# Efficacy of CRP In Combination With D-Dimer In Predicting Adverse Postoperative Outcomes of Patients With Acute Stanford Type A Aortic Dissection

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**Research article**

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# Abstract

**Objectives:** The present study aimed to evaluate the efficacy of CRP and D-dimer and the combination of them as prognostic indicators for patients with acute type A aortic dissection (ATAAD).

**Methods:** This is a retrospective cohort study. From January 2017 to December 2020, all consecutive patients with ATAAD admitted to the emergency medicine center of our hospital within 24 hours after symptoms (chest pain, back pain, abdominal pain and so on) onset were enrolled in our study. Serum concentration of CRP and D-dimer were measured on admission. The univariate and multivariate logistic regression analyses were used to identify these predictors of adverse postoperative outcomes by adjusting other thrombotic or inflammatory biomarkers. Predictive efficacy was defined by area under the curve (AUC) of receiver operating characteristic curve (ROC).

**Results:** A total of 213 patients with ATAAD were finally enrolled. They were categorized as group A (n=160) and group B (n=53) according to postoperative outcomes. Compared with group A, CRP levels of group B were higher (22.40(10.00, 32.51) vs. 11.06(6.21, 22.88), p<0.01)and so were D-dimer levels (12.55(7.74, 30.92) vs 6.21(2.75, 9.45), p<0.01). After controlling for potentially relevant confounding variables, we found admission CRP and D-dimer were independent predictors of adverse postoperative outcomes (odds ratio, 1.163; 95% CI, 1.066 to 1.269; p = 0.001; odds ratio, 1.227; 95% CI, 1.096 to 1.374; p<0.001, respectively). The predictive accuracy of the combination of CRP and D-dimer (AUC 0.849) was superior to that of CRP or D-dimer alone (AUC 0.669 0.763, respectively).

**Conclusion:** CRP and D-dimer on admission are independent predictors of adverse postoperative outcomes in patients with ATAAD, which are easy to get without paying more either for the individual or the medical system. Combination of these two markers will improve the predictive efficacy.


# Background

Acute Stanford type A aortic dissection (ATAAD) is a catastrophic cardiovascular emergency in adults, associated with high morbidity and mortality[1]. Inflammation and thrombosis are two main mechanisms that contribute to the pathogenesis of ATAAD[2]. Based on that, inflammatory and thrombotic biomarkers associated with adverse outcomes are emerging[3,4]. Whether these inflammatory and thrombotic biomarkers as risk-prediction tools for the short-term results remains controversial. Perfect predictive methods can help the surgeon identify patients at higher risk of AD and thus providing appropriate and prompt medical intervention.

In recent years, CRP and D-dimer are proven to have prognostic significance in various cardiovascular diseases[5,6]. Inflammation and thrombosis through a cascade of these markers (such as CRP and D-dimer) result in the onset of aortic dissection along with subsequent aortic rupture[7,8]. It is important to choose the appropriate detection time window for these markers because of their exhibition in different time course of their changes in the acute phase[9,10].

Although the individual prognostic ability of CRP, and D-dimer in ATAAD has been studied extensively, few studies have taken CRP and D-dimer exhibiting different time courses of their changes into consideration and investigated their combined efficacy of predicting adverse postoperative outcomes. In the present study, we aimed at evaluating the efficacy of these two biomarkers obtained from serum tests alone and the combination of them as prognostic indicators for patients with ATAAD.

# Materials And Methods

### Study Cohort

From January 2017 to December 2020, consecutive patients diagnosed with ATAAD who were admitted to the emergency center of Jiangsu Province Hospital were enrolled in our study. The study was approved by the ethical committee of the First Affiliated Hospital of Nanjing Medical University. The diagnosis of ATAAD was mainly confirmed by computed tomographic angiography (CTA). Patients with ATAAD within 24 hours after symptom onset were enrolled in our study. Exclusion criteria were: (1) patients died due to aortic dissection rupture (2) symptoms of patients last more than 24 hours (3) patients died postoperatively within 24 hours.

### Definitions

Adverse postoperative outcomes were defined as acute renal failure requiring dialysis, respiratory insufficiency(prolonged ventilation), limb ischemia and mortality. Symptoms of patients with ATAAD were chest pain, back pain, abdominal pain, severe or worst ever pain, abrupt onset of pain and syncope.

### Data Collection

Baseline characteristics data (such as sex, age, body mass index, hypertension, diabetes mellitus and so on) were recorded in our database. The laboratory results that were obtained by collecting the patients‘ serum samples on the day of admission to the hospital. Serum concentration of leukocyte counts, neutrophil counts, lymphocyte counts, monocyte counts, platelet counts, CRP, D-dimer and fibrinogen were measured.

