Preoperative idiopathic CRP and ESR elevation increase the risk of PJI within 90-day after primary total knee arthroplasty in patients with osteoarthritis

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Research Article

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Abstract

Background: The purpose of this study was to determine the association between preoperative idiopathic serum CRP and ESR elevation in KOA patients with 90-day PJI after primary TKA.

Methods: We reviewed our center's database over a 60-month study period from November 2016 to October 2021. After excluding those with known diseases that elevate CRP and ESR, 882 KOA patients who met the initial screening criteria, namely, 293 males and 589 females aged 67.00±7.91 (range, 43-91) years, were divided into four groups based on the preoperative CRP level and ESR: 44 patients, CRP+ESR+; 27 patients, CRP+ESR-; 176 patients, CRP-ESR+; and 635 patients, CRP-ESR-. All patients underwent primary TKA, and the prevalence of PJI was evaluated based on the 2014 MSIS acute diagnostic criteria. The risk factors for CRP and ESR elevation were analyzed by binary logistic regression.

Results: The total infection rate was 1.59% (14/882); infection rates in the CRP+ESR+, CRP+ESR-, CRP-ESR+ and CRP-ESR- groups were 6.82% (3/44), 0 (0/27), 2.27% (3/176), and 1.10% (7/635), respectively. There was a significant relationship between preoperative idiopathic ESR or CRP elevation and the prevalence of 90-day PJI (P=0.022). Diabetes mellitus (P=0.0004) and an elevated body mass index (BMI) (P<0.0001) were risk factors for CRP elevation; being female (P<0.0001) and having an elevated BMI (P<0.0001) or diabetes mellitus (P=0.0036) were risk factors for ESR elevation.

Conclusion: Preoperative idiopathic CRP and/or ESR elevation increase the risk of 90-day PJI after primary TKA. Demographic characteristics and complications should be considered before deciding whether surgery can be performed, or additional perioperative treatment is needed to reduce the occurrence of PJI.

Introduction

Total knee arthroplasty (TKA) is the most effective treatment for advanced knee osteoarthritis (KOA). Between 2017 and 2018, 1.3 million primary TKA procedures were performed in the United States, and researchers have projected that the number would increase by 401% from 2014 to 2040 [1]. The increased demand for TKA will likely result in a higher volume of complications, including periprosthetic joint infection (PJI), which is the most frequent reason (36.1%) for revision [2]. PJI is a disastrous complication, with high morbidity and mortality rates, given the significant clinical and economic burden. Therefore, preoperative risk stratification is important for patient optimization and improving the safety of primary TKA.

To screen for occult infection, preoperative CRP and ESR are commonly used to evaluate the preoperative status of patients. Interpreting preoperative idiopathic CRP and ESR elevation in primary TKA patients requires an understanding of how these variables are influenced by patient characteristics. Research has shown that after excluding known diseases that affect the CRP level and ESR, these factors are influenced by age, sex, race, and body mass index (BMI) in the general population and in people with certain disease states, and even KOA itself contributes to the CRP level and ESR compared with those in patients without KOA [3–6].

For patients with obvious causes for such elevation, it is generally recommended to postpone the operation and treat the primary disease; otherwise, additional treatment would have to be performed during the operation or the duration of treatment with sensitive antibiotics would have to be extended to reduce the incidence of postoperative PJI. However, there are still many patients with idiopathic CRP and ESR elevation; to date, the largest and most recent study was among 3376 consecutive unilateral primary TKA patients, including 140 (4.1%) patients with preoperative ESR and/or CRP elevation [7]. In an abstract at the 2013 American Association of Hip and Knee Surgeons and American Academy of Orthopedic Surgeons (AAOS/AAHKS) conference, the author reported an elevated ESR in 38.5% and an elevated CRP level in 26.9% of 94 patients [8]. However, there are no specific statistical data on the distribution of these patients or suggestions for treatment. The purpose of this study was to investigate the prevalence of idiopathic CRP and/or ESR elevation before surgery and evaluate any association with 90-day PJI in patients with KOA following primary TKA.

Methods

A retrospective review of patients who underwent primary TKA from November 2016 to October 2021 was conducted at a single institution. The central database was searched over the 60-month study period. Patients with known diseases that cause CRP and ESR elevation were not included based on the criteria. All patients underwent routine urine tests, chest X-ray examination, electrocardiography (ECG) and preoperative blood tests, and all chest X-rays and ECG results were reviewed by specialists, increasing the likelihood of correctly identifying cardiac complications. Patients had a normal body temperature and no signs of local infection of the knee joint. The included patients had a complete medical history, including basic information, history of medical treatment, comorbidities, length of hospital stay (LOS) and duration of treatment with antibiotics. If the CRP level and ESR were still elevated after excluding comorbidities that contribute to the elevation of these indicators, synovial fluid tests was performed to exclude causes of CRP and ESR elevation. All the patients were followed up for at least 90 days or until infection occurred.

Inclusion and exclusion criteria

Patients who underwent primary unilateral or bilateral TKA for KOA at our institution between November 2016 and October 2021 were included. The exclusion criteria were as follows: 1. autoimmune diseases, metabolic diseases, and previous hormone use history; 2. previous/current history of local joint infection, history of urinary tract infection within one month and other systemic infectious diseases; 3. a history of fracture or trauma within three months; 4. malignant tumor or history of tumor-related surgery within five years and uncontrolled cardiovascular or cerebrovascular diseases; and 5. history of any surgery within the past three months.

Determination of the CRP level and ESR

CRP and ESR were measured preoperatively on the first day of admission. An elevated ESR was defined as >30 mm/h, and an elevated CRP level was defined as >10 mg/L. Elevated values are denoted by + in this study. All the patients underwent primary TKA at our hospital using a standard surgical technique. Preoperative antibiotics were administered within 30 minutes before skin incision. Hyperplastic synovial membrane tissue was completely removed, and local irrigation with 0.5% mucosal iodophor was performed in each patient. Local analgesia was administered via periarticular injection. Patellar replacement was not routinely performed, and a wound drain was not routinely placed during surgery. Postoperative antibiotics were prescribed for 24 h. The diagnosis of PJI was based on the 2014 Musculoskeletal Infection Society (MSIS) acute diagnostic criteria [9], and the patients were followed up based on readmission, telephone and outpatient follow-up results.

