

# Can the Preoperative Prognostic Nutrition Index (PNI) Predict Surgical Site Infection Following Primary Total Knee Arthroplasty?

**JINGSHENG SHI**

Huashan Hospital Fudan University

**JIE YU**

Huashan Hospital Fudan University

**JINGDE DENG**

Xingguo people's hospital

**CHAOJUN ZHENG**

Huashan Hospital Fudan University

**GUANGLEI ZHAO**

Huashan Hospital Fudan University

**JUN XIA**

Huashan Hospital Fudan University

**YIBIN WEI**

Huashan Hospital Fudan University

**GANGYONG HUANG**

Huashan Hospital Fudan University

**SIQUN WANG**

Huashan Hospital Fudan University

**JIE CHEN** (✉ [chenjie4@huashan.org.cn](mailto:chenjie4@huashan.org.cn))

Huashan Hospital Fudan University

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## Research article

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# Abstract

## Background:

Malnutrition is reported as one of the risk factors for surgical site infection (SSI). The prognostic nutritional index (PNI) is a simple method for nutritional evaluation. However, few studies have discussed the effectiveness of PNI as a nutritional assessment in predicting SSI after primary total knee arthroplasty (TKA). The aim of this study is to investigate the relationship between SSI and malnutrition as identified by the PNI scores following TKA.

## Methods:

A retrospective analysis of 483 patients (SSI vs. non-SSI group: 19 vs. 464; follow-up period: at least 1 year) was performed to confirm the risk factors, including the PNI, associated with SSI after primary TKA using both univariate and multivariate analyses.

## Results:

Postoperatively, nineteen patients (19/483, 3.9%) experienced SSI (deep vs. superficial SSI: 12 vs. 7), and periprosthetic joint infection was observed in all deep SSI cases. Univariate analysis showed that male sex, body weight, body mass index (BMI), diabetes mellitus, steroid usage, operative time and PNI differed between the SSI and non-SSI groups ( $P < 0.05$ ). Multivariate logistic regression analysis identified that the preoperative PNI (odds ratio [OR]: 0.859; 95% confidence interval [CI]: 0.762-0.969; cutoff [CV]: 49.27), operative time (OR: 1.005; 95% CI: 1.000-1.010; CV: 131.0 min), male sex (OR: 4.127; 95% CI: 1.165-14.615), diabetes mellitus (OR: 6.133; 95% CI: 2.067-18.193) and steroid usage (OR: 6.034; 95% CI: 1.521-23.935) were independently associated with SSI ( $P < 0.05$ ).

## Conclusions:

A low preoperative PNI associated with malnutrition was demonstrated to be an independent risk factor for SSI following primary TKA. Patients with preoperative low PNI should be cautioned and provided with adequate nutritional intervention to reduce postoperative SSI.

## Background:

Surgical site infection (SSI) is a serious complication after total knee arthroplasty (TKA) [1–3]. Approximately 1–2% patients accepting elective knee replacement will develop SSI in the subsequent year [4, 5], suggesting that a large number of potential patients may develop postoperative infections every year. Importantly, treatment of SSI following joint replacement usually requires aggressive surgical debridement and long-term antibiotics [6–8]. Many patients need to remove the prosthesis, and some cases even develop recurrent infections despite surgical and medical management [5, 9, 10], which will result in increased financial and medical burdens and sometimes litigation. Therefore, efforts to minimize infection rates are a high priority.

The impact of malnutrition on surgical outcomes following orthopaedic surgeries, especially primary and revision hip and knee arthroplasty, has been widely reported [11–13]. Increasing evidence has demonstrated that malnutrition is closely associated with postoperative wound complications including healing problems, persistent drainage, and deep infections [11–13]. A recent study further suggested that more than half of in-hospital elderly patients may have malnutrition [14]. Thus, preoperative screening and improvements are important for patients suspected of malnutrition to reduce SSI following primary TKA. Unfortunately, although a variety of methods for detecting malnutrition have been proposed in previous studies [11, 15–18], there is still no gold standard for defining malnutrition.

The prognostic nutritional index (PNI) is a new index that can be simply calculated by serum albumin level and lymphocyte count, reflecting both the inflammatory and nutritional status of a patient. A recently published study further demonstrated that preoperative low PNI was closely related to SSI after orthopedic surgery [19]. Unfortunately, few studies have discussed the effectiveness of PNI as a nutritional assessment in predicting SSI after primary TKA.

Therefore, the purpose of this study was to assess the incidence of SSI after primary TKA and to clarify the risk factors for this SSI, including malnutrition. Furthermore, the appropriate predictive cutoffs of these factors were also analyzed in this study.

## **Methods:**

### **Subjects**

In total, 483 patients with advanced knee arthritis accepting primary TKA were retrospectively included in this study (Fig. 1). All of these patients were recruited at the Huashan Hospital between January 2013 and September 2019. The Human Ethics Committee of Huashan Hospital, Fudan University, China, granted ethical committee approval, and each subject provided informed consent.

The inclusion criteria of this study were as follows: (1) follow-up period of at least 1 year, and (2) consent to participate this study. The exclusion criteria were: (1) insufficient assessment of blood sampling and/or clinical data preoperatively, (2) previous knee joint surgery, (3) surgery for the treatment of inflammatory or infectious knee joint diseases, (4) patients with other coexisting diseases that cause inflammatory marker abnormalities, and (5) perioperative death.

