

# Postoperative C-Reactive Protein Predicts Postoperative Delirium in Colorectal Cancer Following Surgery

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**Background:** Postoperative delirium (POD) is a common complication in operative patients. Neuroinflammation has been reported to be a potential mechanism associated with the development of POD. Identifying available inflammatory markers such as C-reactive protein (CRP) would aid clinicians in early detection of POD. Previous studies have demonstrated that CRP may be a promising predictive marker for POD. Thus, this study aimed to explore the association between CRP and POD among those elderly colorectal cancer (CRC) patients.

**Methods:** 643 patients with CRC were included in this study. CRP levels were measured before operation and on postoperative day 1. The univariate and multivariate regression analyses were used to identify risk factors for POD.

**Results:** Of 643 patients with CRC, 112 cases (17.4%) had POD. CRC patients with POD showed older age, higher CRP level on postoperative day 1, and higher percentage of smoking, diabetes mellitus, and chronic obstructive pulmonary disease (COPD) than CRC patients without POD. Preoperative CRP level was not associated with the POD. Univariate and multivariate regression analyses showed that older age (> 70 years), diabetes mellitus, COPD, and higher CRP level on postoperative day 1 (> 48 mg/L) were risk factors for POD in CRC patients.

**Conclusion:** Postoperative CRP level is an independent indicator for POD among CRC patients, suggesting the predictive role of postoperative CRP levels for POD in elderly CRC patients undergoing surgery.

**Keywords:** postoperative delirium, C-reactive protein, colorectal cancer

## Introduction

Delirium, an acute brain dysfunction, is characterized by inattention and fluctuating levels of consciousness.<sup>1</sup> It is primarily triggered by multiple factors, including drug use or withdrawal, acute medical illness, surgery, or trauma.<sup>2</sup> Postoperative delirium (POD) is a common complication in operative patients, which affects nearly 15 to 50% of older patients undergoing major surgery.<sup>3</sup> A host of studies have demonstrated that age, poor nutritional status, cognitive impairment, alcohol use, acute medical illness, trauma, and surgery were risk factor for delirium.<sup>3–6</sup> POD was associated with longer hospital stay time, long-term cognitive impairment, more postoperative complications, and overall prognosis for patients.<sup>7–11</sup>

Up to date, pharmacological treatments for POD are not effective, suggesting that substantial gaps in the understanding of its pathophysiology existed.<sup>12</sup> Studies indicated that immune activation, oxidative stress and inflammation may involve in the pathogenesis of delirium.<sup>12,13</sup> Identifying useful biomarkers to screen out high-risk individuals may help to the early diagnosis of POD and understanding its pathophysiology of POD. Inflammation was a well-established trigger of POD.<sup>14–17</sup> C-reactive protein (CRP), an acute-phase protein, is used to indicate acute systemic inflammation for clinicians. CRP was shown to be related to the development of mental disorders.<sup>18,19</sup> A host of studies showed that elevated CRP level was associated with the risk of dementia.<sup>20–23</sup> In addition, increased CRP level could predict delirium in critically ill patients,<sup>24</sup> elderly patients,<sup>25</sup> and surgical patients.<sup>26,27</sup> CRP was reported to be associated with the risk of

POD.<sup>28–30</sup> Several studies explored the association between CRP level and the risk of POD, but with contradictory results. For patients receiving orthopedic surgery, three studies found that postoperative CRP could predict POD,<sup>28,30,31</sup> while two studies indicated that preoperative CRP could not.<sup>32,33</sup> For non-orthopedic surgeries, CRP could predict POD in patients receiving esophagectomy,<sup>34</sup> vascular surgery,<sup>35</sup> laparoscopic surgery for colon carcinoma.<sup>36</sup> No association was observed between CRP and the risk of POD among oncological patients<sup>37</sup> or patients after cardiac surgery.<sup>38</sup> However, no studies investigated the relationship between preoperative and postoperative CRP levels and the risk of POD among patients with colorectal cancer (CRC) after surgery in Suzhou city. In this study, we aimed to explore the association of CRP levels with the risk of POD in CRC patients following surgery.