Ethical issues

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (K202110-11). An informed consent to review medical files was not required and waived by the institution as the study was a retrospective review. Patient confidentiality and privacy of information were secured by the principal investigator.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as the mean and standard deviation (SD). If the data conformed to a normal distribution, the clinical characteristics were compared between groups by ANOVA, or the Kruskal-Wallis H test was used for comparison of quantitative data. The chi-square test was for the comparison of categorical variables. The effects of preoperatively elevated CRP and ESR on the development of PJI were evaluated using Kaplan–Meier curves. Differences in the cumulative PJI rate were assessed using a log-rank test. A Spearman rank correlation test was used to analyze the correlation between the CRP level and ESR with KOA, and a scatter plot was used to compare the discrete data. Differences in the infection rate among the four groups were compared by a chi-square test. A binary logistic regression was used to analyze the risk factors for CRP and ESR elevation while estimating the OR and 95% CI of elevated CRP and ESR; then, a prediction model was established based on the results after screening by a logistic multivariate analysis and plotting a nomogram. The discrimination ability and prediction performance of the nomogram are represented by the ROC curve. A P-value of 0.05 was considered significant. All statistical analyses were performed with the statistical software package R x64 4.1.2.

Results

Elevated CRP and/or ESR occurred in 247 patients, including 10 patients with CRP++ESR++ (CRP³20, ESR³60), 24 patients with CRP++ESR+ (CRP³20,60 ³ESR³30) and 20 patients with CRP+ESR++ (40³CRP³20, ESR³60). There was no significant difference in age, the unilateral or bilateral status, LOS, or comorbid hypertension, heart disease, brain disease, or thyroid dysfunction among the four groups (P > 0.05), but there was a significant difference in sex (P = 0.001), BMI (P<0.001) and diabetes mellitus (P = 0.001) (Table 1).

Table 1

Patient demographics based on the grouping of the preoperative ESR and CRP values

	CRP+ ESR+	CRP+ ESR-	CRP- ESR+	CRP- ESR-	P-Value
n	44	27	176	635	
Age, year (mean ± SD)	68.98±1.76	65.96±4.39	67.07±1.06	66.88±0.62	0.319
Female, n (%)	30(68.18)	15(55.56)	148(84.09)	396(62.36)	0.001
BMI (mean ± SD)	30.25±1.48	29.19±1.83	29.22±0.74	25.74±0.29	<0.001
Diabetes, n (%)	15(34.09)	10(37.04)	38(21.59)	101(15.91)	0.001
Hypertension, n (%)	23(52.27)	16(59.26)	118(67.05)	350(55.12)	0.036
Heart disease, n (%)	14(31.82)	7(25.93)	31(17.61)	124(19.53)	0.161
Cerebral disease, n (%)	3(6.82)	0(0)	10(5.68)	33(5.2)	0.617
Thyroid dysfunction, n (%)	1(2.27)	1(3.7)	7(3.98)	14(2.2)	0.603
Unilateral, n (%)	24(54.55)	15(55.56)	101(57.39)	344(54.17)	0.901
Preoperative					
CRP mg/L (mean ± SD)	30.22±7.58	17.07±4.69	4.83±0.39	3.39±0.15	<0.001
ESR mm/h (mean ± SD)	49.02±4	21.89±3.11	41.08±1.24	17.53±0.58	<0.001
LOS, days (mean ± SD)	10.86±0.73	10.96±0.85	11.13±0.38	10.91±0.2	0.792
Infection, n (%)	3(6.82)	0(0)	4(2.27)	7(1.1)	0.022
Postoperative 1 month					
CRP mg/L (mean ± SD)	27.68±7.38	12.44±2.58	5.19±0.94	4.81±0.6	<0.001
ESR mm/h (mean ± SD)	39.23±3.23	26.59±3.61	38.23±1.62	18.82±0.72	<0.001
Postoperative 3 month					
CRP mg/L (mean ± SD)	22.56±7.58	16.28±3.86	4.97±0.49	3.68±0.16	<0.001
ESR mm/h (mean ± SD)	37.25±2.87	26.48±3.82	36.2±1.78	17.68±0.61	<0.001

Abbreviations: CRP>10 mg/L and ESR>30 mm/h denoted as (+); LOS: length of hospital stay

The total infection rate was 1.59% (14/882), and the infection rate in the CRP+ESR+, CRP +ESR-, CRP-ESR+, and CRP-ESR- groups was 6.82% (3/44), 0 (0/27), 2.27% (4/176), and 1.10% (7/635), respectively (Fig. 1), with significant differences in the 90-day infection rate among the four groups (P = 0.022). Kaplan-Meier curves showed the cumulative infection rates in the four groups (Fig. 2), and a log rank test was used to demonstrate the difference in the incidence of cumulative PJI among the four groups (P = 0.021). The cumulative incidence of PJI in the (CRP +, ESR +) group was 2.27 % (95 % CI: 0%-6.58%) at 1 month and 6.82 % (95 % CI: 0%-13.98%) at 3 months after the operation. The cumulative incidence of PJI in the (CRP +, ESR-) group was 0 (95 % CI: 0 % -0 %) at 1 month and 3 months after the operation. The cumulative incidence of PJI in the (CRP-, ESR +) group was 1.14% (95 % CI: 0%-2.69%) at 1 month and 2.27 % (95 % CI: 0.05%-4.45%) at 3 months after the operation. The cumulative incidence of PJI in the (CRP-, ESR-) group was 0.31 % (95 % CI: 0%-0.75%) at 1 month and 1.10 % (95 % CI: 0.29%-1.91%) at 3 months after the operation.

Infection occurred in 14 patients, with a positive culture in 9 patients (positive for bacteria in 7 patients and fungi in 2 patients). The culture result was negative for the other 5 patients, 3 of which had sinus tracts connecting with the prosthesis; the other 2 patients had a CRP level and ESR double those observed preoperatively as well as an increased WBC count and synovial fluid PMN% and a positive finding on histopathological examination of the periprosthetic region. Of the 14 patients with infection, 7 underwent bilateral TKA (3 patients had only a unilateral joint infection, and the contralateral knee showed no signs of infection, with normal synovial fluid), and 7 underwent unilateral TKA. For treatment, 4 patients underwent one-stage revision surgery because of clinical symptoms lasting >4 weeks, with a negative culture or no resistant organisms and no extensive comorbidities; 9 patients underwent treatment with debridement, antibiotics and implant retention (DAIR) (one of these patients underwent DAIR a second time on the 8th postoperative day because of relapse); and 1 patient required readmission due to clinical symptoms occurring within <2 weeks and had well-fixed prostheses with stable conditions, so this patient underwent conservative treatment with intravenous antibiotics. Infection was controlled in all the patients, and there were no cases of relapse in the follow-up period.

The mean CRP level and ESR are shown in Table 1. The distribution of the ESR and CRP level is shown in a scatter plot, and the data of patients who developed PJI are marked (Fig. 3). The percentage of patients in the four groups: 5%, CRP+ESR+; 3%, CRP+ESR-; 20%, CRP-ESR+; and 72%, CRP-ESR-. Spearman correlation analysis showed that there was a significant correlation between the preoperative CRP level and ESR in patients with KOA (P < 0.001). The mean values of the CRP and ESR levels before the operation, 1 month after the operation and 3 months after the operation statistically differed among the four groups (P < 0.001), and the elevated CRP and ESR levels before the operation remained high after the operation (Fig. 4, Fig. 5).

