Factors related to infection after fixation in the process of late healed bone fracture

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Abstract. We studied the factors related to infection after fixation in the process of bone late healed fracture and explored the factors that could predict the risk of postoperative infection. A total of 100 patients with open fractures of the tibia and fibula diagnosed in Zhengzhou No. 7 People's Hospital from 2007 to 2016 were enrolled in this study. Patients were subjected to staging surgery treatment. We divided them into the infection group (n=52) and the non-infection group (n=48) according to whether or not infection occurred after operation. Pearson correlation was used to analyze the relationship between postoperative infection and preoperative factors, and ROC curve was used to explore the factors which could predict the risk of postoperative infection. As a result, surgical timing and C-reactive protein were correlated with postoperative infection ($P<0.05$), and surgical timing was negatively correlated with postoperative infection. C-reactive protein was positively correlated with postoperative infection. Using 7 days as the cut-off point of surgical timing, false positive and false negative rates were 0 and 27.7%, respectively. Youden index value was 72.3%, and positive predictive and negative predictive values were 42.5 and 100%, respectively. With 54.55 mg/l as the cut-off point of C-reactive protein, the sensitivity and specificity of prediction were 88.2 and 94.1%, while the false negative and false positive rates were 11.8 and 5.9%, respectively. The Youden index value was 82.3%, and the positive predictive and negative predictive values were 75 and 96.7%, respectively. With 7 days as the cut-off point of surgical timing and 54.55 mg/l as the cutoff point of C-reactive protein at the same time, the positive predictive and negative predictive values were 88.2 and 97.6%, respectively. The false negative and false positive rates were 11.8 and 2.4%, respectively. The Youden index value was 85.8%. The positive predictive and negative predictive values were 88.2 and 97.6%, respectively. In conclusion, surgical timing and C-reactive protein were strongly correlated with postoperative infection and this correlation was not affected by age, sex or other inflammatory indexes. The incidence of postoperative infection was reduced when both factors were applied for the determination of surgery. In addition, incidence of complications will be reduced and the cure rate improved.

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Introduction

With the development of science and technology, people's living standards are improving. Considerable progress has also been made in transportation, causing an increase in the number of traffic accidents. Most of the traffic injuries are caused by open injury and usually accompanied by contamination (1). Due to these contaminations, one-time operation usually can lead to postoperative infection, which may affect wound-healing, limb function, and even cause bloodstream infection induced shock (2-5). Therefore, the second-stage surgery has become increasingly widely used, thus, infection should be controlled first and then the fixation would be performed with the secondary surgery (6-9). However, there are some discussions regarding the timing of the secondary surgery. If the secondary surgery is performed at an early stage after the first surgery, the surgical outcomes may be affected by the infection which is not fully controlled (10-12). However, if the secondary surgery is performed at a late stage after the first surgery, the financial burden can increase significantly. Also, the healing time can be extended, and the psychological burden on patients and their families can also increase. This may negatively impact the recovery process (13-16). Therefore, it is significantly useful if we can find a way to accurately predict the timing of the secondary surgery. However, due to the application of antibiotics after the first surgery, the differences in clinical indicators such as erythrocyte sedimentation rate (ESR), white blood cell and neutrophil count and other indexes between infected and non-infected patients are not noticeable. Prior studies have shown that the C-reactive protein levels are significantly different between these two groups of patients (17). So, this study aimed to find a surgical index that can accurately determine the timing of secondary surgery in order to promote early rehabilitation.

Table I. Comparison of general information between the infection and non-infection groups.

Items	Non-infection group	Infection group	t-value	P-value
Surgical timing (days)	9.23±5.74	4.30±1.03	6.091	<0.001
C- reactive protein level before surgery (mg/l)	20.53±17.60	21.64±15.37	0.337	0.737
White cell count ($^*10^9$/l)	8.73±2.56	9.24±1.95	1.126	0.263
Neutrophil count ($^*10^9$/l)	5.43±1.98	6.02±1.87	1.532	0.129
Proportion of neutrophil (%)	67.01±11.76	66.22±1.93	0.478	0.634
Body temperature (˚C)	36.38±0.33	36.40±0.28	0.328	0.743
ESR (mm/l)	50.63±25.68	54.57±33.79	0.652	0.516
Age (years)	45.66±14.32	43.54±13.96	0.749	0.455

ESR, erythrocyte sedimentation rate.