## Patients and Methods

### Participants

643 patients with CRC were included in this study from our hospital from July 2021 to July 2022 ([Supplementary Figure 1](#)). All included participants were elderly patients with CRC receiving surgery. The baseline characteristics and clinical data were collected. General characteristics of the participants included age, sex, drinking, smoking, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), types of CRC, body mass index (BMI), education, intestinal stoma, Mini-mental State Examination (MMSE) score, and anemia. Operation-related characteristics including surgical methods, blood loss, ASA score, operation time, anesthesia time, and narcotic drugs were recorded. The CRP levels were measured before operation (admission to our hospital within 24h) and on postoperative day 1. All individuals provided the signed informed consent. This study was approved by the Ethics Committee of First Affiliated Hospital of Soochow University. This study conformed to the *Helsinki declaration*.

### Inclusion and Exclusion Criteria

The inclusion criteria for CRC should include: (1) aged  $\geq 60$  years; (2) CRC patients received surgery; (3) ASA score ranged from I to III. Exclusion criteria were as follows: (1) patients without complete data; (2) patients with preexisting cognitive impairment or a history of delirium or dementia before surgery; (3) patients took antipsychotic drugs before surgery which may induce delirium; (4) patients had history of stroke or Alzheimer's disease; (5) patients had infection before operation or after operation; (5) patients had autoimmune diseases or myocardial infarction or other diseases could result in the increase of CRP level.

### Diagnosis of POD

The diagnosis of POD was according to the Confusion Assessment Method (CAM).<sup>39</sup> Delirium had the following features: (a) fluctuating course or acute change of mental status; (b) inattention; (c) confused thinking; (d) change in status of consciousness. The diagnosis of POD required the presence of feature (a) and (b), and either (c) or (d). POD in CRC patients was evaluated from postoperative day 1 to 7. POD was evaluated at the same time everyday once a day.

### Statistical Analysis

Categorical variables were presented as number (percentage) and analyzed by Fisher exact test or Chi-square test. Continuous variables were shown as means ( $\pm$  standard deviations) or median (with interquartile range) and analyzed by the Student's *t*-test or Mann–Whitney *U*-test. Receiver operating characteristic (ROC) curve was utilized to identify the optimal CRP level for POD. The risk factors for POD were identified using univariate and multivariate logistic regression analyses. Odds ratio (OR) and 95% confidence interval (CI) were calculated.  $P < 0.05$  was considered significant. SPSS (version 21.0, Chicago, IL, USA), and GraphPad Prism (version 8.0, La Jolla, CA, USA) software, MedCalc 20, and R software (version 4.1.3) were used to perform statistical analyses.

## Results

### Characteristics of the Participants

General characteristics and operation-related characteristics are shown in Table 1. A total of 643 patients with CRC were included; among them, 112 cases (17.4%) had POD. The association between POD and participants characteristics was investigated in this study. We found that CRC patients with POD showed older age, higher CRP level on postoperative day 1, and higher percentage of smoking, diabetes mellitus, and COPD than CRC patients without POD (Table 2). However, no significant differences were shown in sex, drinking, hypertension, types of CRC, anemia, surgical

**Table 1** The Demographic Characteristics of All CRC Patients

Variables	CRC Patients (n=643)
Age, mean (SD), (years)	69.31±5.12
Sex, n (%)	
Male	397 (61.7%)
Female	246 (38.3%)
Smoking, n (%)	
Yes	185 (28.8%)
No	458 (71.2%)
Drinking, n (%)	
Yes	132 (20.5%)
No	511 (79.5%)
Hypertension, n (%)	
Yes	354 (55.1%)
No	289 (44.9%)
Diabetes mellitus, n (%)	
Yes	69 (10.7%)
No	574 (89.3%)
COPD, n (%)	
Yes	75 (11.7%)
No	568 (88.3%)
Anemia, n (%)	
Yes	106 (16.5%)
No	537 (83.5%)
Types of CRC, n (%)	
Colon cancer	382 (59.4%)
Rectal cancer	261 (40.6%)
TNM stage, n (%)	
I	57 (8.8%)
II	390 (60.7%)
III	196 (30.5%)
Surgical methods, n (%)	
Laparoscopic surgery	625 (97.2%)
Open surgery	18 (2.8%)
Blood loss, mL	146.73±24.63
ASA score, n (%)	
I	35 (5.5%)
II	505 (78.5%)
III	103 (16.0%)
Education, n (%)	
> High school	250 (38.9%)
≤ High school	393 (61.1%)
MMSE score	25.53±1.73
BMI	21.42±1.71

