacterial

Bacteria	Frequency
Single-bacteria causing SSI	33
Staphylococcus aureus	8
Pseudomonas aeruginosa	6
Enterobacter cloacae	4
Escherichia coli	3
Acinetobacter baumannii	3
Staphylococcus epidermidis	2
Proteus mirabilis	2
Klebsiella pneumoniae pneumoniae	2
Streptococcus pyogenes	1
Coagulase-negative staphylococcus	1
Enterobacter cinerum	1
Mixed-bacteria causing SSI	8
S aureus + *Coagulase-negative staphylococcus*	2
S aureus + *E cloacae*	1
S aureus + *Alcaligenes xylosoxidans*	1
S aureus + *S epidermidis* + *Acinetobacter baumannii*	1
S epidermidis+	1
E cloacae + *Citrobacter freundii* + *P aeruginosa*	1
Coagulase-negative staphylococcus + *E cloacae*	1

Abbreviation: SSI, surgical site infection.

TABLE 2 Univariate analyses of risk factors associated with SSI following ankle fracture surgeries

Variables	Number (%) of DVT (n = 45)	Number (%) of non-DVT (n = 1487)	*P*
Gender (male)	37 (82.2)	851 (57.2)	.001
Age (years)	55.6 ± 14.6	43.4 ± 15.0	<.001
18–44	22 (48.9)	783 (52.7)	.881
45–64	18 (40.1)	555 (37.3)	
65 or older	5 (11.1)	149 (10.0)	
Residence			.002
Rural	35 (77.8)	815 (54.8)	
Urban	10 (22.2)	672 (45.2)	
BMI (kg/m^2)	26.4 ± 3.3	25.9 ± 4.1	.573
18.5–23.9	7 (15.6)	31 (2.1)	<.001
<18.5	0	441 (29.7)	
24.0–27.9	21 (46.7)	606 (40.8)	
≥28.0	17 (37.8)	379 (25.5)	
Cigarette smoking	10 (22.2)	236 (15.9)	.253
Alcohol consumption	14 (31.1)	395 (26.7)	.497
Diabetes mellitus	9 (20.0)	196 (13.2)	.186
Hypertension	6 (13.3)	202 (13.6)	.961
Chronic heart disease	3 (6.7)	67 (4.5)	.494
Cerebrovascular disease	0	28 (1.9)	.353
Chronic liver disease	2 (4.4)	33 (2.2)	.325
History of allergies to any medications	7 (15.6)	215 (14.5)	.837
History of any surgery	8 (17.8)	126 (8.5)	.030
Injury mechanism (high energy)	15 (33.3)	375 (25.2)	.218
Fracture location			.010
Unimalleolar	28 (62.2)	674 (45.3)	
Bimalleolar	12 (26.7)	332 (22.3)	
Trimalleolar	5 (11.5)	481 (32.3)	
Accompanied dislocation or subluxation	7 (15.6)	275 (18.5)	.616
Preoperative stay	6.6 ± 6.5	5.7 ± 3.9	.151
Total hospital stay	37.4 ± 28.2	15.8 ± 13.3	<.001
Anaesthesia (general)	11 (24.4)	314 (21.1)	.591
ASA class			.268
I	5 (11.1)	258 (17.4)	
II	32 (71.1)	1062 (71.4)	
III or above	8 (17.8)	167 (11.2)	
Operation timing			.092
Day	42 (93.3)	1449 (97.4)	
Night	3 (6.7)	38 (2.6)	
Type of fracture reduction			.780
Closed	4 (8.9)	41 (2.8)	
Open	41 (91.1)	1420 (97.2)	
Fixation type			.298
Screw or pins only	10 (22.2)	437 (29.4)	
Plate and screws	35 (77.8)	1050 (70.6)	
Bone grafting	0	58 (3.9)	.177
Intraoperative bleeding	338.2 ± 396.4	170.2 ± 211.0	<.001

(Continues)

TABLE 2 (Continued)