The risk factors for an elevated CRP level and ESR were analyzed by a binary logistic regression. Diabetes mellitus (P = 0.0007) and an elevated BMI (P < 0.0001) were risk factors for an elevated CRP level. The female sex (P < 0.0001), BMI (P < 0.0001), and diabetes mellitus (P = 0.0059) were risk factors for an

elevated ESR (Table 2, Table 3). Using R software, according to the risk factors screened by the logistic multivariate analysis, a nomogram graph model was established to predict the risk of CRP elevation (Fig. 6). According to the line graph model, BMI = 20 was 0, BMI = 22 was 9, and BMI = 24 was 18. The score without diabetes was 0, and the score with diabetes was 28. The scores of the above factors in the nomogram increased in turn, and the corresponding total score was the risk of increasing CRP in patients. Similarly, according to the risk factors screened by the logistic multivariate analysis, a nomogram model was established to predict the risk of increased ESR (Fig. 7). According to the line diagram model, the score of being a male was 0, and that of being a female was 24; BMI = 20 is 0, BMI = 22 is 9, BMI = 24 is 18, etc.; the score without diabetes was 0, and the score with diabetes was 15. The scores of the above factors in the nomogram increased in turn, and the corresponding total score was the risk of increasing ESR in patients. The nomogram demonstrated valuable prediction performance with an AUROC of 0.7 (95 % CI: 0.55 – 0.84) for CRP and 0.62 (95 % CI: 0.46 – 0.77) for ESR (Fig. 8, Fig 9).

Table 2

Results after screening by a multivariate analysis of CRP

	B	95%CI	S.E.	Wald	Exp(B)	95%CI	Sig
Constant	-7.113		0.8221	-8.65			<0.0001
BMI	0.9459	0.62429-1.2676	0.0274	5.76	2.5751	1.86690-3.5523	<0.0001
Diabetes	0.9667	0.42877-1.5046	0.2744	3.52	2.6293	1.53540-4.5023	0.0004

Abbreviations: B: coefficient, S.E.: standard error

Table 3

Results after screening by a multivariate analysis of ESR

	B	95% CI	S.E.	Wald	Exp(B)	95%CI	Sig
Constant	-7.1421		0.6173	-11.57			<0.0001
Sex	0.9936	0.593-1.3941	0.2044	4.86	2.7009	1.8095-4.0314	<0.0001
BMI	0.1885	0.8901-1.3718	0.0205	9.2	1.2074	2.4354-3.9423	<0.0001
Diabetes	0.6024	0.1971-1.0076	0.2068	2.91	1.8265	1.2179-2.739	0.0036

Abbreviations: B: coefficient, SE: standard error

Discussion

This study enrolled 882 KOA patients after those with known causes of increased CRP level and ESR were excluded; the enrolled patients were divided into four groups based on the preoperative CRP level and ESR. In total, 7 of the 247 patients with idiopathic CRP and/or ESR elevation had PJI within 90 days after primary TKA as a complication. Being a female and having elevated BMI and diabetes mellitus were all found to contribute to CRP and ESR elevation.

To date, there is no consensus or reliable clinical evidence on whether preoperative idiopathic CRP and ESR elevation is sufficient to affect the occurrence of PJI within 90 days after TKA. The results of this study suggest that preoperative idiopathic CRP and/or ESR elevation increase the risk of 90-day PJI after primary TKA. Xu C found that the rate of PJI was significantly higher in patients with both ESR and CRP elevation (12.5%, 4/32), which is similar to our results but with a higher infection rate. They found that patients with preoperative ESR and CRP elevation had a significantly greater risk of PJI than those with normal serum inflammatory marker levels (HR: 15.8, 95% CI: 2.57–96.7, P=0.003) after adjusting for confounding factors [7]. We think that one of the reasons for this result is the long follow-up period in that study (mean follow-up after TKA, 43.7±11.7 months), which led to the influence of other factors, such as hematogenous infection, long-term smoking, or lack of control of chronic diseases in patients with poor basic health, which contributed to the onset of PJI. Another reason could be that in our study, the hyperplastic synovial membrane tissue was completely removed in all patients, and the duration of irrigation with 0.5% mucosal iodophor was prolonged in the CRP+ESR+ group in this study, which may have led to a much lower infection rate. However, Godoy G also found no statistically significant relationship between postoperative complications and the preoperative CRP level (P=0.5005) or ESR (P=0.1610) [10]. In their study, 0 of 87 patients with preoperative CRP elevation developed infection, and only 3 of 151 patients with preoperative ESR elevation developed infection. However, in this study, CRP³8.3 mg/L and ESR³21 mm/h as elevated standards inevitably decrease the difference with the normal group. Another 2008 study by Pfitzner et al. [11] compared 25 patients with postoperative infections against a control group of 25 patients. The infected group had a higher average preoperative CRP (13-25 mg/L) than the control group (4-7mg/L), but this result was not statistically significant and not only KOA patients were included in those two studies. Meanwhile, based on the preoperative CRP and ESR level, CRP>10 mg / L and ESR> 30 mm/h were considered elevation in our study. However, elevation is determined by whether it exceeds the normal value twice in clinical practice. In this study, no patient developed PJI in the CRP++ESR++ (CRP³20, ESR³60) group and CRP+ESR++ (40³CRP³20, ESR³60) group, but 2 patients had infection in the CRP++ESR+ (CRP³20,60 ³ESR³30) group. Moreover, due to the limitation of the number of patients with idiopathic elevation in clinical practice, no further grouping and analysis of the difference in the infection rate among these groups were performed.

In this study, it was found that the CRP level and ESR in most patients with KOA were within the normal range. However, 28.00% (247/882) of patients had idiopathic CRP or ESR elevation; of these, patients with both CRP and ESR elevation accounted for 17.81%, and patients with either CRP or ESR elevation accounted for 10.93% and 71.26%, respectively. Per an abstract presented at the 2013 AAOS/AAHKS conference, 78 of 94 patients with KOA showed preoperative CRP and ESR elevation, with a rate of CRP and ESR elevation of 26.9% and 38.5%, respectively [8]. Xu C found that patients with both CRP and ESR elevation and either CRP or ESR elevation accounted for 22.86% and 77.14%, respectively [7]. CRP/ESR discordance occurred in 212 patients (12%), 105 of whom had high CRP/low ESR discordance (6%), and 107 of whom had high ESR/low CRP discordance (6%) among 1753 patients [14]. Colombet I found a disagreement was observed in 33% (elevated ESR/normal CRP in 28%, normal ESR/elevated CRP in 5%) among 5777 patients [15]. We believe that differences in the population and prevalence of multiple diseases in combination among regions may lead to differences in the distribution of the data.