(Continued)

**Table 1** (Continued).

Variables	CRC Patients (n=643)
Intestinal stoma, n (%)	
Yes	268 (41.7%)
No	375 (58.3%)
Operation time, h	3.67±0.32
Anesthesia time, h	3.92±0.32
Narcotic drugs, n (%)	
Dexmedetomidine	354 (55.1%)
Propofol	412 (64.1%)
Sevoflurane	643 (100%)
Sufentanil	643 (100%)
CRP levels (mg/L)	
Preoperatively, median (IQR)	3.7 (3.1–4.4)
Postoperative day 1, median (IQR)	48.1 (38.8–59.3)

**Abbreviations:** TNM, tumor node metastasis; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CRP, C-reactive protein; IQR, interquartile range; BMI, body mass index; MMSE score, Mini-mental State Examination score.

**Table 2** The Demographic Characteristics of CRC Patients in Patients with or Without Delirium

Variables	Delirium (112)	Non-Delirium (531)	P-value
Age, mean (SD), (years)	70.94±6.38	68.97±4.75	<b>0.002</b>
Sex, n (%)			0.143
Male	76 (67.9%)	321 (60.5%)	
Female	36 (32.1%)	210 (39.5%)	
Smoking, n (%)			<b>0.013</b>
Yes	43 (38.4%)	142 (26.7%)	
No	69 (61.6%)	389 (73.3%)	
Drinking, n (%)			0.197
Yes	28 (25.0%)	104 (19.6%)	
No	84 (75.0%)	427 (80.4%)	
Hypertension, n (%)			0.890
Yes	61 (54.5%)	293 (55.2%)	
No	51 (45.5%)	238 (44.8%)	
Diabetes mellitus, n (%)			<b>0.007</b>
Yes	20 (17.9%)	49 (9.2%)	
No	92 (82.1%)	482 (90.8%)	
Types of CRC, n (%)			0.166
Colon cancer	60 (53.6%)	322 (60.6%)	
Rectal cancer	52 (46.4%)	209 (39.4%)	
TNM stage, n (%)			0.939
I	9 (8.0%)	48 (9.0%)	
II	69 (61.6%)	321 (60.5%)	
III	34 (30.4%)	162 (30.5%)	
Surgical methods, n (%)			0.303
Laparoscopic surgery	111 (99.1%)	514 (96.8%)	
Open surgery	1 (0.9%)	17 (3.2%)	
Blood loss, mL	148.84±26.77	146.29±24.15	0.320

(Continued)

Table 2 (Continued).

Variables	Delirium (112)	Non-Delirium (531)	P-value
ASA score, n (%)			0.574
I	4 (3.6%)	31 (5.8%)	
II	88 (78.6%)	416 (78.4%)	
III	20 (17.8%)	84 (15.8%)	
Education, n (%)			0.907
>High school	43 (38.4%)	207 (39.0%)	
≤High school	69 (61.6%)	324 (61.0%)	
MMSE score	25.28±1.48	25.59±1.78	0.084
BMI	21.45±1.74	21.41±1.71	0.858
Intestinal stoma, n (%)			0.123
Yes	54 (48.2%)	214 (40.3%)	
No	58 (51.8%)	317 (59.7%)	
Operation time, h	3.67±0.30	3.67±0.32	0.910
Anesthesia time, h	3.93±0.30	3.92±0.33	0.868
Narcotic drugs, n (%)			
Dexmedetomidine	63 (56.3%)	291 (54.8%)	0.780
Propofol	75 (67.0%)	337 (63.5%)	0.483
Sevoflurane	112 (100%)	531 (100%)	-
Sufentanil	112 (100%)	531 (100%)	-
COPD, n (%)			<b>&lt;0.001</b>
Yes	27 (24.1%)	48 (9.0%)	
No	85 (75.9%)	483 (91.0%)	
Anemia, n (%)			0.477
Yes	21 (18.7%)	85 (16.0%)	
No	91 (81.3%)	446 (84.0%)	
CRP levels (mg/L)			
Preoperatively	3.7 (3.3–4.6)	3.7 (3.0–4.4)	0.138
Postoperative day 1	58.1 (50.6–67.8)	45.7 (36.6–56.5)	<b>&lt;0.001</b>