### Statistical Analysis

All statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) software (SPSS, Inc., Chicago, Illinois, USA), version 23.0. Categorical variables were expressed in the form of frequencies and percentages. Quantitative data were statistically presented according to its distribution. Normally distributed continuous variables are presented as mean± standard deviation (SD), while non-normally distributed continuous variables are presented as median (interquartile range [IQR]). Variations between interventions are reported as mean differences with 95% confidence intervals (95% CI). Unpaired Student‘s t-tests and Wilcoxon-Mann-Whitney tests were applied for continuous data according to their different distributions. Chi-square tests were applied for categorical data. The univariate and multivariate logistic regression analyses were used to identify these three in-hospital

mortality predictors by adjusting other thrombotic or inflammatory biomarkers (such as fibrinogen, leukocyte and so on). Receiver operating characteristic (ROC) analysis was performed to determine the cut-off value for CRP and D-dimer in predicting adverse postoperative outcomes with high sensitivity and specificity. The statistical difference of AUC was evaluated between the two individual biomarkers and their combination using the Delong method. P<0.05 was considered statistically significant (two-sided).

## Results

# Baseline Characteristics of Participants

A total of 345 patients diagnosed with type A AAD were identified in the present study between January 1, 2017 and December 31, 2020. Of these patients, 121 were excluded for symptoms lasting more than 24 hours. 9 were excluded because of aortic dissection rupture. After exclusion of two patients because of death within 24 hours postoperatively. Finally, a total of 213 patients with ATAAD were studied (Fig. 1). There were 162 male and 51 female patients. Baseline characteristics of two cohorts grouped by postoperative outcomes were listed in Table 1. Higher levels of WBC, D-dimer, fibrinogen and C-reactive protein were significantly associated with adverse postoperative outcomes. The D-dimer was 6.21(2.75, 9.45) in group A and 12.55(7.74, 30.92) in group B. The C-reactive protein was 11.06(6.21, 22.88) in group A and 22.40(10.00, 32.51) in group B (P < 0.01). Additionally, there were no significant differences between the groups in terms of age, gender, BMI, smoke, alcohol consumption, diabetes mellitus, hypertension, Marfan syndrome, NLR, MLR and platelet.

Table 1
Baseline characteristics of patients for adverse postoperative outcomes.

| Variables | Group A(n = 160) | Group B(n = 53) | *p* value |
|---|---|---|---|
| Age(years) | 54.38 ± 12.77 | 53.43 ± 11.06 | 0.63 |
| Male gender (n,%) | 115(71.9) | 43(81.1) | 0.18 |
| BMI | 24.90 ± 3.44 | 24.91 ± 3.17 | 0.98 |
| Smoker, n (%) | 80(50.0) | 23(43.4) | 0.40 |
| Alcohol consumption, n (%) | 47(29.4) | 22(41.5) | 0.10 |
| Diabetes mellitus, n (%) | 24(15.0) | 5(9.4) | 0.31 |
| Hypertension, n (%) | 130(81.3) | 45(84.9) | 0.55 |
| Marfan syndrome, n (%) | 8(5.0) | 2(3.8) | 0.53 |
| WBC ($10^9$/L) median(IQR) | 11.43(9.01, 14.37) | 12.44(10.15, 16.96) | < 0.01 |
| NLR | 8.46(3.60, 14.65) | 10.94(6.00, 14.97) | 0.16 |
| MLR | 0.58(0.32, 0.96) | 0.70(0.47, 0.93) | 0.30 |
| Platelet ($10^9$/L) | 164.00(127.00, 212.00) | 166.00(136.50, 210.00) | < 0.59 |
| D-dimer (mg/L) | 6.21(2.75, 9.45) | 12.55(7.74, 30.92) | < 0.01 |
| Fibrinogen (mg/L) | 2.39(1.77, 3.60) | 1.85(1.43, 3.02) | 0.01 |
| CRP (mg/L) | 11.06(6.21, 22.88) | 22.40(10.00, 32.51) | < 0.01 |

## Univariate Analysis and Multivariate Logistic Regression Analysis of Predictors for Adverse Postoperative Outcomes

Univariate analysis detected WBC, D-dimer and CRP demonstrating a significant association with adverse postoperative outcomes (Table 2). Table 3 showed that after controlling for potentially relevant confounding variables, C-reactive protein, D-dimer and were independent predictors for in-hospital mortality in multivariate logistic regression analysis (odds ratio, 1.163; 95% CI, 1.066 to 1.269; p = 0.001; odds ratio, 1.227; 95% CI, 1.096 to 1.374; p < 0.001, respectively).