In this study, diabetes mellitus (P = 0.0004) and an elevated BMI (P < 0.0001) were risk factors for an elevated CRP level. The female sex (P < 0.0001), BMI (P < 0.0001), and diabetes mellitus (P = 0.0036) were risk factors for an elevated ESR. Previous studies have shown that race, sex, BMI, comorbidities, a history of

intraarticular injections, smoking, and even osteoarthritis severity and muscle strength changes [3-6] also affect the baseline CRP level and ESR,_and female endocrine instability, atherosclerosis, plaque composition, obesity and chronic inflammation caused by local injection are more accepted reasons. In this study, since the patients in the CRP+ESR+ group underwent a synovial fluid test to exclude infection, this factor was not included as a variable.

The current criteria for CRP and ESR elevation do not take patient characteristics, which influence the baseline CRP level and ESR, into consideration. Meanwhile, the mean peak CRP level and ESR after surgery were similar among the groups of patients; however, in patients with preoperative CRP elevation, the CRP level and ESR may not normalize until 2 months after surgery [12], which is similar to our result; in our study, the mean CRP level and ESR in the CRP+ESR+ group persisted at an elevated level after the operation, and there was a significant difference in the CRP level and ESR among the four groups at 1 month ($P < 0.001$) and 3 months ($P < 0.001$) after the operation (Table 1); therefore, the baseline preoperative CRP level and ESR could affect the pattern of change in the CRP level and ESR over time after surgery. Thus, importantly, the CRP and ESR values or thresholds are dependent on the time period or the basic condition of the patient at the index arthroplasty [13]. Therefore, whether we need to adjust or optimize the CRP and ESR thresholds in these patients to ensure the reliability of CRP and ESR in the preoperative evaluation and postoperative diagnosis of PJI requires further research.

There are several limitations to this study. First, the design was retrospective, and certain biases of retrospective studies cannot be avoided. Information such as smoking status, which can confound the results, may not have always been accurately documented. Second, changes in the ESR and CRP level should be dynamically detected before and after surgery, as the occurrence of PJI cannot be well predicted only by single preoperative ESR and CRP values. Third, the MSIS standard of PJI is not 100% and missed diagnosis may occur. Fourth, there were no cases of infection in the CRP+ESR- group, and we still need to increase the sample size to obtain more reliable results.

Conclusion

After excluding patients with known preoperative risk factors, preoperative idiopathic CRP and/or ESR elevation increase the risk of 90-day PJI after primary TKA. For these patients, demographic characteristics and complications should be considered when deciding whether surgery can be performed, or additional perioperative treatment is needed to reduce the occurrence of PJI.

Declarations

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Conflicts of interest/Competing interests

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

Availability of data and materials

All data analyzed in this study are provided in the manuscript.

Code availability

None

Authors' contributions

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

Clinical trial registration

None

Conflicts of interest statement

No conflicts of interest exist in the submission of this manuscript, and the final manuscript was approved for publication by all authors. The work described in the manuscript is original research that has not been published previously, and the manuscript is not under consideration for publication elsewhere either in

whole or in part.

Ethical review committee statement

The study was approved by the Institutional Review Board (IRB).

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Figures

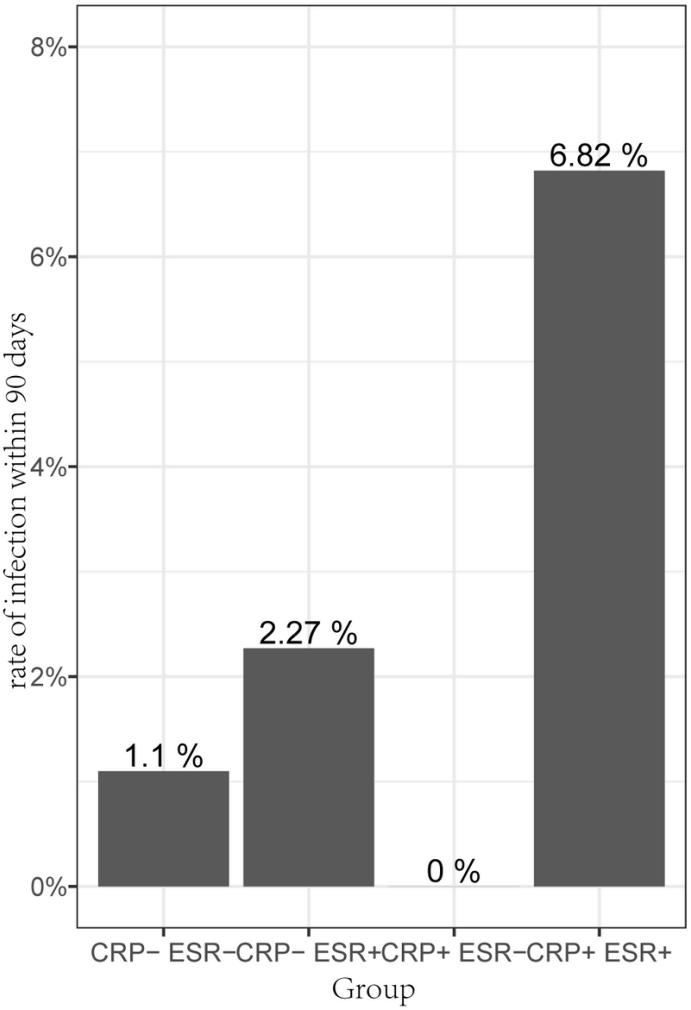

Figure 1

Bar graph showing the rate of PJI in 4 groups after a mean follow-up of 90 days.