In the present study, superficial and deep SSI were defined according to the Centers for Disease Control and Prevention (CDC) [20], and periprosthetic joint infection (PJI) was defined according to the Musculoskeletal Infection Society (MSIS) criteria [21]. The patients with SSI in this study were divided into the superficial or deep SSI group, and PJIs were included in the deep SSI group.

### **Data acquisition:**

Patient characteristics were collected from medical records and a standardized questionnaire developed for this study, including age, gender, height, body weight, body mass index (BMI), alcohol consumption, current smoking, preoperative complications and current medications. Surgical-related information was obtained by reviewing the operative and anesthetic records, including length of surgery, intraoperative blood loss, blood transfusion, and usage of suction drains.

Blood sampling data were evaluated within 1 week preoperatively, including white blood cell count, lymphocyte count, neutrophil count, hemoglobin and serum albumin, and PNI was calculated by the following formula:  $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/}\mu\text{L)}$ . All of these blood sampling markers were measured by the department of Laboratory Medicine, and no blood specimen was obtained solely for the purpose of this study.

## Perioperative infection control:

All patients received 1.0 g cefazolin intravenously within 15 minutes of skin incision. If the patient had a history of a significant allergy, vancomycin was considered as a secondary choice. Antibiotics were redosed if the operation lasted for more than three hours. Antibiotics were continued for 24 h postoperatively. Until the end of 2017, wound drainages were left routinely in all patients undergoing TKA in our institution and removed 1–2 days postoperatively. Since 2018, the use of wound drainages has been gradually reduced in patients undergoing primary TKA, although the operation mode and approach have not changed.

## Statistical methods:

SPSS 20.0 (IBM, Armonk, NY) was used to analyze the data. The Kolmogorov-Smirnov test was used to test the normality of the distributions. The measurements for the non-SSI group and SSI group/subgroup were compared using independent t-tests or Mann-Whitney tests, and the frequencies of the different measurements between the non-SSI group and SSI group/subgroup were compared by Fisher's exact test or chi-square test. Statistically significant covariates based on these univariate analyses were subjected to multivariate logistic regression analysis, and the cutoff values and area under the curve (AUC) of the results of the multivariate logistic regression analysis were identified by a receiver operating characteristic (ROC) curve. A P-value of less than 0.05 was considered significant.

## Results:

### Comparison between the SSI and non-SSI group

Among 483 patients, nineteen patients (19/421, 3.9%) experienced postoperative SSI (superficial vs. deep SSI: 7 vs. 12), and 17 (17/19, 89.5%) cases reached a definite diagnosis of SSI as their microbiological cultures were positive (*Staphylococcus aureus*: 3/17, 17.6%; *Staphylococcus epidermidis*: 5/17, 29.4%; *Pseudomonas aeruginosa*: 1/17, 5.9%; *Escherichia coli*: 3/17, 17.6%; *Klebsiella pneumoniae*: 4/17, 23.5%;

*Pseudomonas stutzeri*: 1/17, 5.9%). The other two patients were diagnosed as SSI by two senior surgeons according to the abnormal biomarkers in combination with clinical symptoms. We conducted debridement in all cases with deep SSI, and PJI was identified in all 12 of these patients. All 12 patients with SSI recovered after therapy.

In this study, the patients with SSI had an obviously higher proportion of males, cases with diabetes, and cases with usage of steroid compared to those without SSI ( $P < 0.05$ , Table 1). Furthermore, the SSI group had higher body weight, greater BMI, longer operative time and lower PNI ( $P < 0.05$ , Table 1). In addition, including both time and cost of readmission, the patients with SSI exhibited longer total hospital stay and higher total medical expenses ( $P < 0.05$ , Table 1).

Table 1  
Measurements between the SSI and non-SSI groups

	SSI group	Non-SSI group	P
<b>Number of subjects</b>	19	464	
<b>Age range (years)</b>	71.9 ± 7.7	69.7 ± 7.3	0.23
<b>Height (cm)</b>	164.9 ± 6.3	164.1 ± 7.3	0.59
<b>Weight (kg)</b>	72.9 ± 12.0	64.5 ± 10.7	< 0.01*
<b>BMI</b>	26.6 ± 3.0	24.0 ± 3.6	< 0.01*
<b>Gender (male vs. female)</b>	9 vs. 10	94 vs. 370	< 0.01*
<b>Alcohol consumption</b>	5/19 (26.3%)	92/464 (19.8%)	0.50
<b>Current smoking</b>	3/19 (15.8%)	47/464 (10.1%)	0.43
<b>Preoperative complications</b>			
Hypertension	6/19 (31.6%)	97/464 (20.9%)	0.27
Diabetes mellitus	8/19 (42.1%)	55/464 (11.9%)	< 0.01*
Chronic renal dysfunction	1/19 (5.3%)	19/464 (4.1%)	0.80
Respiratory diseases	3/19 (12.5%)	56/464 (12.1%)	0.63
<b>Current medication</b>			
Steroid	4/19 (21.1%)	23/464 (5.0%)	< 0.01*
Immunosuppressant	0/19 (0.0%)	9/464 (1.9%)	1.00
Anticoagulation	3/19 (15.8%)	84/464 (18.1%)	0.80
<b>Laboratory data</b>			
White blood cell (x10 <sup>9</sup> /L)	6.2 ± 1.6	6.6 ± 1.7	0.31
Hemoglobin (g/L)	123.6 ± 11.8	128.7 ± 12.8	0.08
Neutrophils count (x10 <sup>9</sup> /L)	3.8 ± 1.2	3.8 ± 1.3	0.95
Serum albumin (g/L)	37.9 ± 2.8	39.3 ± 3.2	0.05
Lymphocyte count (x10 <sup>9</sup> /L)	1.8 ± 0.6	2.1 ± 0.7	0.06
PNI	46.8 ± 3.5	49.6 ± 5.1	< 0.01*
<b>Surgical data</b>			
Operative time (min)	122.9 ± 40.9	94.2 ± 41.7	0.01*