Table 2
Univariate analyses of relationship between inflammatory and thrombotic markers and adverse postoperative outcomes in patients with TAAD.

| Variables | OR | 95%CI | *p* value |
|---|---|---|---|
| WBC | 1.127 | 1.045 to 1.216 | .002 |
| Fibrinogen(mg/L) | 0.817 | 0.651 to 1.026 | .082 |
| D-dimer(mg/L) | 1.083 | 1.052 to 1.115 | < 0.001 |
| C-reactive protein | 1.046 | 1.022 to 1.070 | < 0.001 |

Table 3
Multivariate logistic regression analyses of the prognostic factors for adverse postoperative outcomes in patients with TAAD.

| Variables | OR | 95%CI | *p* value |
|---|---|---|---|
| WBC | 0.760 | 0.567 to 1.019 | .067 |
| Fibrinogen (mg/L) | 0.943 | 0.718 to 1.240 | .675 |
| D-dimer (mg/L) | 1.227 | 1.096 to 1.374 | < 0.001 |
| C-reactive protein (mg/L) | 1.163 | 1.066 to 1.269 | 0.001 |

## ROC Curves of Biomarkers for Adverse Postoperative Outcomes

ROC curves for adverse postoperative outcomes of D-dimer and C-reactive protein were shown in Fig. 2. It was shown in the Table 4 that with a cutoff value of 13.98, CRP exhibited sensitivity of 67.9%, specificity of 66.9%. With a cutoff value of 9.77, D-dimer exhibited sensitivity of 64.2%, specificity of 78.1%. The AUC of CRP and D-dimer was 0.669 (95% CI 0.583–0.755, p < 0.001) and 0.763(95% CI 0.689–0.836, p < 0.001).

Table 4
Comparison of predictive efficacy between individual biomarkers and their combination

| | AUC | 95%CI | P value | P* |
|---|---|---|---|---|
| C-reactive protein | 0.669 | 0.583 to 0.755 | < 0.001 | 0.013 |
| D-dimer | 0.763 | 0.689 to 0.836 | < 0.001 | < 0.001 |
| Combined two biomarkers | 0.849 | 0.800 to 0.902 | < 0.001 | |

* The statistical difference of AUC was evaluated between the two individual biomarkers and their combination using the Delong method.

**Combination of Biomarkers to Predict Adverse Postoperative Outcomes**

To get a better prediction for adverse postoperative outcomes, we combined these two biomarkers (CRP and D-dimer) that could predict adverse postoperative outcomes in multivariate regression models of each patient on a ROC. The AUC was 0.849 (95% CI 0.800 to 0.902, $p < 0.001$) (Fig. 2). The statistical difference of AUC was evaluated between CRP and combination ($p = 0.013$) and between D-dimer and combination ($p < 0.001$) using the Delong method.The AUC values for the combined biomarkers were more predictive than any individual one.

# Disscussion

This study showed that CRP and D-dimer are useful predictors of adverse postoperative outcomes in patients with ATAAD. Those who had high CRP level and high D-dimer level on admission within 24 hours after symptom onset were prone to adverse postoperative outcomes. Moreover, combined these two biomarkers (CRP, and D-dimer) were more predictive than any marker alone, which was the strongest. The calculation of these two inexpensive biomarkers is easy to get without paying more either for the individual or the medical system, which increases the potential value.

Biomarkers in the acute inflammatory and thrombotic response were associated with the prognosis of ATAAD [11–15]. The inflammation within the wall damages the aorta, making it easily enlarge and vlunrable to rupture. The coagulation system is activated by extensive inflammation and the reverse is also true via crosstalk[16]. Attention have been focused on the prognostic value of individual indicators such as MLR and NLR for ATAAD in previous studies[17,18], which is unable to obtain an ideal prediction efficacy. New research demonstrates that ATAAD results from a combination of inflammation and thrombosis[19]. CRP plays an important role in the inflammatory state of ATAAD, while platelets and D-dimer reflect the thrombotic state in ATAAD[20,21]. Although previous studies confirmed that CRP and D-dimer exhibited different time course of their changes in the acute phase[9,10], time from the symptom onset of patients in the present study is within 24 hours, which attenuates the impact. Hence, these two biomarkers namely CRP and D-dimer that integrate multiple pathways of inflammatory and thrombotic processes may provide a more predictive assessment of the prognosis of ATAAD patients. We have also demonstrated that the combination of inflammatory biomarkers (CRP) and thrombotic marker (D-dimer) is a strong

predictor of adverse postoperative outcomes than either of these two biomarkers alone. Besides, the two biomarkers were obtained from serum samples, which were readily available and greatly significant in terms of economy for poor areas, compared to other laboratory tests for ATAAD.