Materials and methods

Clinical data and *general information*. A total of 100 patients with open fractures of the tibia and fibula diagnosed in Zhengzhou No. 7 People's Hospital from 2007 to 2016 were enrolled in this study. They were all subjected to staging surgery treatment. Patients were divided into the infection group (n=52) and the non-infection group (n=48) according to whether or not infection occurred after operation. There was no significant difference between those two groups except a significant difference in surgical timing (Table I). This study was approved by the Ethics Committee of Zhengzhou Orthopaedics Hospital. Signed written informed consents were obtained from all participants before the study.

Methods. Clinical indexes of the patents before and after surgery, including Gustilo-Anderson classification, white cell and neutrophil counts, ESR, body temperature, and timing of surgery were evaluated and recorded. Patients' pathological data were also collected.

Information on Gustilo-Anderson, timing of surgery, C-reactive protein, white cell and neutrophil counts, proportion of neutrophil, body temperature, ESR, sex and age were all subjected to univariate analysis. C-reactive protein levels and surgical timings were selected from univariate logistic correlation analysis for multivariate logistic regression analysis.

Observation indexes. Fasting venous blood (3-5 ml) was collected from the patients (fasting for >8 h) in both groups after 7:00 in the morning before and after surgery. Serum was separated and C-reactive protein levels were measured using enzyme-linked immunosorbent assay (ELISA). ELISA kits were provided by Beckman Coulter, Inc. (Brea, CA, USA). White cell and neutrophil counts were also conducted. ESR and body temperature were determined and the timing of the surgery was recorded.

Statistical analysis. SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The data are expressed as mean ± standard deviation and tested by t-test. The categorical variables were assigned with numbers to facilitate logistic analysis. Univariate logistic regression analysis with odds ratio (OR) and 95% confidence interval was used to select correlated variables for multivariate correlation analysis. The correlation was analyzed by Pearson correlation analysis. The effects of C-reactive protein levels on postoperative infection were analyzed by ROC curve. P<0.05 was considered to be statistically significant.

Table II. Value assignment for the related categorical variables.

Items	Categories	Assigned value
Sex	Male	1
	Female	0
Infection	Yes	1
	No	0
Gustilo-Anderson classification	I	1
	II	2
	IIIA	3
	IIIB	4
	IIIC	5

Results

Value assignment for the related categorical variables. Value was assigned to non-numerical variables for logistic regression analysis (Table II).

Univariate logistic regression analysis on indexes before surgery. The relevant factors were first subjected to univariate analysis, if P-value was <0.05, then the relevant factor was related to postoperative infection. Univariate analysis showed that timing of surgery and C-reactive protein were correlated with postoperative infection (P<0.05). There was a negative correlation between timing of surgery and postoperative infection. A positive correlation was established between C-reactive protein and postoperative infection (Table III).

Multivariate logistic regression analysis on C-reactive protein and timing of surgery. Timing of surgery and C-reactive protein levels were subjected to multivariate logistic regression

Table III. Univariate logistic regression analysis on indexes before surgery.

Items	P-value	OR-value	OR and 95% confidence interval
Gustilo-Anderson classification (X1)	0.076	1.97	0.084-4.125
Surgical timing (X2)	0.025	0.196	0.034-0.067
C-reactive protein (X3)	0.019	1.055	1.002-1.072
White cell count (X4)	0.215	1.584	0.851-1.863
Neutrophil count (X5)	0.291	1.197	0.734-1.652
Proportion of neutrophil (X6)	0.521	0.857	0.749-1.023
Body temperature (X7)	0.452	0.371	0.014-5.774
ESR (X8L)	0.521	1.052	0.845-1.013
Sex (X9)	0.256	0.351	0.027-2.954
Age (X10)	0.295	1.026	0.857-1.032

ESR, erythrocyte sedimentation rate.

Table IV. Multivariate logistic regression analysis on C-reactive protein and timing of surgery.

Items	P-value	OR-value	OR and 95% confidence interval
Timing of surgery (X2)	0.023	0.684	0.575-0.958
C-reactive protein (X3)	0.016	1.052	1.003-1.065

Table V. Pearson correlation analysis of C-reactive protein and timing of surgery.