	SSI group	Non-SSI group	P
Intraoperative blood loss (ml)	313.9 ± 54.6	293.2 ± 65.0	0.13
Blood transfusion	2/19 (10.5%)	23/464 (5.0%)	0.28
Application of wound drainage	6/19 (31.6%)	242/464 (52.2%)	0.08
<b>Consumption of medical resources</b>			
Total hospital stays (day)#	35.1 ± 14.1	8.7 ± 3.0	< 0.01*
Total medical expenses (yuan)#	114548.7 ± 49876.8	74270.9 ± 10399.6	< 0.01*
*Statistically significant difference between the SSI and non-SSI groups			
#: Total hospital stays and medical expenses included both time and cost of readmission in SSI cases.			
SSI: Surgical site infection; BMI: Body mass index; PNI: Prognostic nutritional index; P: P-value			

## Subgroup analysis of SSI

The superficial SSI group showed higher BMI and a higher proportion of cases with diabetes mellitus compared to the non-SSI group ( $P < 0.05$ , Table 2). In the deep SSI group, patients presented with longer operative time and a higher proportion of males, cases with diabetes and cases with usage of steroid compared to the those without SSI ( $P < 0.05$ , Table 2); decreased serum albumin, reduced lymphocyte count and low PNI were also observed in these patients with deep SSI ( $P < 0.05$ , Fig. 2).

Table 2  
Patient characteristics and surgical data between the SSI subgroups and non-SSI group

	Superficial SSI group	Deep SSI group	Non-SSI group
<b>Number of subjects</b>	7	12	464
<b>Age range (years)</b>	71.6 ± 11.6	72.1 ± 5.0	69.7 ± 7.3
<b>Height (cm)</b>	165.3 ± 6.5	164.7 ± 6.4	164.1 ± 7.3
<b>Weight (kg)</b>	71.6 ± 8.8	73.7 ± 13.9*	64.5 ± 10.7
<b>BMI</b>	26.1 ± 1.8*	26.8 ± 3.6*	24.0 ± 3.6
<b>Gender (male vs. female)</b>	3 vs. 4	6 vs. 6*	94 vs. 370
<b>Alcohol consumption</b>	2/7 (28.6%)	3/12 (25.0%)	92/464 (19.8%)
<b>Current smoking</b>	0/7 (0.0%)	3/12 (25.0%)	47/464 (10.1%)
<b>Preoperative complications</b>			
Hypertension	1/7 (14.3%)	5/12 (41.7%)	97/464 (20.9%)
Diabetes mellitus	3/7 (42.9%)*	5/12 (41.7%)*	55/464 (11.9%)
Chronic renal dysfunction	0/7 (0.0%)	1/12 (8.3%)	19/464 (4.1%)
Respiratory diseases	0/7 (0.0%)	3/12 (25.0%)	56/464 (12.1%)
<b>Current medication</b>			
Steroid	1/7 (14.3%)	3/12 (25.0%)*	23/464 (5.0%)
Immunosuppressant	0/7 (0.0%)	0/12 (0.0%)	9/464 (1.9%)
Anticoagulation	1/7 (14.3%)	2/12 (16.7%)	84/464 (18.1%)
<b>Surgical data</b>			
Operative time (min)	109.0 ± 28.0	131.1 ± 45.9*	94.4 ± 48.2
Intraoperative blood loss (ml)	306.6 ± 59.0	318.2 ± 54.2	293.2 ± 65.0
Blood transfusion	0/7 (0.0%)	2/12 (16.7%)	23/464 (5.0%)
Application of wound drainage	2/7 (28.6%)	4/12 (33.3%)	242/464 (52.2%)
*Statistically significant difference between the superficial/deep SSI and non-SSI groups			
SSI: Surgical site infection; BMI: Body mass index; P: P-value			

## Risk factor analysis of SSI

All statistically significant measurements between the SSI and non-SSI groups based on the univariate analysis, including male sex, body weight, BMI, operative time, PNI, cases with diabetes mellitus, and steroid usage, were subjected to multivariate logistic regression analysis. The results of the multivariate analysis showed that male sex (odds ratio [OR]: 4.127; 95% confidence interval [CI]: 1.165–14.615; B: 1.427; P = 0.028), operative time (OR: 1.005; 95% CI: 1.000–1.010; B: 0.005; P = 0.041), PNI (OR: 0.859; 95% CI: 0.762–0.969; B: -0.152; P = 0.013), cases with diabetes mellitus (OR: 6.133; 95% CI: 2.067–18.193; B: 1.814; P = 0.001) and usage of steroids (OR: 6.034; 95% CI: 1.521–23.935; B: 1.797; P = 0.011) were independently associated with SSI. Furthermore, ROC curve analysis revealed the cutoff values of PNI (cutoff value: 49.27; AUC: 0.670) and operative time (cutoff value: 101.5 min; AUC: 0.715) for predicting SSI after primary TKA (P < 0.05; Fig. 3).