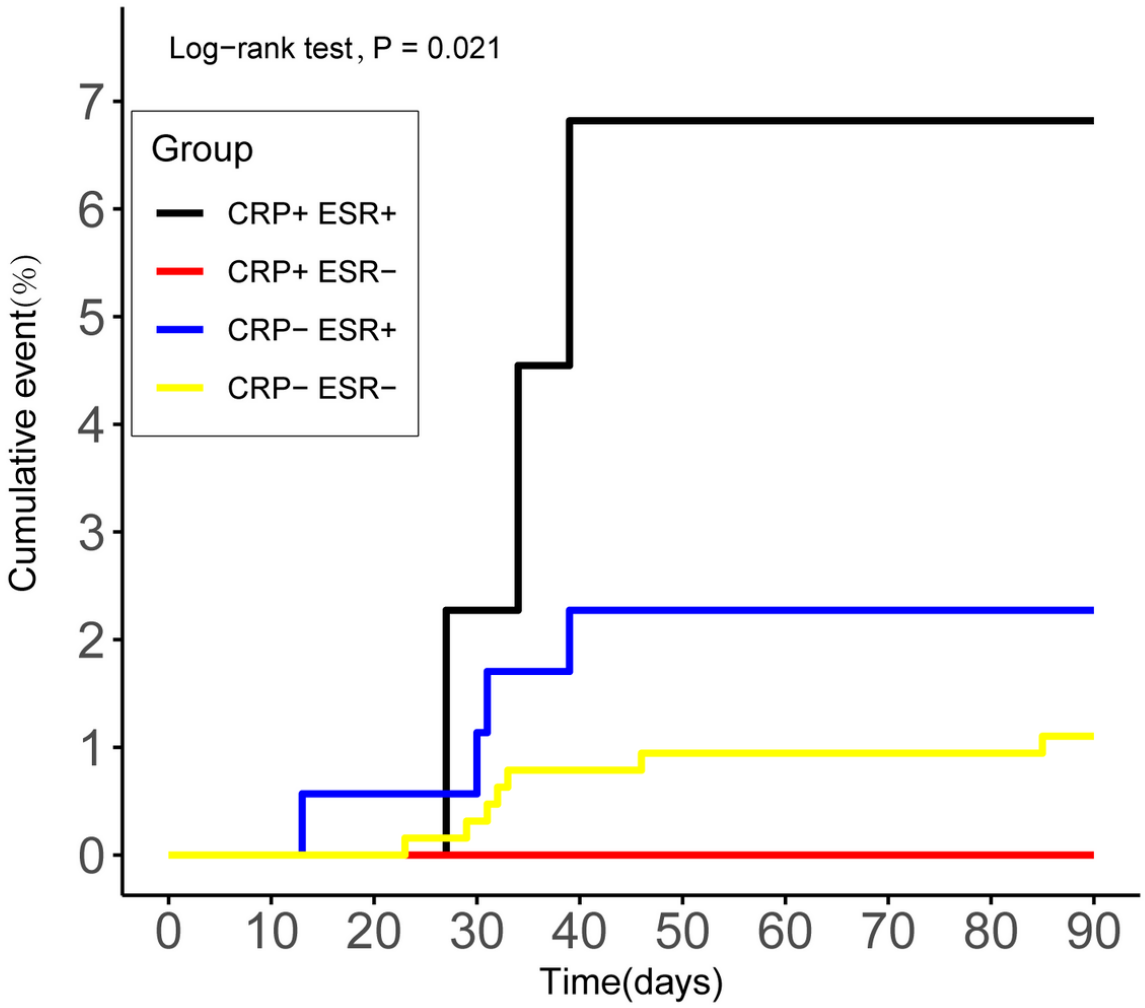

Figure 2

Kaplan–Meier graph illustrating the cumulative PJI rate in the 4 groups.

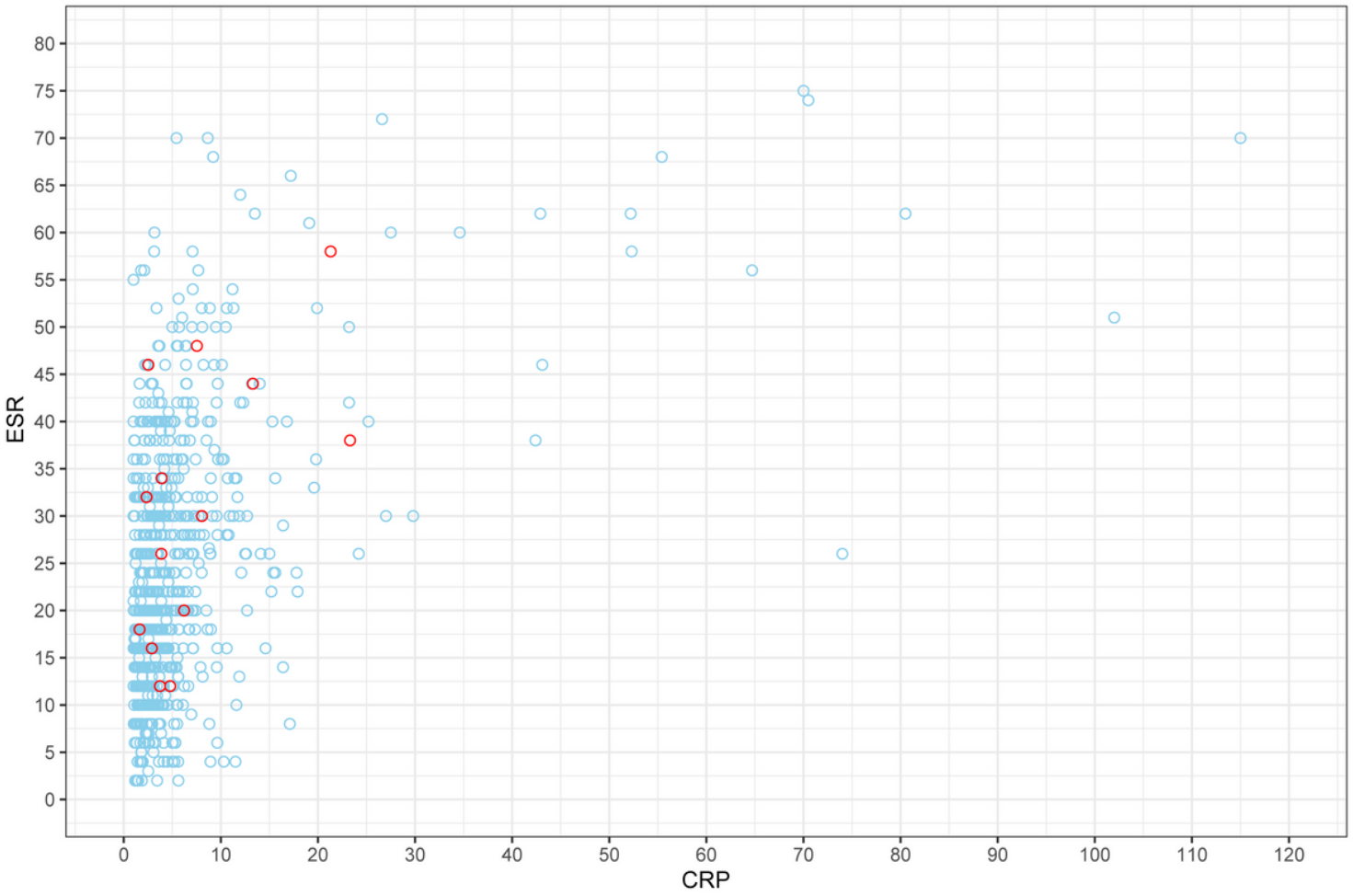

Figure 3

Scatter plot of preoperative CRP and ESR (patients who developed PJI are marked)