Item	Pearson correlation value	P-value
C-reactive protein and timing of surgery	0.039	0.841

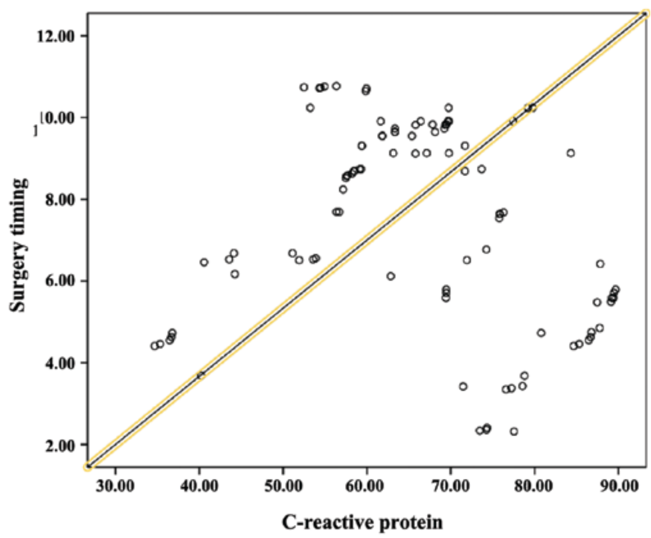

Figure 1. Scattergraph of the timing of surgery and C-reactive protein level. The timing of surgery and C-reactive protein levels tend to be positively distributed. Pearson correlation analysis showed a positive correlation (P<0.05).

analysis. Results showed that OR of timing of surgery was 0.648. There was a negative correlation between postoperative infection and timing of surgery. The OR-value of C-reactive protein was 1.052. We detected a positive correlation between postoperative infection and C-reactive protein (Table IV).

Pearson correlation analysis of C-reactive protein and timing of surgery. In order to determine the possible correlation between C-reactive protein and timing of surgery, Pearson correlation analysis was applied. The P-value was >0.05 and Pearson correlation coefficient value was 0.039, therefore no correlation between the two factors was established (Table V, Fig. 1).

Analysis of cut-off point of surgical timing and postoperative infection. Using 7 days as the cut-off point of surgical timing, the ROC curve analysis showed that the sensitivity and specificity were 100 and 72.3%, respectively. The false negative and false positive rates were 0 and 27.7%, respectively. The Youden index value was 72.3%. The positive and negative predictive values were 42.5 and 100%, respectively (Table VI, Fig. 2).

Table VI. Analysis of cut-off point of surgical timing and postoperative infection.

Timing of surgery	Infection		Total
	Positive (cases)	Negative (cases)	
Positive (<7 days)	17	23	40
Negative (>7 days)	0	60	60
Total	17	83	100

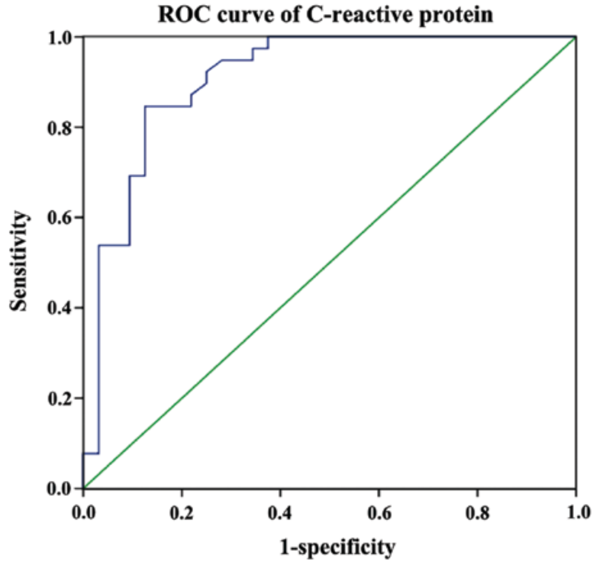

Figure 2. ROC curve of the timing of surgery on positive prediction. Sensitivity and specificity were 100 and 72.3%, respectively. P<0.05.

Table VII. Analysis on cut-off point of C-reactive protein and postoperative infection.

	Infection		
C-reactive protein	Positive (cases)	Negative (cases)	Total
Positive (>54.55 mg/l)	15	5	20
Negative (<54.55 mg/l)	2	78	80
Total	17	83	100

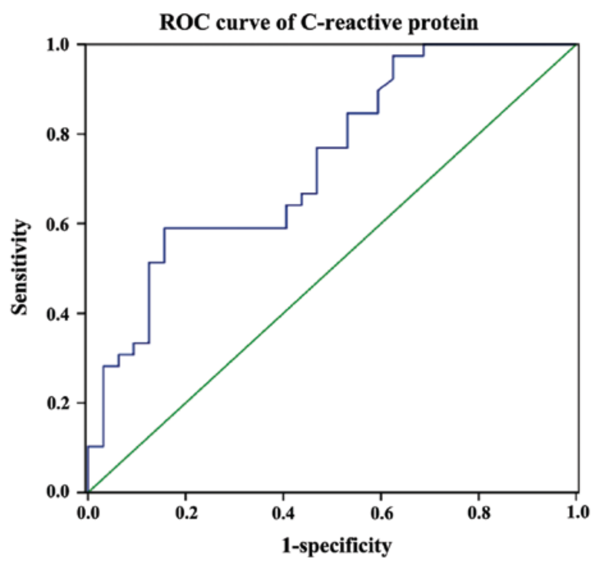

Figure 3. ROC curve of the C-reactive protein on positive prediction. Sensitivity and specificity were 88.2 and 94.1%, respectively. P<0.05.