**Note:** Bold values are statistically significant ( $P < 0.05$ ).

**Abbreviations:** TNM, tumor node metastasis; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CRP, C-reactive protein.

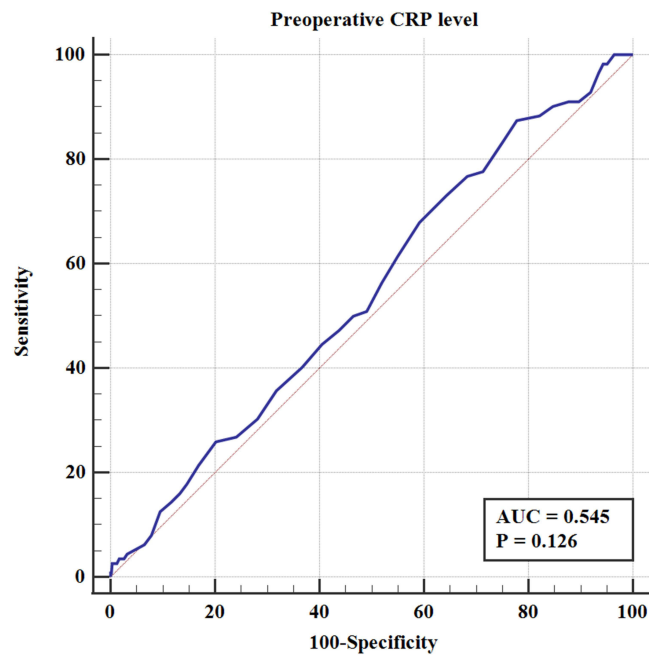
methods, blood loss, ASA score, education, BMI, MMSE score, operation time, anesthesia time, narcotic drugs, and CRP level before operation between POD and non-POD group.

## Diagnostic Value of CRP for POD

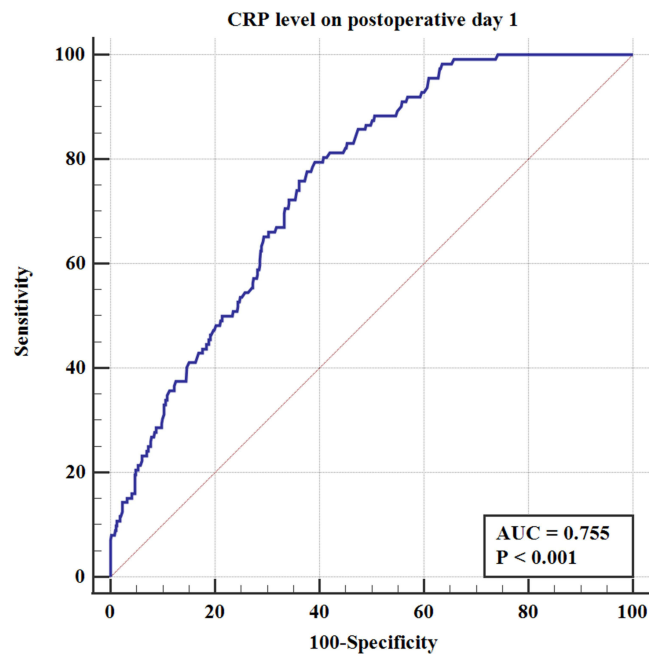
The diagnostic value of CRP levels for POD was investigated. ROC curve analysis presented high accuracy for CRP level on postoperative day 1 to predict POD with AUC of 0.755 (Figure 1), and the sensitivity and specificity were 79.46 and 60.83, respectively. However, the AUC of preoperative CRP level was 0.545 (Figure 2). To sum up, the diagnostic ability of CRP level on postoperative day 1 for POD was good.