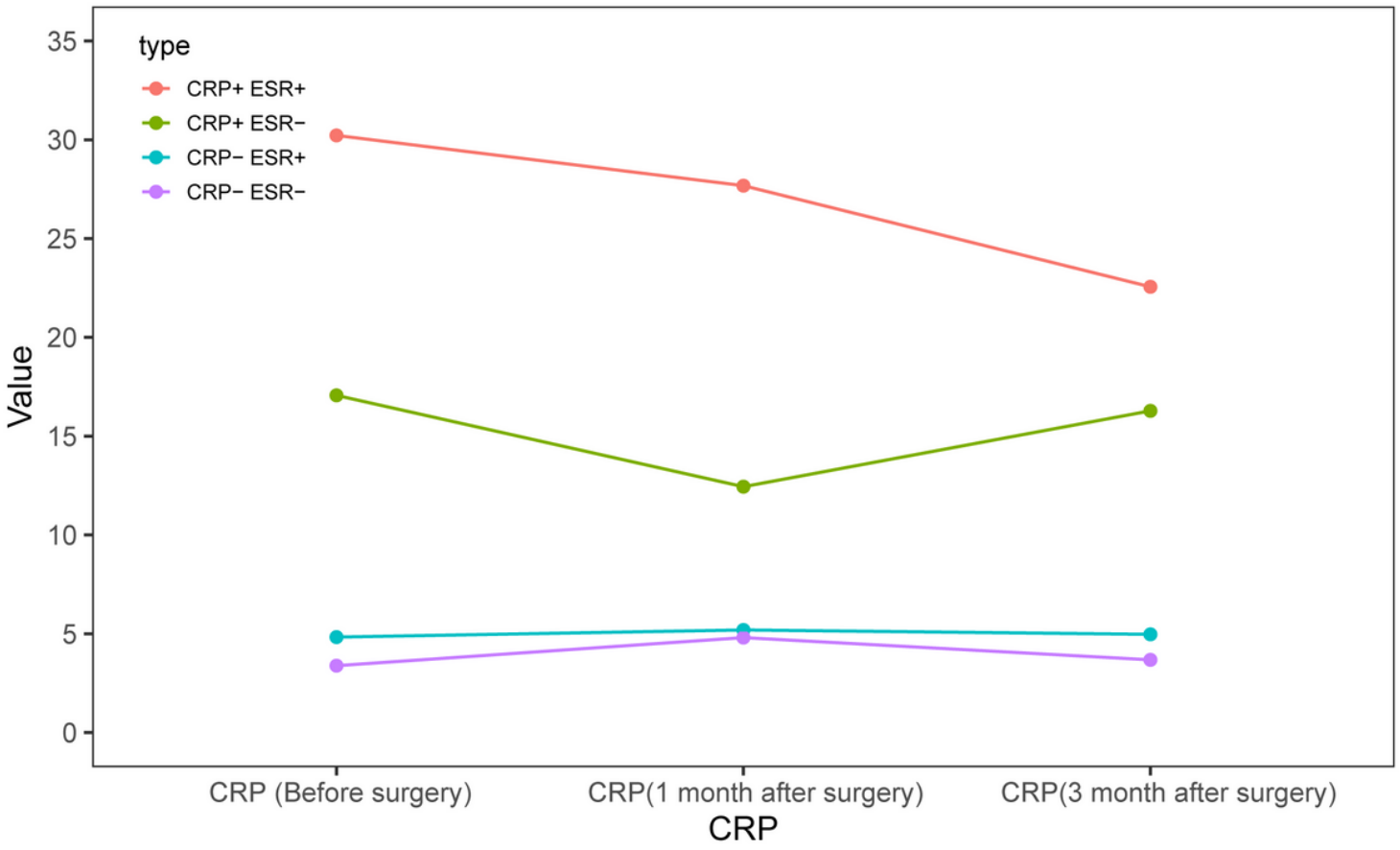

Figure 4

Variation tendency of the perioperative CRP level

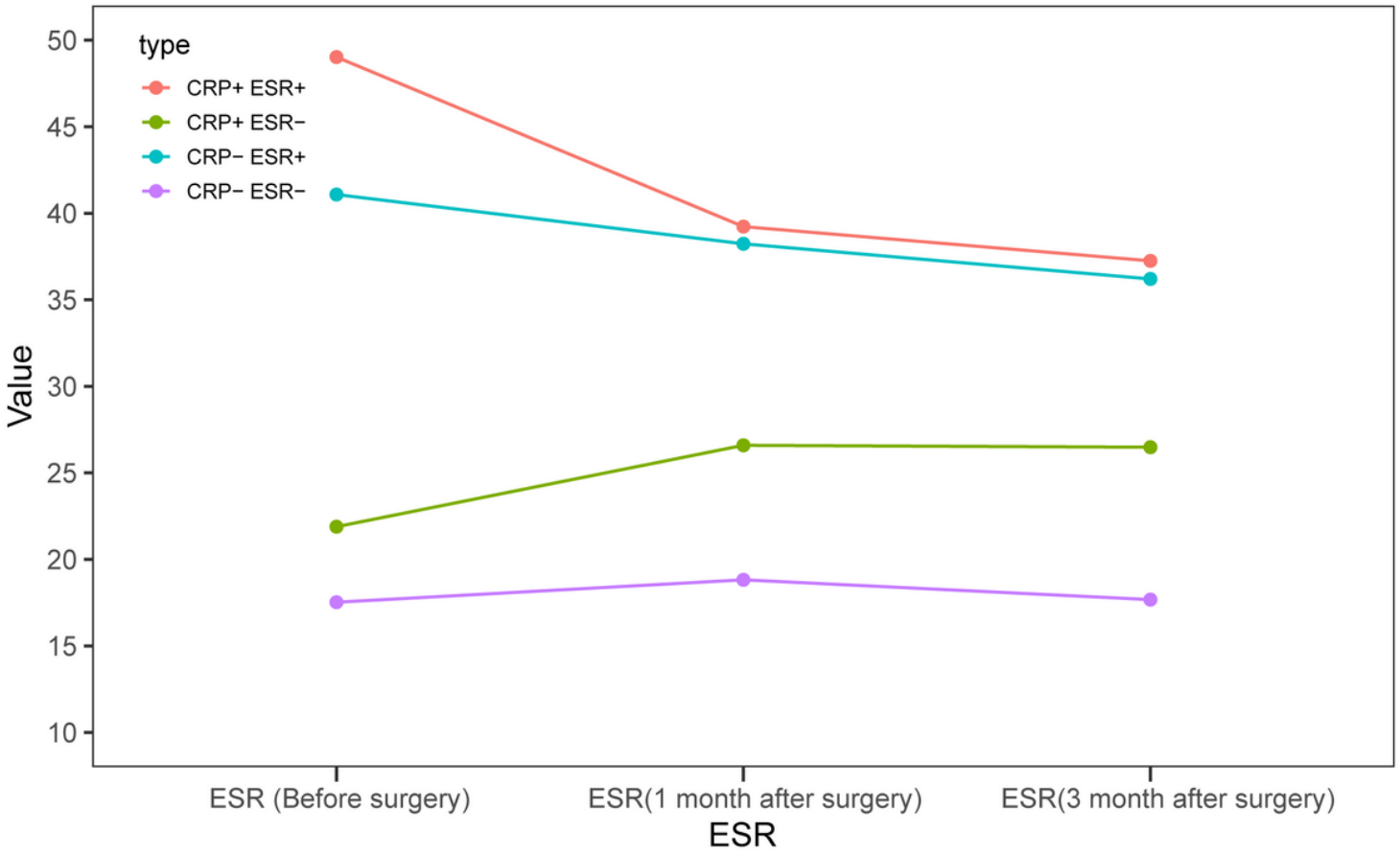

Figure 5

Variation tendency of the perioperative ESR level

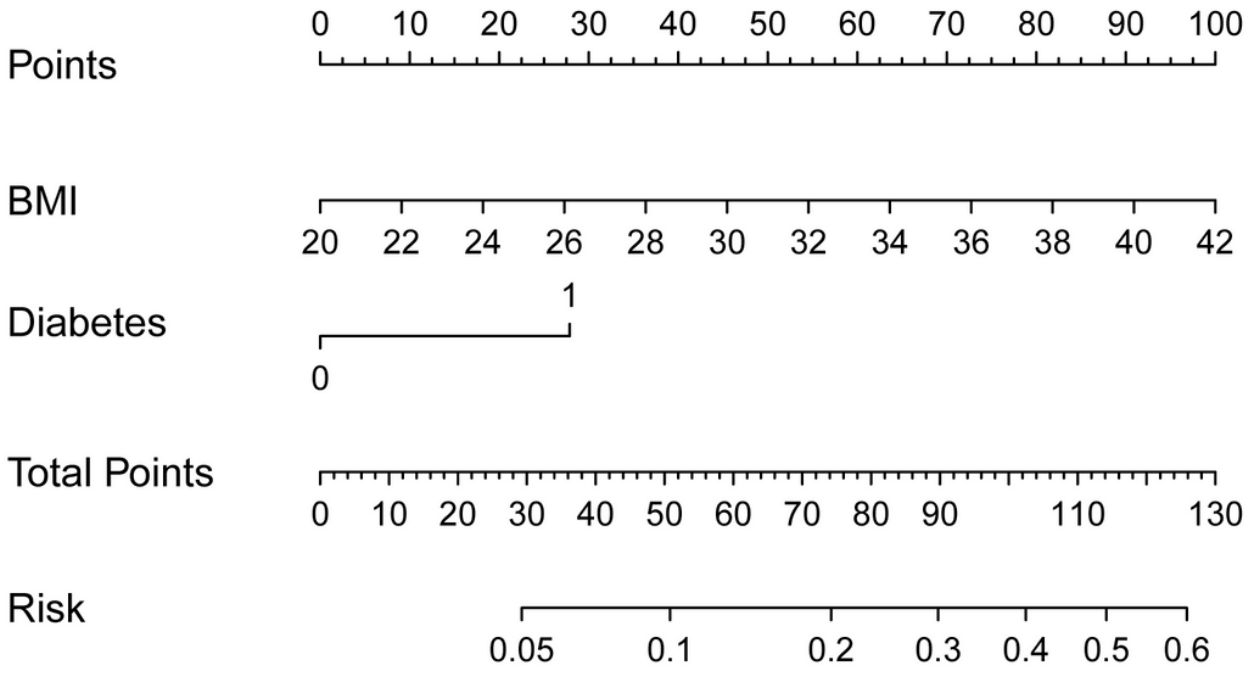

