Correlation between surgical site infection and time-dependent blood platelet count in immunocompromised patients after femoral neck fracture

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Abstract
Objective: The incidence of surgical site infection (SSI) after femoral neck fracture is significantly higher in immunocompromised patients. This study was performed to explore the temporal changes of blood-related parameters in immunocompromised patients after femoral neck fracture repair and to determine the correlation between the platelet (PLT) count and SSI.

Methods: This study involved 101 immunocompromised patients who underwent repair of a femoral neck fracture from April 2018 to August 2019. SSI was confirmed by postoperative observation of the incision and B-mode ultrasound imaging examination. Blood parameter measurements and dynamic observation were performed 1, 3, 5, 7, and 14 days postoperatively.

Results: The procalcitonin concentration, D-dimer concentration, and PLT count were strongly correlated with temporal changes. The PLT count changes crossed between patients with and without SSI 3 to 5 days after surgery, and the PLT count increased in patients with SSI 3 to 5 days after surgery. The PLT count had high specificity and sensitivity for predicting SSI with a cut-off value of 167.5×10^9/L.

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Conclusion: The temporal changes of the PLT count in immunocompromised patients who have undergone femoral neck fracture repair can serve as an early warning of SSI.

Introduction

The incidence of postoperative infection in immunocompromised patients is increasing year by year. Such patients mainly include those with limb joint fractures caused by various types of trauma, fragility fractures caused by hypoimmunity-related osteoporosis, chronic degenerative diseases of the spine and joints, and various infections and bone tumors.[1,2]

Surgical site infection (SSI) is defined as a surgery-related infection that occurs within 30 days after surgery without implants and within 1 year after surgery with implants (such as surgery involving the use of pedicle screws, interbody cages, artificial discs, or prostheses). The various types of SSI include superficial incisional infection, deep incisional infection, and organ and tissue space infection. Surgical repair of femoral neck fractures often involves acute invasive procedures requiring implants or prostheses, and such patients are more likely to develop postoperative SSI.[3] The incidence of postoperative SSI is significantly higher in immunocompromised patients than in the general population because of the defective immune function of immunocompromised patients.[4] Few studies to date have focused on the risk factors for SSI related to femoral neck fracture in immunocompromised patients. Studies on the early warning signs and prevention of SSI are also lacking.

After femoral neck fracture in immunocompromised patients, many blood-related parameters change over time; these parameters include the platelet (PLT) count, erythrocyte sedimentation rate (ESR), procalcitonin (PCT) concentration, C-reactive protein (CRP) concentration, neutrophil count, white blood cell (WBC) count, blood glucose (GLU) concentration, albumin (ALB) concentration, and hemoglobin concentration. The present study focused on the changes in the following blood parameters preoperatively and at 1, 3, 5, 7, and 14 days postoperatively: PCT concentration, ESR, ALB concentration, aspartate aminotransferase (AST) concentration, PLT count, GLU concentration, lymphocyte count, red blood cell (RBC) count, WBC count, D-dimer concentration, alanine aminotransferase (ALT) concentration, CRP concentration, neutrophil count, CD4 count, CD8 count, creatinine concentration, hemoglobin concentration, blood urea nitrogen (BUN) concentration, and globulin (GLOB) concentration. Studies have shown that patients with postoperative SSI after surgery have an increased ESR and CRP concentration.[5,6] Risk factors for developing periprosthetic joint infection after orthopedic joint replacement include hypoimmunity and chronic renal failure. Correlations have also been found between SSI and the PCT concentration, ESR, CRP concentration, and D-dimer

concentration.[7] Changes in blood parameters during the postoperative rehabilitation period have the potential to be predictive of SSI in immunocompromised patients.

The present study was performed to explore the temporal changes of blood-related parameters in immunocompromised patients after femoral neck fracture repair and to determine the correlation between the PLT count and SSI.

Methods

Patients and ethics

This study involved 101 immunocompromised patients who underwent repair of femoral neck fractures from April 2018 to August 2019. Table 1 shows the relevant characteristics of the patients and SSIs.

The inclusion criteria were an age of 18 to 80 years, performance of femoral neck fracture repair and vertebroplasty with prosthesis implantation, and no history of other surgical procedures.

The exclusion criteria were an age of <18 or >80 years; poor cardiac, pulmonary, liver, or kidney function resulting in the inability to tolerate surgery; open femoral neck fractures requiring emergency repair; and preoperative SSI.