## Risk Factors for POD

Univariate and multivariate analyses were used to identify risk factors for POD among CRC patients. The univariate analysis showed that older age ( $> 70$  years), smoking, diabetes mellitus, COPD, and higher CRP level on postoperative day 1 ( $> 48$  mg/L) were associated with POD (Table 3). The multivariate analysis indicated that older age ( $> 70$  years), diabetes mellitus, COPD, and higher CRP level on postoperative day 1 ( $> 48$  mg/L) were risk factors for POD (Figure 3, and Table 4). In addition, we found that older age ( $> 70$  years), smoking, diabetes mellitus, COPD, and higher CRP level on postoperative day 1 ( $> 48$  mg/L) were risk factors for POD among CRC patients following laparoscopic surgery (Supplementary Tables 1 and 2).



**Figure 1** ROC curve of preoperative CRP with postoperative delirium.



**Figure 2** ROC curve of CRP on postoperative day 1 with postoperative delirium.

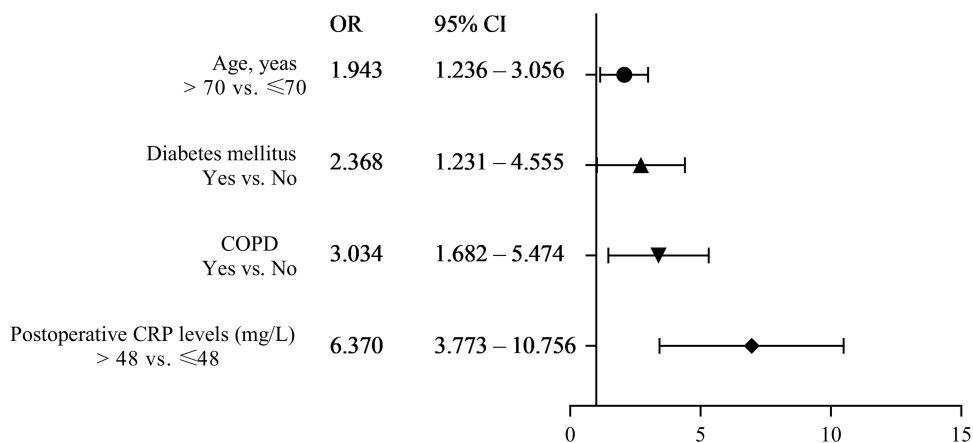
Last, a nomogram model was built to predict POD according to the results of multivariate logistic regression analysis (Figure 4). This nomogram showed a good predictive ability for POD, which was shown by the C-index value of 0.762 (95% CI= 0.710–0.815). In addition, the calibration curve suggested that this nomogram model showed a good consistency between the predicted probability and actual results (Figure 5).