Figure 6

Nomogram predicting the CRP level in KOA patients (1 denoted as YES, 0 denoted as NO)

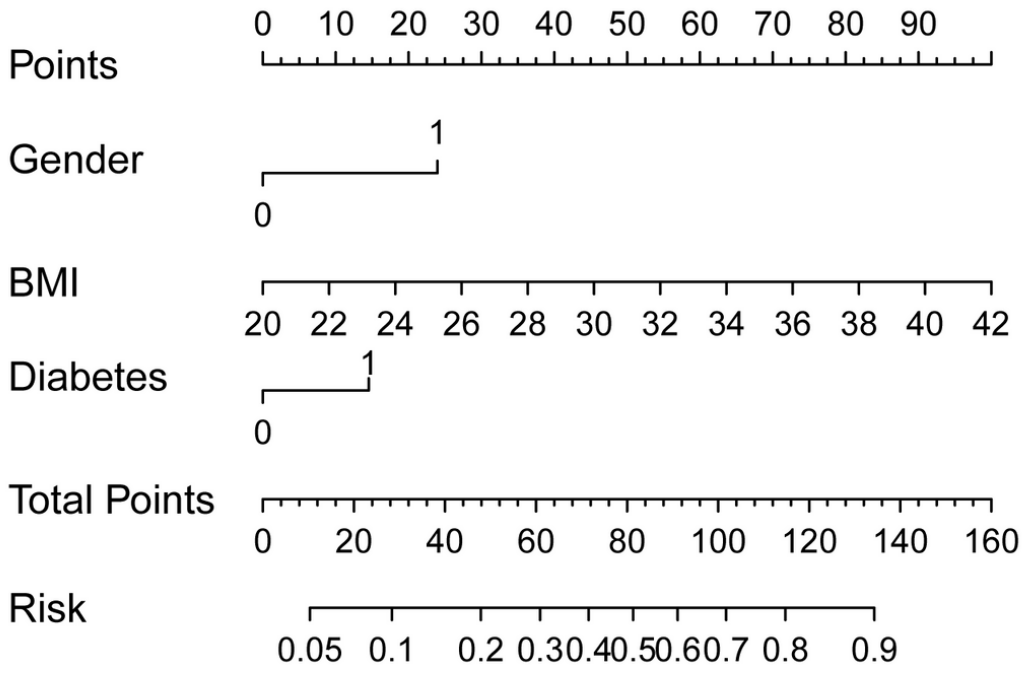

Figure 7

Nomogram predicting the ESR level in KOA patients (1 denoted as YES, 0 denoted as NO)