This study was approved by the Ethics Committee of the Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine (No. SHFH2017023). Written informed consent was obtained from all patients. The reporting of this study conforms to the STROBE guidelines.[8]

Diagnosis of SSI

The diagnosis of SSI was confirmed by postoperative observation of the incision and B-mode ultrasound imaging examination. All patients underwent femoral neck fracture repair with a sterile prosthesis and were assessed for the occurrence of postoperative SSI.

Table 1. Relevant characteristics of patients and SSIs.

Parameters			SSI		P
			No	Yes	
Sex	Male	98	83 (82.2)	15 (14.9)	0.614
	Female	3	3 (3.0)	0 (0.0)	
Age, years	<65	91	77 (76.2)	14 (13.9)	0.543
	≥65	10	9 (8.9)	1 (1.0)	
Diabetes	Yes	63	51 (50.5)	12 (11.9)	0.106
	No	38	35 (34.7)	3 (3.0)	
Smoke	Yes	56	48 (47.5)	8 (7.9)	0.538
	No	45	38 (37.6)	7 (6.9)	
Drinking	Yes	54	47 (46.5)	7 (6.9)	0.384
	No	47	39 (38.6)	8 (7.9)	
Hypertension	Yes	47	38 (37.6)	9 (8.9)	0.197
	No	54	48 (47.5)	6 (5.9)	
Obesity	Yes	35	28 (27.7)	7 (6.9)	0.220
	No	66	58 (57.4)	8 (7.9)	

Data are presented as n or n (%).
Fisher's exact test (including Yate's continuity correction) was used.
SSI, surgical site infection.

Blood parameters and dynamic observation

Changes in blood parameters (PCT, ESR, ALB, AST, PLTs, GLU, lymphocytes, RBCs, WBCs, D-dimers, ALT, CRP, neutrophils, CD4, CD8, creatinine, hemoglobin, BUN, and GLOB) and the observation time were monitored (changes in blood parameters were observed preoperatively and 1, 3, 5, 7, and 14 days postoperatively).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation. G*Power was used to calculate the sample size (the test family was t tests; the statistical test was "Means: Difference between two dependent means (matched pairs)"; the type of power analysis was "A priori: Compute required sample size-given α, power, and effect size"; the input parameter ("Tails") was two; the effect size dz was 0.5; the α error probability was 0.01; the power ($1 - β$ error probability) was 0.9905; the output parameter was a noncentrality parameter δ of 5.0249378; the critical t value was 2.6258905; Df was 100; the total sample size was 101; and the actual power was 0.9909837). Fisher's exact test (including Yate's continuity correction) was used. We used the correlation ratio ($η^2$) for interval and ratio variables and Cramér's V (a measure of association) for nominal variables. The Wilcoxon–Mann–Whitney test was used to calculate the effect size and conduct a power analysis of PLTs, D-dimers, ESR, and PCT between patients with and without SSI. Student's t-test was used to compare the data between two groups, and one-way analysis of variance was used for comparisons among three or more groups. Finally, we constructed receiver operating characteristic (ROC) curves and applied the area under the curve (AUC) to assess the accuracy and sensitivity of the PLT count, D-dimer concentration, ESR, and PCT concentration in diagnosing the degree of SSI. All graphics were drawn using R version 3.6.3 (https://www.r-project.org/).

Results

General changes in blood-related indicators over time

PCT, ESR, ALB, AST, and PLTs were at low levels before surgery and at 1 and 3 days after surgery; began to increase at 5 days after surgery; and remained at high levels thereafter. GLU, lymphocytes, RBCs, WBCs, D-dimers, ALT, and CRP increased only at 5 days after surgery and then remained at low levels before surgery, at 1 and 3 days after surgery, and at 7 and 14 days after surgery. Neutrophils, CD4, CD8, creatinine, hemoglobin, BUN, and GLOB were at high levels before surgery and at low levels after surgery (Figure 1).

Correlations among blood parameters

Pearson correlation was used to test the correlations among blood-related indicators. The absolute value of the correlation coefficient was used to assess the correlation: the closer the correlation coefficient was to 1 or −1, the stronger the correlation was, and the closer the correlation coefficient was to 0, and the weaker the correlation was. PLTs were positively correlated with GLOB, ALB, ESR, PCT, D-dimers, AST, ALT, and CD4 and negatively correlated with CD8, neutrophils, and CRP (Figure 2).