## Discussion:

The results of this study demonstrated that malnutrition is a risk factor associated with the development of SSI after primary TKA, and a similar result has been reported in several previous studies [11–13]. However, recently published large cohort studies contradicted this finding [22–24]. This contradiction may be ascribed to the different criteria for defining malnutrition. Although a recently published meta-analysis demonstrated that serologic malnutrition showed a greater association with increased risk of wound complication after total joint replacement compared to both anthropometric measurements and standardized nutrition score [11], there are still a large number of different serological indicators (albumin, transferrin, prealbumin and lymphocyte count) used to evaluate malnutrition [15, 16, 25, 26]. According to a previous study [27], the mechanism by which malnutrition may cause increased rates of SSI involves both impairment of the immune system to fight infections due to reduced lymphocyte count and impairment of wound healing due to reduced protein synthesis. Therefore, compared with using a single indicator, such as serum protein or lymphocytes, the PNI, which combines both serum albumin and peripheral lymphocytes, may be a better index to quantify malnutrition. This was further supported by the results of the present study and a previous study [19] demonstrating that the PNI, but not albumin or peripheral lymphocytes, was independently associated with SSI. Therefore, it is important to assess the patient's nutritional status using the preoperative PNI score to predict SSI.

Consistent with previous large cohort studies [28–31], the present study demonstrated that both diabetes mellitus and steroid usage were associated with a higher risk of SSI after total joint arthroplasty (TJA). Despite the dispute, preoperative steroid use was reported to be a risk factor for SSI on joint replacement patients in several previous studies [28, 30], and a recent study further demonstrated that patients with preoperative steroid therapy over 15 mg/day had a 21 times higher risk of SSI than patients without steroid therapy [32]. Similar to the steroid usage, the impact of diabetes on postoperative wound complications has been widely reported [29, 31]. According to a previous study [33], the microvascular lesions caused by hyperglycemia and poor concentration of prophylactic antibiotics in the tissue due to this microvascular lesion may be the main reason for increased risk of SSI caused by diabetes. Therefore, strict control of blood glucose and appropriate adjustment of steroid use are critical to reduce SSI and promote wound healing in the perioperative period.

In the present study, prolonged operative time was especially associated with SSI, which was commensurate with previous systematic reviews [34, 35]. Although this view is still controversial, a recent study further demonstrated that surgeons with shorter median operative durations had a lower risk of SSI than surgeons with relatively longer median operative durations [36], implying that individual differences among surgeons may have a greater impact on SSI. Therefore, it may be more effective to reduce postoperative SSI following TKA by improving the individual technical level of operators compared to taking intensive interventions to decrease operative duration.

When reviewing these findings, one limitation was that this is a retrospective study from a single center, which may have limited our ability to deduce causal relationships and caused selection bias in patient enrollment. Therefore, we tried to minimize this bias by enrolling consecutive patients. Another clinical limitation of this study is the low sample size due to the rare incidence of SSI cases. However, the incidence of SSI varied depending on different operative procedures. Therefore, only primary TKA patients were included in this study. Furthermore, although both the current study and a systematic review of 62 observational studies [37] demonstrated a significantly higher pooled estimate of risk of SSI in male patients, the underlying mechanism is not clear. More significant results might be achieved in a well-designed prospective study with a larger sample size.

## **Conclusion:**

The present study demonstrated that male sex, operative time ( $> 131.0$  min), diabetes mellitus, steroid usage, and malnutrition identified by PNI values ( $< 49.27$ ) are independent risk factors associated with the development of SSI after primary TKA. Patients with low preoperative PNI values should be cautioned about the risks of SSI, and perioperative nutritional intervention could reduce the incidence of SSI following primary TKA.

## **List Of Abbreviations:**

PNI: Prognostic nutritional index

SSI: Surgical site infection

TKA: Total knee arthroplasty

BMI: Body mass index

OR: Odds ratio

CI: Confidence interval

CV: Cutoff

CDC: Centers for Disease Control and Prevention

PJI: Periprosthetic joint infection

MSIS: Musculoskeletal Infection Society

AUC: Area under the curve

ROC: Receiver operating characteristic

## **Declarations:**

### **Ethics approval and consent to participate**

All authors declare that the study protocol was approved by Human Ethics Committees (Huashan Hospital, Fudan University, China). All subjects gave informed consent through written.

### **Consent for publication**

Written informed consent for publication was obtained from all participants.