**Table 3** Univariate Logistic Regression Analyses to Identify the Risk Factors for Postoperative Delirium

Variables	B	S.E.	Wals	P-value	OR	95% CI
Age, years >70 vs ≤70	0.540	0.209	6.654	<b>0.010</b>	1.715	1.138–2.584
Sex Male vs Female	0.323	0.221	1.136	0.144	1.381	0.896–2.130
Smoking Yes vs No	0.535	0.218	6.040	<b>0.014</b>	1.707	1.114–2.615
Drinking Yes vs No	0.314	0.244	1.653	0.199	1.369	0.848–2.208
Hypertension Yes vs No	−0.029	0.209	0.019	0.890	0.972	0.645–1.463
Diabetes mellitus Yes vs No	0.760	0.289	6.931	<b>0.008</b>	2.138	1.214–3.766
Types of CRC Rectal cancer vs Colon cancer	0.289	0.209	1.909	0.167	1.335	0.886–2.012
TNM stage III vs I–II	−0.007	0.226	0.001	0.975	0.993	0.637–1.546
Surgical methods Open surgery vs Laparoscopic surgery	−1.301	1.034	1.581	0.209	0.272	0.036–2.068
Blood loss, mL >140 vs ≤140	0.105	0.208	0.256	0.613	1.111	0.739–1.671
ASA score III vs I–II	0.146	0.274	0.283	0.595	1.157	0.676–1.979
Education >High school vs. ≤high school	−0.025	0.214	0.014	0.907	0.975	0.642–1.483
MMSE score ≤26 vs >26	0.243	0.251	0.939	0.333	1.275	0.780–2.084
BMI ≤24 vs >24	−0.213	0.371	0.329	0.567	0.809	0.391–1.672
Intestinal stoma Yes vs No	0.321	0.209	2.371	0.124	1.379	0.916–2.076
Operation time, h >3.7 vs ≤3.7	−0.210	0.216	0.949	0.330	0.810	0.530–1.237
Anesthesia time, h >3.9 vs ≤3.9	−0.132	0.210	0.391	0.532	0.877	0.580–1.324
Narcotic drugs Dexmedetomidine Yes vs No	0.059	0.209	0.078	0.780	1.060	0.703–1.599
Propofol Yes vs No	0.154	0.220	0.491	0.483	1.167	0.758–1.797
COPD Yes vs No	1.162	0.268	18.830	<b>&lt;0.001</b>	3.196	1.891–5.402
Anemia Yes vs No	0.191	0.269	0.504	0.478	1.211	0.714–2.053
CRP levels (mg/L) Preoperatively >3.7 vs ≤3.7	0.070	0.208	0.112	0.738	1.072	0.713–1.612
Postoperative day I >48 vs ≤48	1.743	0.257	45.835	<b>&lt;0.001</b>	5.715	3.450–9.466

**Note:** Bold values are statistically significant ( $P < 0.05$ ).

**Abbreviations:** TNM, tumor node metastasis; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CRP, C-reactive protein; BMI, body mass index; MMSE score, Mini-mental State Examination score.



**Figure 3** The multivariate logistic regression analyses of the factors of postoperative delirium.

## Discussion

Herein, this study found that serum CRP level on postoperative day 1 was associated with the risk of POD in CRC patients following surgery, suggesting that postoperative CRP was an independent indicator for POD for CRC patients.

POD is an important issue for patients receiving surgery, especially for the elderly patients.<sup>40</sup> POD could increase the hospital stay time, and was related with survival of patients.<sup>9</sup> Identifying helpful biomarkers for early diagnosis of POD in high-risk patients is necessary for clinicians. Recently, CRP has been regarded as a good predictor for POD in many studies. Lee et al found that CRP levels on postoperative day 1 and 3 were significantly higher in the delirium group than in the non-POD group in elderly patients after hip surgery.<sup>28</sup> Two studies showed that postoperative CRP level predicted POD among patients receiving cervical or lumbar surgery<sup>31</sup> and older patients after hip surgery.<sup>30</sup> Neerland et al indicated that preoperative cerebrospinal fluid level of CRP was associated with delirium.<sup>26</sup> However, Lemstra et al<sup>32</sup> and Pan et al<sup>33</sup> showed that preoperative CRP level was not an independent predictor for POD among orthopedic patients after surgery.

Except for orthopedic surgery, previous studies investigated the association between POD and preoperative and postoperative CRP levels in other major elective surgery. Two studies found a significant association between preoperative and postoperative CRP levels and the risk of POD,<sup>27,41</sup> while Hasegawa et al revealed that preoperative and postoperative CRP levels were not associated with the risk of POD after surgery for oral cancer.<sup>42</sup> In addition, preoperative CRP level was