Correlation analysis among blood-related indicators and time

There were no correlations of temporal changes with CD8, CD4, WBCs, neutrophils, lymphocytes, RBCs, hemoglobin,
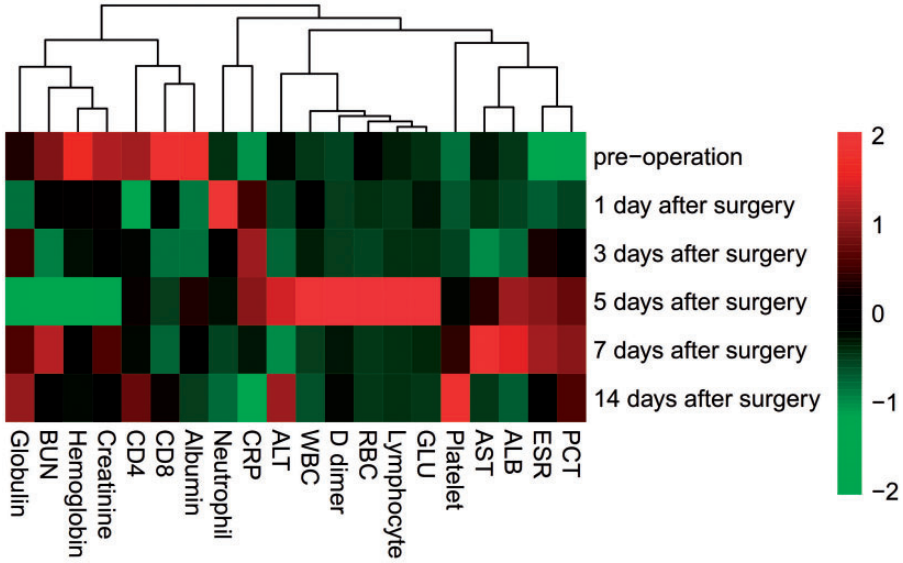
Figure 1. Heat map of general changes in blood-related indicators over time. BUN, blood urea nitrogen; CRP, C-reactive protein; ALT, alanine aminotransferase; WBC, white blood cells; RBC, red blood cells; GLU, glucose; AST, aspartate aminotransferase; ALB, albumin; ESR, erythrocyte sedimentation rate; PCT, procalcitonin.
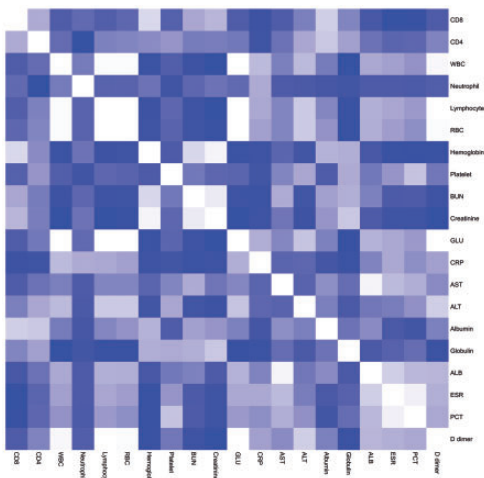

Figure 2. Correlations among blood parameters. WBC, white blood cells; RBC, red blood cells; BUN, blood urea nitrogen; GLU, glucose; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; ESR, erythrocyte sedimentation rate; PCT, procalcitonin.

BUN, creatinine, GLU, CRP, AST, ALT, ALB, GLOB, ALB, or ESR. However, a strong correlation was present between temporal changes and PCT, D-dimers, and PLTs (R = 0.73, 0.73, and 0.98, respectively; $P < 0.05$) (Figure 3). Furthermore, the power analysis of PLTs, D-dimers, ESR, and PCT showed significant differences between patients with and without SSI ($P < 0.05$) (Table 2).

Changes in PLT count stratified by presence or absence of SSI

The changes in the PLT count crossed between patients with and without SSI 3 to 5 days after surgery, and the PLT count increased in patients with SSI 3 to 5 days after surgery (Figure 4).