### **Availability of data and materials**

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

### **Competing interests**

All authors declare that they have no competing interests

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### **Authors' contributions**

CHEN J and WANG S have made substantial contributions to conception and design; YU J, ZHAO G and ZHENG C have made substantial contributions to acquisition of data, or analysis and interpretation of data; XIA J, SHI J, HUANG G and WEI Y have been involved in drafting the manuscript or revising it critically for important intellectual content; all authors have given final approval of the version to be published

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## Figures

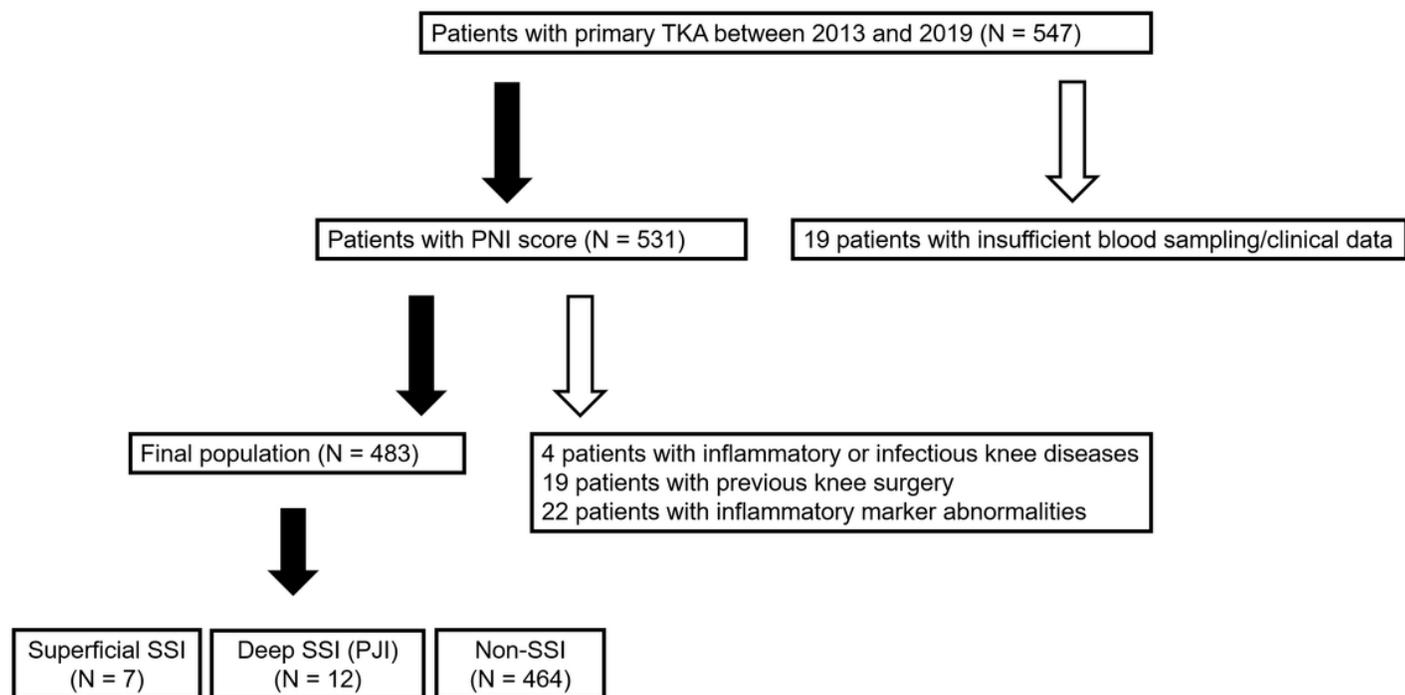
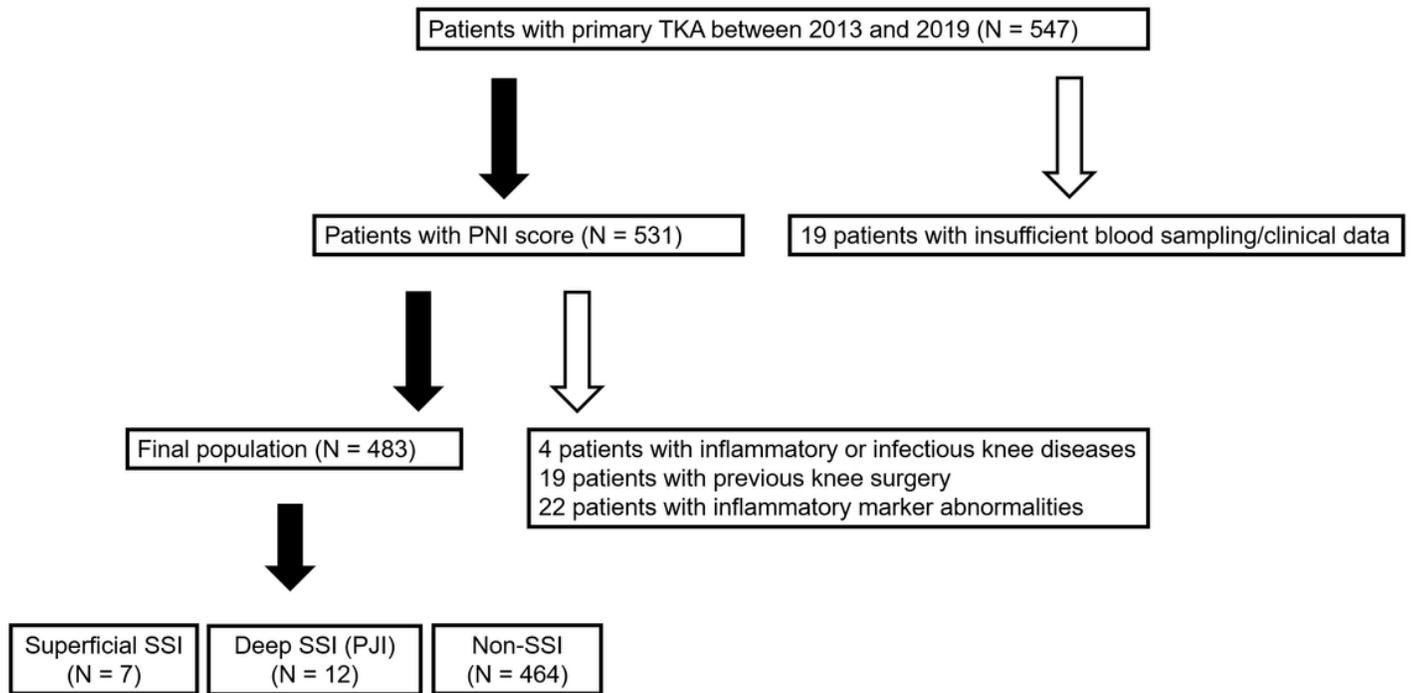