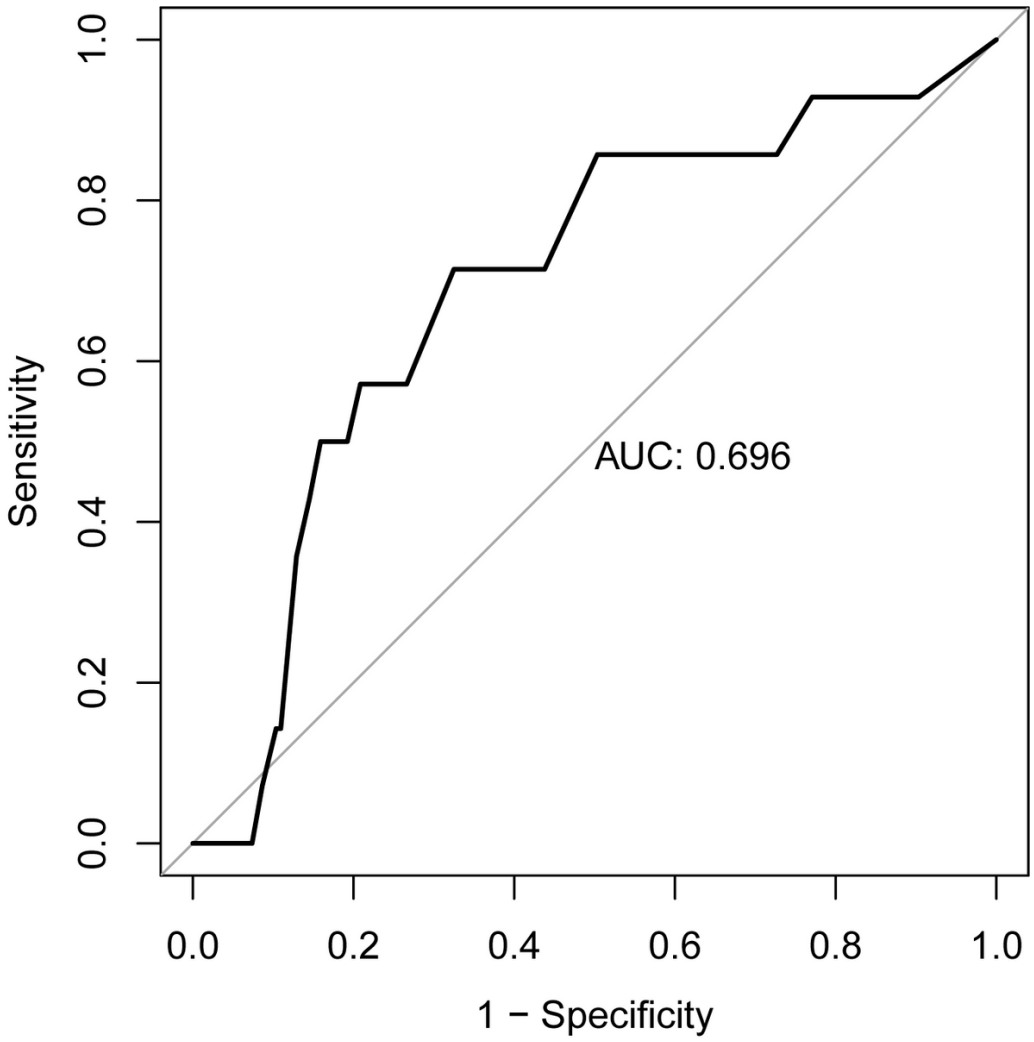

Figure 8

ROC curve of CRP for evaluating the predictive ability of the nomogram (AUC: AUROC)

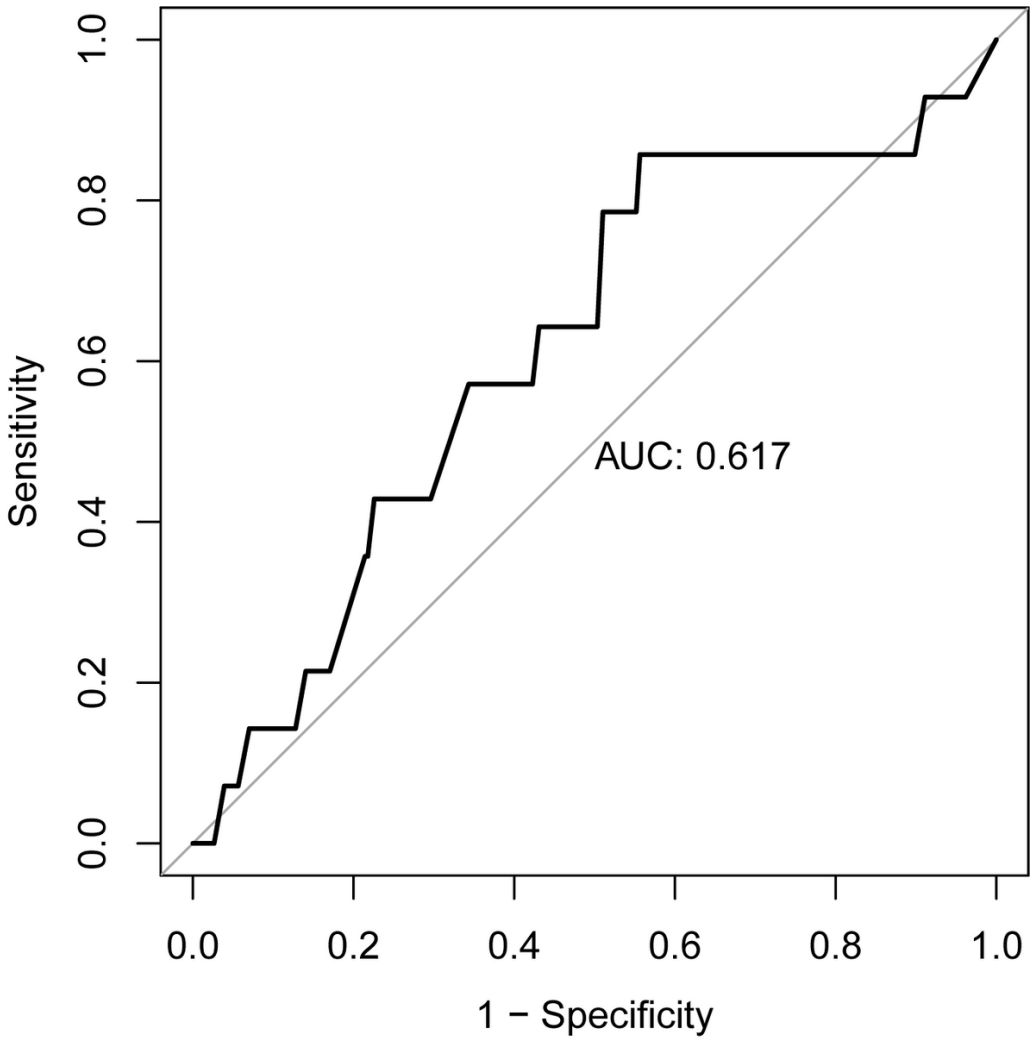

Figure 9

ROC curve of ESR for evaluating the predictive ability of the nomogram (AUC: AUROC)