ROC curve analysis

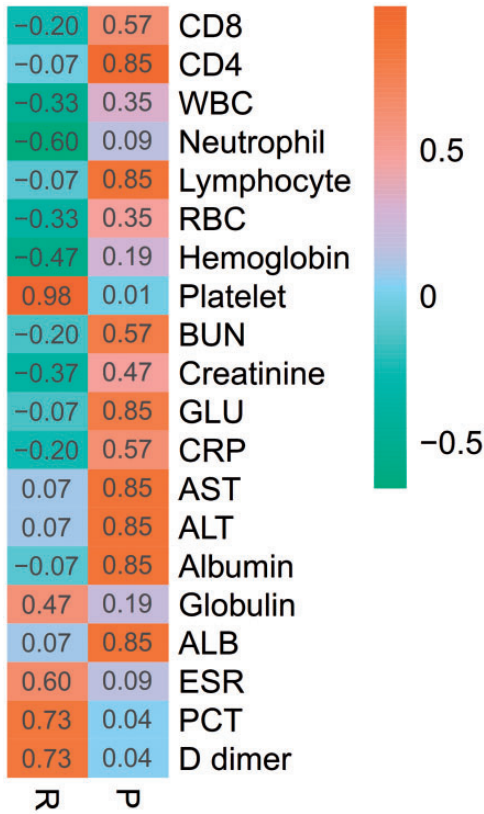Finally, we constructed ROC curves to determine the effect of the PLT count on

Figure 3. Correlations between blood-related indicators and time. WBC, white blood cells; RBC, red blood cells; BUN, blood urea nitrogen; GLU, glucose; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; ESR, erythrocyte sedimentation rate; PCT, procalcitonin.

the occurrence of SSI after femoral neck fracture repair in immunocompromised patients, and the AUC was used as a judgment of confidence. The PLT count had high specificity and sensitivity for predicting the occurrence of SSI after femoral neck fracture repair in immunocompromised patients (AUC, 0.921; $P < 0.001$), and the cut-off value of the PLT count was 167.5×10^9/L (sensitivity, 0.933; specificity, 0.767). The AUC of the D-dimer concentration for the occurrence of SSI via ROC analysis was 0.713 ($P = 0.008$). The AUC of the ESR for the occurrence of SSI via ROC analysis was 0.818 ($P < 0.001$). The AUC of the PCT concentration for the occurrence of SSI via ROC analysis was 0.790 ($P < 0.001$) (Figure 5).

Discussion

SSI, one of the most common nosocomial infections in surgical patients,[9] is a serious surgical complication that occurs after approximately 2% of surgical procedures and accounts for 20% of health care-associated infections. SSI significantly prolongs patients' postoperative hospital stay while increasing the cost of treatment, placing a huge economic burden on patients.[10] With the development of the transportation industry in recent years, the number of

Table 2. Power analysis between patients with and without SSI.

Parameters		SSI		Mann–Whitney	Wilcoxon	P
		No	Yes			
PLT count	Mean of rank	44.69	87.20	102.00	3843.00	<0.001
	Sum of rank	3843.00	1308.00			
D-dimers	Mean of rank	47.80	4111.00	370.00	4111.00	0.009
	Sum of rank	69.33	1040.00			
ESR	Mean of rank	46.23	3975.50	234.50	3975.50	<0.001
	Sum of rank	78.37	1175.50			
PCT	Mean of rank	46.65	4011.50	270.50	4011.50	<0.001
	Sum of rank	75.97	1139.50			

SSI, surgical site infection; PLT, platelet; ESR, erythrocyte sedimentation rate; PCT, procalcitonin.
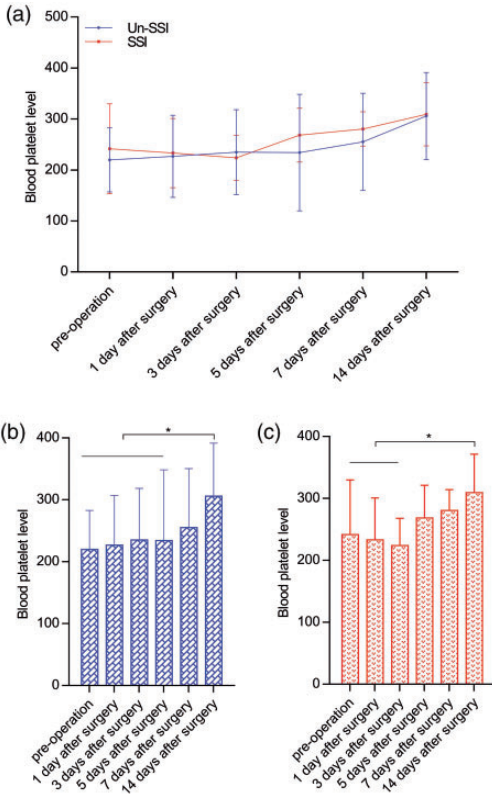
Figure 4. Changes in platelet count stratified by presence or absence of SSI. SSI, surgical site infection.