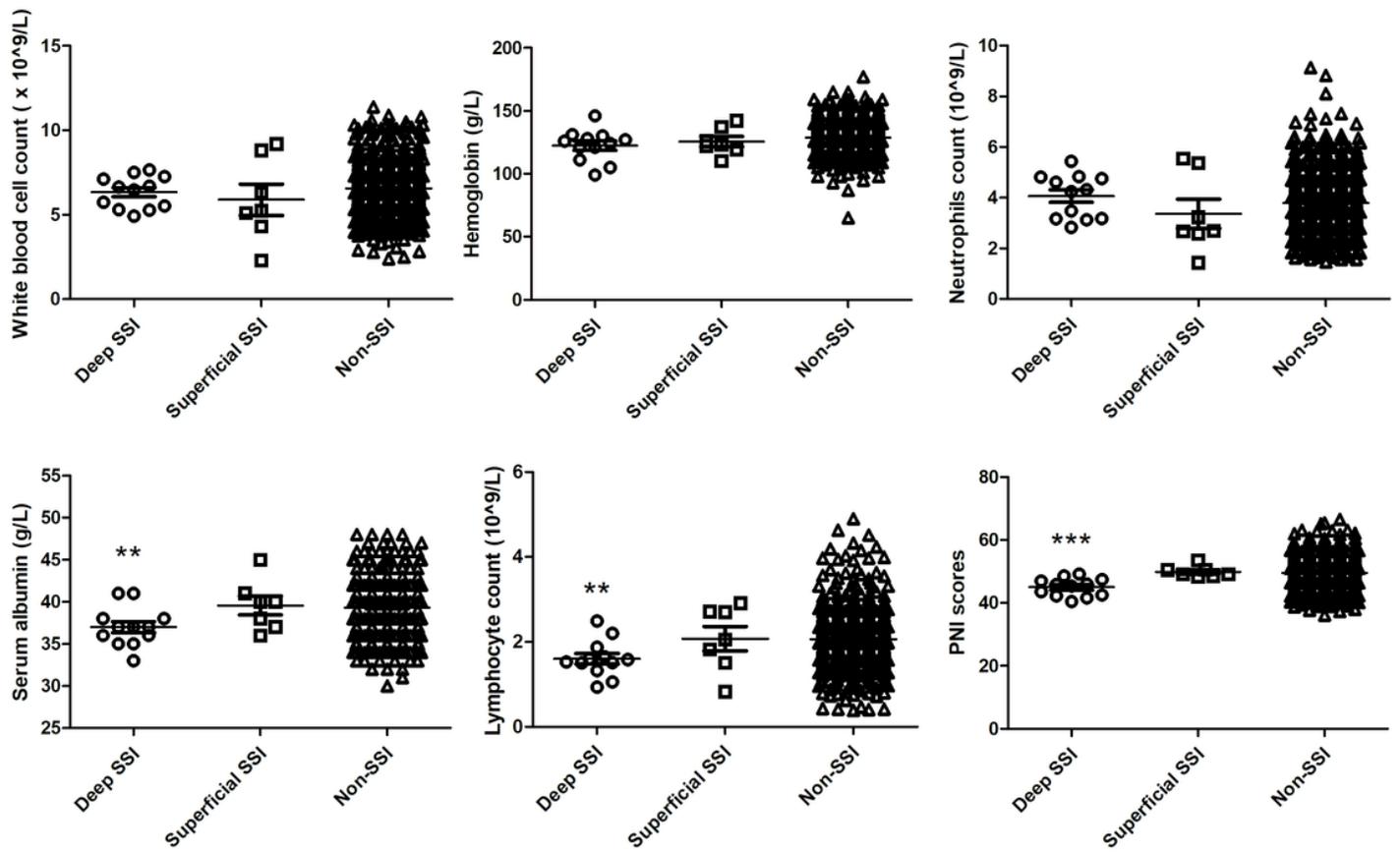
Figure 1

Design of the present study. TKA: Total knee arthroplasty; PNI: Prognostic nutrition index; SSI: Surgical site infection; PJI: Periprosthetic joint infection; N: Number.