Variables	Number (%) of DVT (n = 45)	Number (%) of non-DVT (n = 1487)	*P*
Perioperative blood transfusion (yes)	10 (22.2)	49 (3.3)	<.001
Surgical duration	134.9 ± 74.4	130.7 ± 58.2	.664
Intraoperative prophylactic use of antibiotics	43 (95.2)	1416 (95.2)	1.000
Postoperative use of antibiotics	41 (91.1)	1386 (93.2)	.583
TP (<60 g/L)	23 (51.1)	264 (17.8)	<.001
ALB (<35 g/L)	20 (44.4)	185 (12.4)	<0.001
FBG (>6.1 mmol/L)	14 (31.1)	433 (29.1)	.772
UA (> upper limit)	3 (6.7)	186 (12.5)	.240
NA+(mmol/L)			.163
135–145	36 (80.0)	1324 (89.0)	
<135	7 (15.6)	123 (8.3)	
>145	2 (4.4)	40 (2.7)	
TC (>5.2 mmol/L)	1 (2.2)	251 (16.9)	.009
TG (>1.7 mmol/L)	10 (22.2)	278 (18.7)	.551
LDL-C (>3.37 mmol/L)	3 (6.7)	265 (17.8)	.052
HDL-C (<1.1 mmol/L)	31 (68.9)	528 (35.3)	<.001
VLDL (>0.78 mmol/L)	10 (22.2)	270 (18.2)	.487
ALT	23 (51.1)	324 (21.8)	<.001
AST	10 (22.2)	226 (15.2)	.198
TBIL	7 (15.6)	101 (6.8)	.024
DBIL	15 (33.3)	340 (22.9)	.101
IBIL	7 (15.6)	234 (15.7)	.974
ALP	4 (8.9)	53 (3.6)	.063
NLR	6.5 ± 5.9	4.6 ± 3.1	<.001
≥7.8	15 (33.3)	166 (11.2)	<.001
PLR	198.9 ± 130.5	170.4 ± 85.0	.028
≥200	18 (40.0)	388 (26.1)	.037
UA (>upper limit)	3 (6.7)	186 (12.5)	.240
LDH	15 (33.3)	205 (13.8)	<.001
HBDH	11 (24.4)	180 (12.1)	.014
UREA	1 (2.2)	40 (2.7)	.848
WBC (>10 × 10^9/L)	17 (37.8)	373 (25.8)	.070
NEUT (>6.3 × 10^9/L)	24 (53.3)	632 (42.5)	.148
LYM (<1.1 × 10^9/L)	12 (26.7)	311 (20.9)	.351
RBC (<lower limit)	24 (53.3)	295 (19.8)	<.001
HGB (<lower limit)	24 (53.3)	289 (19.4)	<.001
HCT (<lower limit)	30 (66.7)	604 (40.6)	<.001
PLT (>300 × 10^9/L)	13 (28.9)	269 (18.1)	.066
PDW (>18.1%)	6 (13.3)	141 (9.5)	.387
RDW (>16.5%)	4 (8.9)	55 (3.7)	.075
D-Dimer (>0.3 mg/L)	21 (46.7)	902 (60.7)	.059

Note: RBC: reference range: female, 3.5-5.0 × 10^{12}/L; males, 4.0-5.5 × 10^{12}/L; HGB: reference range: females, 110-150 g/L; males, 120-160 g/L; UA: males, 208-408 umol/L, females, 155-357 μmol/L; HCT: 40% to 50%; PLT: 100-300 × 10^9/L.

Abbreviations: ALB, albumin; ASA, American Society of Anesthesiologists; BMI, body mass index; FBG, fasting blood glucose; HCT, haematocrit; HDL-C, high density lipoprotein; HGB, haemoglobin; LDL-C, low density lipoprotein; LYM, lymphocyte; NEUT, neutrophile; PDW, platelet distribution width; PLT, platelet; RBC, red blood cell; RDW, red cell distribution width; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid; VLDL, very low-density lipoprotein; WBC, white blood cell.

TABLE 3 Multivariate analyses of risk factors associated with SSI following ankle fracture surgeries

Variable	OR and 95% CI	*P* value
Gender (male vs female)	2.69 (1.33-4.76)	.021
Living area (rural vs urban)	1.94 (0.92-4.26)	.067
Perioperative blood transfusion	3.02 (1.30-7.04)	.010
ALB < 35 g/L	2.87 (1.31-6.31)	.009
HDL-C (<1.1 mmol/L)	2.34 (1.19-4.60)	.013
HGB < lower limit	2.16 (1.03-4.67)	.042
ALT > 40 U/L	2.09 (1.10-3.95)	.024
NLR ≥ 7.8	3.45 (1.33-6.74)	.008

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; CI, confidence interval; HDL-C, high-density lipoproteincholesterol; HGB, haemoglobin; NLR, neutrophile/lymphocyte rate; OR, odd ratio; SSI, surgical site infection.