femoral neck fractures has been increasing year by year. Additionally, along with the widespread application of femoral neck fracture implants, the risk of SSI after various types of femoral neck fractures is also expected to increase.[11] Patients with hypoimmunity are more likely to develop SSI after femoral neck fracture repair than patients with adequate immunity function because of varying degrees of impaired immune function combined with factors such as malnutrition and often opportunistic infections.[3,12] Few studies to date have focused on the early warning signs and prevention of SSI in immunocompromised patients.

In the present study, the changes in blood-related parameters differed over time. PCT, ESR, ALB, AST, and PLTs were at low levels before surgery and at 1 and 3 days after surgery; began to increase at 5 days after surgery; and remained at high levels thereafter. GLU, lymphocytes, RBCs, WBCs, D-dimers, ALT, and CRP increased only at 5 days after surgery and then remained at low levels before surgery, at 1 and 3 days after surgery, and at 7 and 14 days after surgery. Neutrophils, CD4, CD8, creatinine, hemoglobin, BUN, and GLOB were at high levels before surgery and at low levels after surgery.

PCT is a highly specific and sensitive inflammatory marker for infection, and its blood concentration is abnormally high in the presence of bacterial infection and systemic inflammation.[13] Under normal conditions, a very small amount of PCT will be released into the blood circulation. In healthy people, the blood concentration of PCT is 0.1 to 0.5 µg/L and its half-life is about 10 minutes. However, in the presence of toxins or cytokines, proteolysis occurs and the serum concentration of PCT increases.[14,15] Patients with hypoimmunity in the present study had an elevated PCT concentration beginning on postoperative day 5, after which time it remained elevated; this indicated an increased risk of SSI or other postoperative infection. The present study also showed a strong correlation between the PCT concentration and changes in the femoral neck fracture time in immunocompromised patients ($R = 0.83$, $P < 0.05$). The serum ALB concentration reflects the level of nutrition and general well-being, with low serum ALB concentrations indicating a poor nutritional status and greater susceptibility to postoperative SSI.[16] A study by Simpson et al.[17] showed that a low preoperative serum ALB concentration was associated with a longer postoperative hospital stay, higher operative risk, and longer postoperative recovery
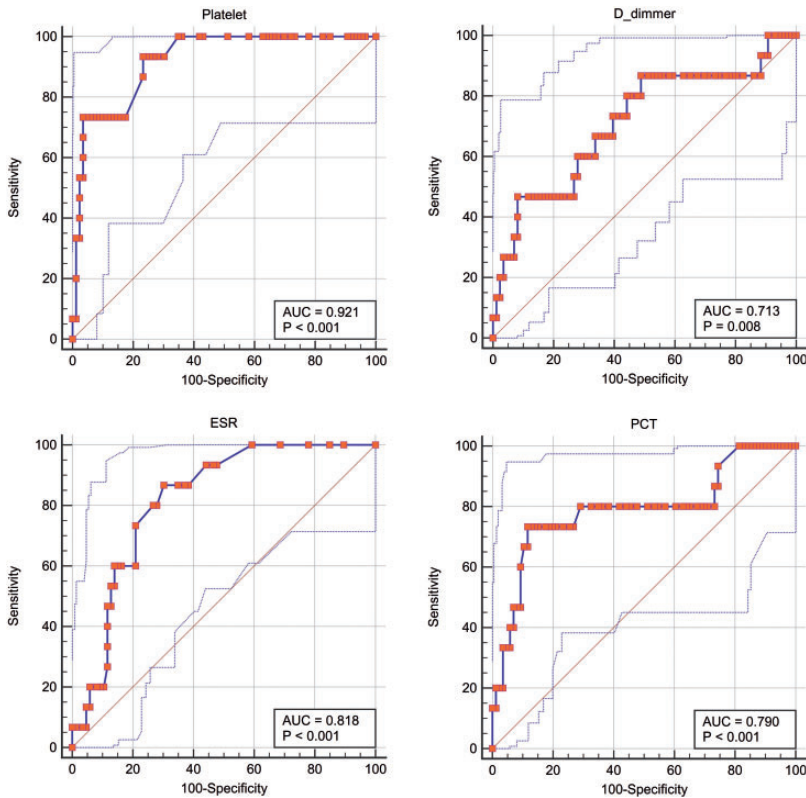
Figure 5. Receiver operating characteristic curve analysis of platelet count, D-dimer concentration, ESR, and PCT concentration for the occurrence of surgical site infection after femoral neck fracture repair in immunocompromised patients. ESR, erythrocyte sedimentation rate; PCT, procalcitonin; AUC, area under the curve.