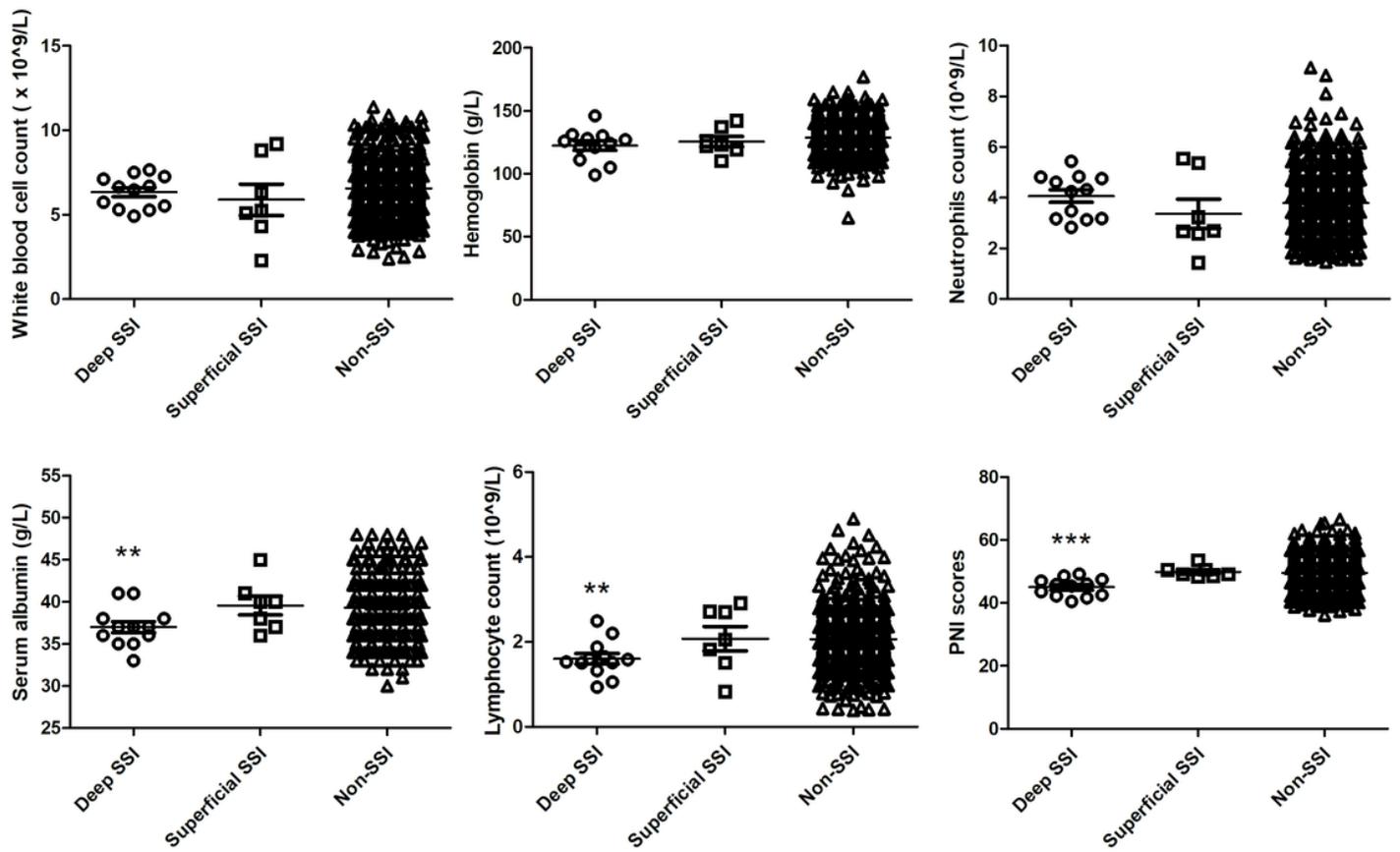
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**Figure 2**

Laboratory data between the superficial/deep SSI and non-SSI groups. Compared with the non-SSI group, the patients with deep SSI showed decreased serum albumin, reduced lymphocyte count and a low PNI compared to the non-SSI group. PNI: Prognostic nutrition index; SSI: Surgical site infection. \*: Statistical differences between superficial/deep SSI and non-SSI groups, \* $P < 0.05$ , \*\* $P < 0.01$ , and \*\*\* $P < 0.001$ .