Analysis on cut-off point of C-reactive protein and postoperative infection. ROC curve analysis was applied. With 54.55 mg/l as the cut-off point of C-reactive protein, the sensitivity and specificity of prediction were 88.2 and 94.1%, respectively. The false negative and false positive rates were 11.8 and 5.9%, respectively. The Youden index was 82.3%. The positive predictive and negative predictive values were 75 and 96.7%, respectively (Table VII, Fig. 3).

Table VIII. Accuracy analysis C-reactive protein and the timing of surgery joint prediction on postoperative infection.

	Infection		
C-reactive protein and the timing of surgery	Positive (cases)	Negative (cases)	Total
Positive	15	2	17
Negative	2	81	83
Total	17	83	100

Accuracy analysis of C-reactive protein and the timing of surgery joint prediction on postoperative infection. ROC curve analysis was used. For the surgery time of 7 days and C-reactive protein level of 54.55 mg/l, the predictive sensitivity and specificity were 88.2 and 97.6%, respectively. The false negative and false positive rates were 11.8 and 2.4%, respectively. The Youden index value was 85.8%; positive predictive value and negative predictive values were 88.2 and 97.6%, respectively (Table VIII).

Discussion

With the improvement of living standards, we have witnessed an increase in the number of multi-level construction and a significant improvement in the modes of transportation. Correspondingly, the high-altitude falling injuries and injuries caused by car accidents are on the rise. Most of those injuries are open injuries and are usually accompanied by infection. In these cases, a two-stage surgery is considered to be beneficial for the victims of these types of accidents. There is no controversy over the first surgery, which contains debridement and external fixation and the surgical approach is fairly matured. However, controversy still exists over the timing of secondary surgery. Ruedi *et al* recommended that the secondary surgery be performed 3 weeks after the first surgery (18). However, Nanchahal *et al* considered that the secondary surgery should be carried out 10 days after the first surgery (19). The reason for this ambiguity in the timing of the secondary surgery is largely due to the inability of determination of the risk of infection. Currently, the indicators used to determine infection mainly include body temperature, white cell and neutrophil counts and ESR. However, due to the use of antibiotics, most studies have shown no significant difference among these clinical indicators in infected and non-infected patients. Nevertheless, some studies have shown a significant difference in C-reactive protein level between infected patients and non-infected patients (17,20). Therefore, in this study, we investigated the relationship between C-reactive protein and postoperative infection to predict the timing of secondary surgery for open fractures.

We discovered that the timing of surgery and C-reactive protein were correlated with postoperative infection (P<0.05). A negative correlation between the timing of surgery and postoperative infection as well as a positive correlation between C-reactive protein and postoperative infection were established. With 7 days as the cut-off point of surgical timing, the sensitivity and specificity of prediction were 100 and 72.3%, respectively. False positive and false negative rates were 0 and 27.7%, respectively. The Youden index was 72.3% and the positive predictive and negative predictive values were 42.5 and 100%, respectively. The sensitivity and specificity were 88.2 and 94.1%, respectively. With 54.55 mg/l as the cut-off point of C-reactive protein, the sensitivity and specificity of prediction were 88.2 and 94.1%, respectively. The false negative and false positive rates were 11.8 and 5.9%, respectively. The Youden index value was 82.3% and the positive predictive and negative predictive values were 75 and 96.7%, respectively. With 7 days as the cut-off point of surgical timing and 54.55 mg/l as the cut-off point of C-reactive protein at the same time, the positive predictive and negative predictive values were 88.2 and 97.6%, respectively. The false negative and false positive rates were 11.8 and 2.4%, respectively. The Youden index was 85.8%. The positive predictive and negative predictive values were 88.2 and 97.6%, respectively.

We showed that surgical timing and C-reactive protein were strongly correlated with postoperative infection and this correlation was not affected by age, sex and other inflammatory indexes. We concluded that the incidence of postoperative infection can be reduced if both factors were applied for the determination of surgery. In addition, incidence of complications could be reduced and the cure rate improved.

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