discharge. Swabs or purulent secretion culture showed positive result in 41/45 patients, with mixed bacterial infection in 8 (19.5%) and single bacterial infection in 33 (80.5%). In SSIs caused by single bacteria, *Staphylococcus aureus* was the most common bacteria (8, 19.5%), followed by *Pseudomonas aeruginosa* (6, 14.6%), *Enterobacter cloacae* (4, 9.8%), and *Escherichia coli* (3, 7.3%), which were detailed in Table 1. The drug susceptibility results showed *Methicillin-Resistant Staphylococcus aureus* (MRSA) in 7 cases, *Methicillin-Resistant Coagulase-Negative Staphylococci* (MRCNS) in 4, *extended-spectrum beta-lactamase* (ESBL) of *Escherichia coli* in 3, and *Carbapenem-resistant acinetobacter baumannii* (CR-AB) in 1. The interval between surgery and diagnosis of SSI was at median of 6.5 days, ranging from 1 to 129 days. The total hospital stay for the index ankle surgery was 43.3 (SD, 28.3) days in patients with SSI, significantly more than that (15.8 ± 13.3) in those without SSI ($P < .001$).

The analyses of ROC curve showed the infection point corresponded to the NLR and PLR was 7.8 and 200, and the area under the curve (AUC) was 0.58 (95% CI, 0.48-0.67; $P = .035$) and 0.61 (95% CI, 0.42-0.78, $P = .047$), respectively. It was significantly different between SSI and non-SSI in terms of gender, age, living residence, BMI in categorical form, history of any surgery, fracture location, intraoperative bleeding, and perioperative blood transfusion ($P < .05$). As for biomarkers, there were 15 significant variables, including TP, ALB, TC, HDH-C, ALT, AST, TBIL, and NLR in continuous and categorical form, PLR in continuous and categorical form, LDH, HBDH, RBC, HGB, and HCT ($P < .05$) (Table 2).

In the multivariate model, the abovementioned 23 variables together with operation timing ($P = .092$), LDL-C ($P = .052$), ALP ($P = .063$), WBC ($P = .070$), PLT ($P = .066$), RDW ($P = .075$) and D-dimer ($P = .059$) were entered. In the final model, 7 factors including 5 biomarkers were identified to be independently associated with SSI: gender, perioperative blood transfusion, ALB, HDL-C, HGB, ALT, and elevated NLR (Table 3**)**. The H-L test demonstrated the adequate fitness of the final model ($X^2 = 3.817$, $P = .873$; Nagelkerke $R^2 = 0.219$).

8 | DISCUSSION

As a simple and inexpensive measurement index, preoperative biomarkers might have special value in predicting a certain complication, but relevant data on SSI following surgeries of ankle fracture are still scarce. In this study, we found the incidence rate of SSI was 2.9% and identified 7 independent associated factors, including 5 preoperative biomarkers. This tested our previous hypothesis.

Due to study design and heterogeneity of included patients among studies, greatly variable incidence rates were reported, 1.1% to 10% for deep SSI and 2.6% to 14.0% for superficial SSI.[16,17] Meng et al[7] reported the incidence rate of deep SSI was 2.83% in 2617 patients with ankle fracture treated by open reduction and internal fixation (ORIF). Shao et al[18] pooled the data in a meta-analysis of 8103 ankle fractures by ORIF and found the overall rate of SSI was 7.2%. In contrast, this study included ankle fractures reduced by either open or closed manner, and reported a comparable incidence of 2.9%. Schepers et al[19] demonstrated the significant effect of ankle fracture surgery on the occurrence of postoperative infection, but not found in this study.

It was of note that types of pathogenic bacteria causing SSI were greatly variable among studies. In the study by Meng et al,[7] no mixed bacteria-causative SSIs were reported and *S aureus* caused 39% of SSIs. In another study, the authors found 36% (9/25) of the SSIs were caused by mixed bacteria and 48% (12/25) were caused by *S aureus*.[16] In a study of spinal surgeries, the authors found that the 47.1% of the SSIs were caused by *S aureus*, but no mixed bacteria-causative SSIs was found.[20] By contrast, in our study, 14 types of pathogenic bacteria were involved, with a remarkable discrete distribution, from 3% to 24.2% in proportion. Another concern was the larger proportion (39.0%) of SSIs caused by the drug-resistant bacteria, about twofold as that in a previous study.[21] Postoperative overuse of antibiotics might be a notable cause, and in our study 93.1% of patients were prescribed postoperative antibiotics.