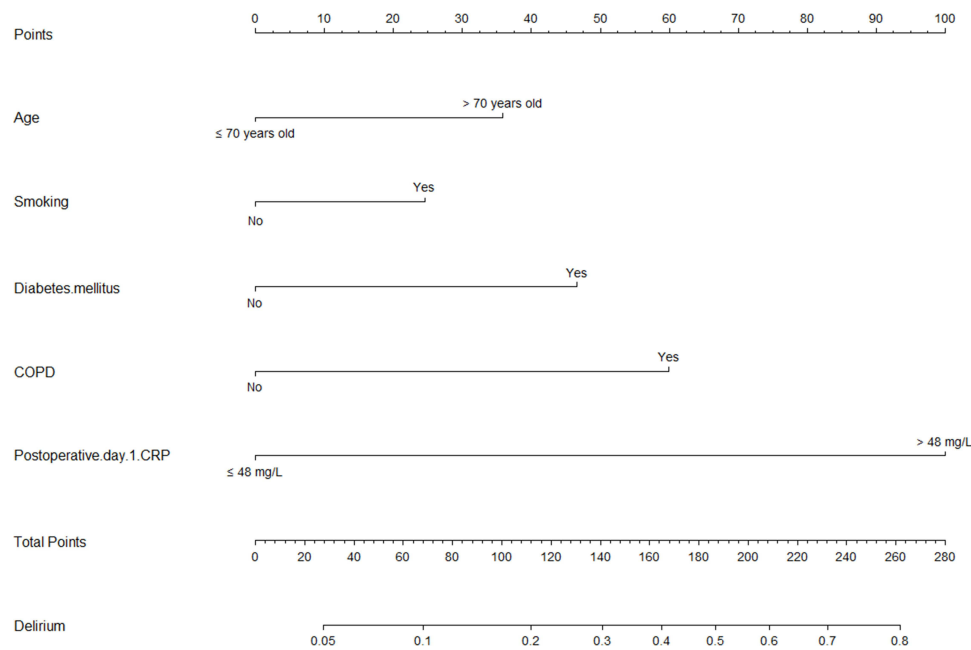
**Table 4** Multivariate Logistic Regression Analyses to Identify the Risk Factors for Postoperative Delirium

Variables	B	S.E.	Wals	P-value	OR	95% CI
Age, years >70 vs ≤70	0.664	0.231	8.270	<b>0.004</b>	1.943	1.236–3.056
Smoking Yes vs No	0.456	0.238	3.652	0.056	1.577	0.988–2.517
Diabetes mellitus Yes vs No	0.862	0.334	6.671	<b>0.010</b>	2.368	1.231–4.555
COPD Yes vs No	1.110	0.301	13.597	<b>&lt;0.001</b>	3.034	1.682–5.474
CRP levels (mg/L) Postoperative day 1 >48 vs ≤48	1.852	0.267	47.995	<b>&lt;0.001</b>	6.370	3.773–10.756

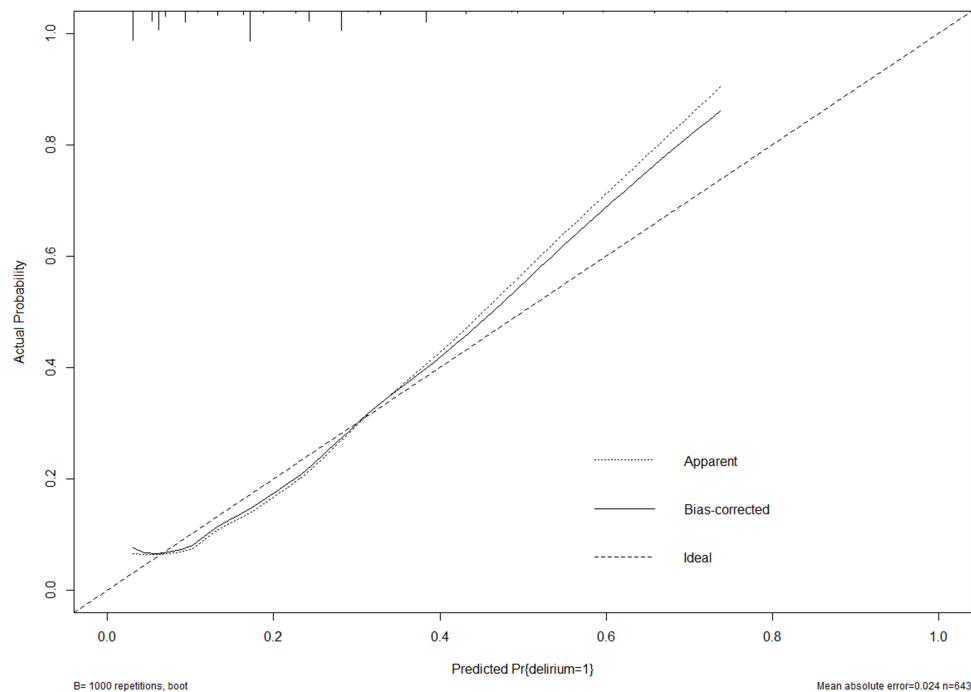
**Note:** Bold values are statistically significant ( $P < 0.05$ ).