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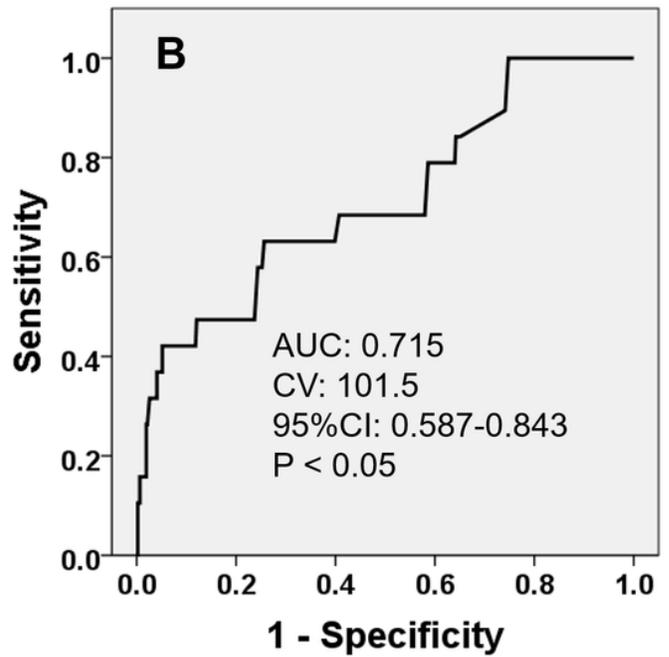
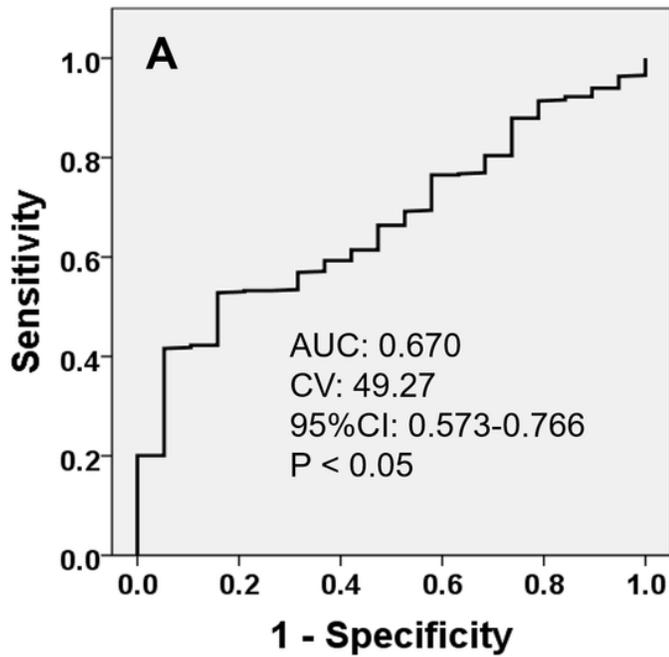


Figure 3

Receiver operating characteristic curve for the risk factors: PNI (A) and operative time (B). PNI: Prognostic nutrition index; AUC: Area under the curve; CV: Cutoff values; CI: Confidence interval; P: P-values

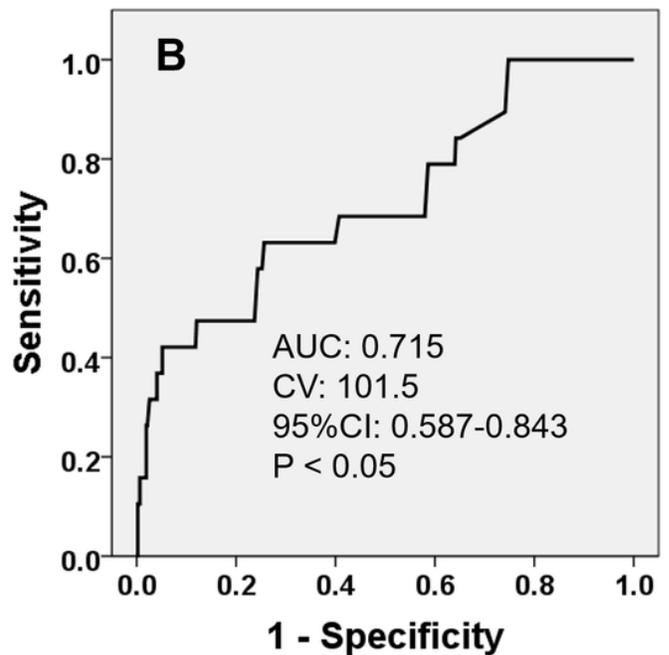
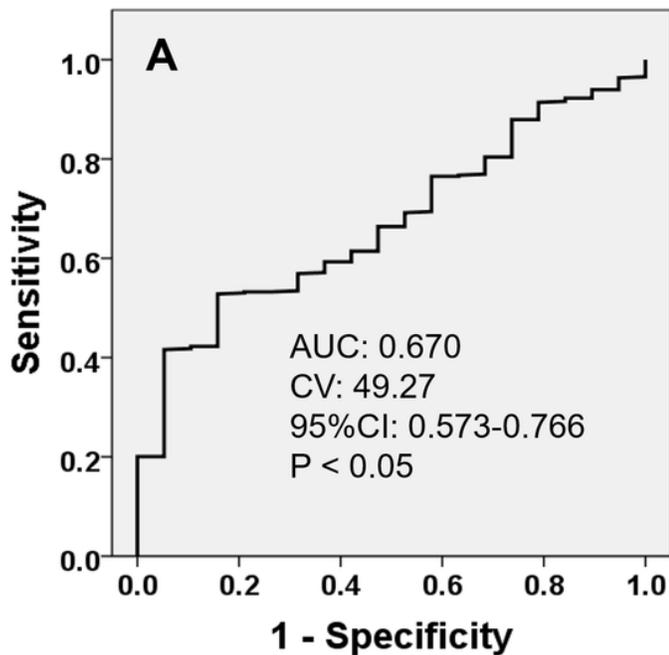


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