time. Therefore, nutritional support is necessary to reduce the risk of infection in immunocompromised patients after femoral neck fracture repair. Routine measurement of the preoperative serum ALB concentration and active correction of hypoproteinemia throughout the perioperative period help to reduce the incidence of postoperative SSI.[18]

PLTs are small, non-nucleated cellular debris that circulate in the blood, and their roles in thrombosis and hemostasis are well known.[19] Inherited or acquired defects in the PLT count or function may be associated with bleeding complications. In recent years, many studies have

highlighted that PLTs are associated with certain infectious and inflammatory diseases.[20,21] Zhang et al.[22] proposed that the PLT distribution width combined with the PLT count can be used as an important additional detection method for the diagnosis of deep SSI after traumatic limb fracture surgery, thereby reducing the cost and time loss. The present study showed a strong correlation between the PLT count and changes in the femoral neck fracture time in immunocompromised patients ($R = 0.99$, $P < 0.05$). The ROC curve was further used to analyze the predictive value of the PLT count for SSI after femoral neck fracture repair in immunocompromised patients.

The results showed that the AUC of the PLT count for predicting SSI was 0.676 (95% confidence interval, 0.540–0.813), indicating that the PLT count has some predictive value for SSI after femoral neck fracture repair in immunocompromised patients.

Many studies to date have shown that the PLT count is associated with infectious and inflammatory diseases,[23] but few studies have focused on the correlation of the PLT count with SSI after femoral neck fracture repair in immunocompromised patients. This study showed that the changes in the PLT count crossed between hypoimmune patients with and without SSI at 3 to 5 days after surgery and that the PLT count increased at 3 to 5 days after surgery in patients with SSI. The results of univariate and multivariate analyses performed by Hu et al.[24] showed that the fracture type, operative duration of >122 minutes, anesthesia time of >130 minutes, intraoperative body temperature of $<36.4°C$, GLU concentration of >100 mg/dL, PLT count of $<288 \times 10^9$, and WBC count of $>9.4 \times 10^9$ were independent risk factors for wound infection after surgical treatment of open fractures. In vitro experiments have shown that PLT interactions enhance the phagocytic capacity of neutrophils against various bacteria.[25] Immunocompromised patients have a crossover of PLT count changes 3 to 5 days after surgery, a steep increase in the PLT count 3 to 5 days after surgery, and an increased risk of wound infection after femoral neck fracture repair. A low preoperative PLT count in immunocompromised patients predisposes them to the development of postoperative SSI, and thrombocytosis may occur after stimulation of bone marrow activity; this may be responsible for the initial rise in the PLT count in immunocompromised patients 3 to 5 days after surgery. In immunocompromised patients with femoral neck fractures, the underlying disease must be actively treated and anemia and hypoproteinemia must be corrected to minimize the incidence of SSI.

The present study has two main limitations. First, number of data samples was small, and the results may be somewhat biased. Expanding the sample size can improve the accuracy of the analysis results. Second, the mechanism by which the PLT count changes according to time and the occurrence of SSI needs to be further explored.

Large-sample multicenter controlled clinical trials should be conducted to further explore the predictive value of the PLT count in patients with SSI. In addition, animal experiments should be designed to further study the relationship between the PLT count and SSI and its molecular mechanism. After performance of a large number of such studies, the PLT count might become an effective predictor of the occurrence of SSI and further guide clinicians' strategies to prevent SSI.

Conclusion

The temporal change of the PLT count in immunocompromised patients who have undergone femoral neck fracture repair can serve as an early warning sign of SSI.

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