**Abbreviations:** COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein.





**Figure 4** A diagnostic nomogram for the prediction of postoperative delirium.



**Figure 5** Calibration curve of the diagnostic nomogram for the prediction of postoperative delirium.

a risk factor for POD;<sup>43,44</sup> however, Çinar et al showed that it was not associated with the risk of POD.<sup>45</sup> In addition, postoperative CRP level was an independent risk factor for POD following vascular surgery<sup>35</sup> or esophagectomy.<sup>34</sup>

In line with most of abovementioned studies, no association between preoperative CRP level and POD in patients with CRC following surgery was observed in this study. However, we found that serum CRP level on postoperative day 1 was associated with the risk of POD in these CRC patients. In contrast to our study, Xiang et al showed that preoperative CRP was an independent predictor for POD in patients with colon carcinoma undergoing laparoscopic surgery.<sup>36</sup>

Obviously, the study by Xiang et al and our study yielded inconsistent results. We thought the following factors may explain it. One, different sample sizes could affect the final results. Our study and the study by Xiang et al<sup>36</sup> included 643 and 160, respectively. Two, the studied populations differed. Xiang et al<sup>36</sup> did not include the patients with rectal cancer. Three, different definitions of POD and/or clinical heterogeneity may also be potential reasons. Collectively, this study showed that postoperative CRP level was a good predictor for POD in CRC patients, which was in consistent with the results by previous meta-analyses.<sup>15,17</sup>

Age was a well-established risk factor for delirium, and was an independent predictor for delirium.<sup>46–49</sup> As expected, we found that older age (> 70 years) was a risk factor for POD in patients with CRC by multivariate analysis, which was not shown in the study by Xiang et al.<sup>36</sup> They showed that the age was a risk factor for POD in univariate analysis, but not in multivariate analysis,<sup>36</sup> which might be due to limited sample size or clinical heterogeneity. Additionally, we observed that diabetes mellitus, and COPD were also risk factors for POD in this study. According to the results of multivariate logistic regression analysis, a nomogram model was generated to predict POD for CRC patients. This nomogram model showed a good predictive ability for POD with a C-index value of 0.762. It is of note that the AUC of CRP level on postoperative day 1 to predict POD was 0.755. It seems that the nomogram model with multi-factors did not significantly increase predictive ability than that of the CRP level on postoperative day 1 (0.762 vs 0.755). On one hand, it indicated that the ability of CRP level on postoperative day 1 to predict POD was good. On the other hand, it may suggest the nomogram model may not include important factors, which may remarkably increase the predictive ability of this nomogram model. Therefore, a nomogram model with more factors is needed to verify it in the future. Furthermore, the calibration curve found that this nomogram model showed a good consistency between the predicted results and actual observations.

Several limitations were summarized in this study. First, this study was a single-center study with moderate sample size. Second, the younger CRC patients (age < 60 years) should be investigated. Third, some potential confounding factors might exert effects on the final results. Fourth, the CRP levels on postoperative day 2 or longer were measured incompletely, which prevented further analysis. Fifth, there were only a few open cases and the majority were laparoscopic. Therefore, the sample size of open cases was limited. Sixth, controlling for anesthetized medications on the BEERs criteria was not performed in this study. In the future, it is necessary to utilize the BEERs criteria. Last, the underlying mechanisms why CRP could predict POD should be explored in future.

## Conclusion

In conclusion, this study shows that postoperative CRP is associated with the risk of POD in CRC patients. Postoperative CRP is an independent indicator for POD for CRC patients.

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## Disclosure

The authors report no conflicts of interest in this work.

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