The gender difference in risk of infection issues has been little consistent across orthopaedic studies, and almost all the studies specified at ankle fractures did not identify the independent association with postoperative SSI.[2,7,16,18,22,23] In this study, we found the 2.69-fold increased risk of SSI in men. The precise mechanism remains unclear, but might be related to differences in skin colonisation or anatomy between men and women.[24] It was suggested in men who had thicker and coarser hair, the risk of infection was higher because hair growth and shaving interfere with wound dressing adherence.[25] However, some confounding factors that were more related to male gender could not be excluded such as lifestyles, fracture severity, and soft tissue damage, which require more studies to explore.

Perioperative blood transfusion has been demonstrated to increase the risk of infection issues in both orthopaedics and other subspecialty surgeries,[26,27] similar to as the preoperative anaemia status.[28] The poorer immunologic status associated with blood transfusion or anaemia status may be an important cause. In a previous study, authors found patients who received any allogeneic blood had a fourfold greater drop in nature killer cell at day 7, and also found the dose-dependent effect on SSI.[29] Dix et al[30] demonstrated the association of preoperative anaemia with infection and the prolonged hospital stay and also the bone union issues in hindfoot and ankle arthrodesis. We suggest that blood transfusion before ankle fracture surgery repair in those with anaemia may be beneficial, but it is more reasonable to determine which population would benefit most from the blood transfusion.

The lower ALB and HDL-C levels, elevated ALT level, and NLR were identified to be associated with increased risk of SSI, which had been extensively discussed in the studies of orthopaedics.[9,31,32] Abnormity of these biomarkers is more likely indication of a poorer nutritional, lower immune, and systematic inflammation status, but the stress effects from trauma could not be ruled out.[33,34] NLR as an inexpensive and readily obtained immune/inflammatory biomarker-derived index has been repeatedly discussed and demonstrated to be predictive of adverse affairs and even mortality, in cancer,[35] trauma,[31] cardiovascular diseases,[36] or autoimmune diseases.[37] In elective lumbar spinal surgery, NLR was also demonstrated to be predictive of postoperative SSI.[38] In fact, neutrophilia can be a manifestation of infection-induced inflammatory, and lymphocytes play an important role in the anti-infection immune response. Accordingly, the NLR, which was calculated by the neutrophils divided by lymphocytes, might combine the level of inflammatory and anti-infection reaction. So, in this study, NLR rather than the count of neutrophils or lymphocytes was identified to be independently associated with SSI. Another point should be noted that after traumatic fractures, these biomarkers have been consistently changing and each one presented the unique feature,[8] which deserved to be well defined on the basis of time since trauma. In our study, if one patient had multiple laboratory tests before the operation, the laboratory test closest to the operation was chosen for data analysis. Therefore, in consideration of the changes of biomarkers after trauma, our results might be of more value in predicting SSI occurrence, compared with the commonly used meaurement of biomarkers at admission.

There were several limitations of this study. Firstly, the retrospective design of this study might compromise the accuracy in data collection. Secondly, as every multivariate analysis, some potential factors that affect the occurrence of SSI could not be evaluated, such as chronic use of glucocorticoids and haemoglobin a1c level. Thirdly, the overall incidence rate of SSI was underestimated, because some patients who had an SSI but went to other hospitals for treatment were deemed to have no SSI. About 18% (275) of patients in this study were followed less than 1 year (4-11 months), which might have somewhat but little influence on the incidence rate of SSI, because the maximum interval between operation and SSI was 129 days.

In summary, we found the incidence rate of SSI following ankle fracture surgery was 2.9%. About 20% of the SSI were caused by mixed bacteria and 39% were drug resistant, representing a serious situation during treatment. Seven factors including multiple biomarkers were identified to be associated with SSI: gender (male vs female), perioperative blood transfusion, lower level of ALB, HDL-C and HGB, elevated ALT, and NLR. These risk factors, although not easily modifiable, may help counsel patients about the risk of SSI, individualised assessment, and accordingly the risk stratification.

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CONFLICT OF INTEREST

All the authors declared no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Yingze Zhang conceived the idea for the study; Yanbin Zhu designed the study. Wei Chen performed the statistical analyses. Song Liu and Ming Li prepared the figures and tables. All the authors interpreted the data and contributed to preparation of the manuscript. Dawei Liu, Yanbin Zhu, and Wei Chen prepared the manuscript and Dawei Liu revised the manuscript.

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