CRP is a sensitive and non-specific inflammatory biomarker, readily available and relatively inexpensive in routine clinical practice[22]. CRP which is mainly synthesized by hepatocytes driven by the stimulation of various cytokines associated with inflammation is upregulated in AAD[23]. Its plasma levels depend on inflammatory stages. CRP has been thought to be significantly linked to the occurrence and development of AD, suggesting its participation in the inflammatory pathways in AAD[24,25]. CRP values were significantly higher in patients who suffered adverse postoperative outcomes compared with those who did not suffer, indicating that CRP was useful for prognostic stratification of patients with type A AAD. In line with the results of previous studies, the present study further proved the value of admission CRP in predicting adverse postoperative outcomes in acute type A AD. Levels of CRP were associated with an odds ratio of 1.163 (95% CI, 1.066 to 1.269; $p = 0.001$) for adverse postoperative outcomes. With a cutoff value of 13.98, CRP exhibited sensitivity of 67.9%, specificity of 66.9% and the AUC was 0.669.

D-dimer represents a protein fragment produced by crosslinked fibrin detectable in plasma following thrombus fibrinolysis. D-dimer is majorly tested for the diagnosis and prognosis of pulmonary embolism, disseminated intravascular coagulation and aortic dissection. Levels of D-dimer not only are elevated in patients with pulmonary embolism, deep-vein thrombosis and disseminated intravascular coagulation but also increase in cancer, infections, elder age and surgery, resulting in high diagnostic sensitivity but low specificity as a result[26–29]. D-dimer has a longer half-life period and it is a meaningful biomarker in predicting in-hospital mortality. In the present study, levels of D-dimer were associated with an odds ratio of 1.227 (95% CI, 1.096 to 1.374; $p < 0.001$) in predicting adverse postoperative outcomes demonstrating that D-dimer was an independent risk factor for adverse postoperative outcomes in type A AAD. With a cutoff value of 9.77, D-dimer exhibited sensitivity of 64.2%, specificity of 78.1% and the AUC was 0.763.

Previous studies demonstrated that AD is associated with platelet activation and adhesion to the damaged vessel walls, which may form a thrombosis in the false lumen[30]. Platelet dysfunction which marks serious thrombotic burden has been observed in patients with ATAAD[14]. The excessive consumption of platelets after thrombosis may make the damaged aortic wall prone to rupture, which increases mortality[13]. Huang et al. found that admission levels of platelet count $< 119\times10^9$/L was associated with an odds ratio of 3.90 (95%CI: 1.67 to 9.09) for in-hospital mortality[15]. However, in the present study, platelet counts had no statistical difference between the two groups, which may improve the predictive accuracy of D-dimer and CRP between two groups.

Chen et al. demonstrated that individual biomarker like neutrophil to lymphocyte ratio and monocyte to lymphocyte ratio was unable to predict in-hospital mortality in patients with type A AAD[18]. Liu Jun et al. observed that fibrinogen was a powerful predictor of mortality in patients with ATAAD[4]. There is no statistical significance of biomarkers discussed above in the present study.

The limitations of the present study were as follows: (1) this is a retrospective study and the outcome may be affected by many confounding factors. Large multicentric randomized controlled trials are needed in the future. (2) we recorded inflammatory and thrombotic markers at admission, but changes in these markers in the different time course during hospitalization were not recorded, which may be more valuable in the prognosis of type A AAD. (3) it tends to exaggerate the predictive value based on the existing data to explore the appropriate predictive cut point on ROC curves. We need to divide the study population into test queue and validation queue, so we can get the cut point in test queue and evaluate its predictive efficacy in validation queue.

# Conclusion

CRP and D-dimer were independent predictors of adverse postoperative outcomes of patients with ATAAD within 24 hours after symptoms onset. Combination of these readily available markers would improve the efficacy.

# Abbreviations

NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; ROC: Receiver Operating Characteristic; OR: odds ratio; AUC: Area under the curve; CTA: Computed Tomography angiography; ATAAD: Acute Stanford type A Aortic Dissection; CRP: C-reactive protein.

# Declarations

**Ethics approval and consent to participate:** This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (ID: IRB-SOP-AF17)and conformed to the Declaration of Helsinki.

**Consent for publication:**Not applicable

**Availability of data and materials:** Please contact author for data requests.

**Competing interests:** The authors declare that they have no conflict of interest.

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**Authors' contributions:** Shao Yongfeng designed the study and submitted the manuscript. Tang Zhiwei prepared the first draft of the manuscript and made the literature review. Du Junjie made substantial changes in the manuscript together. Ni Buqing and Gu Weidong were experienced surgeons who performed vascular surgery on patients.

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# Figures

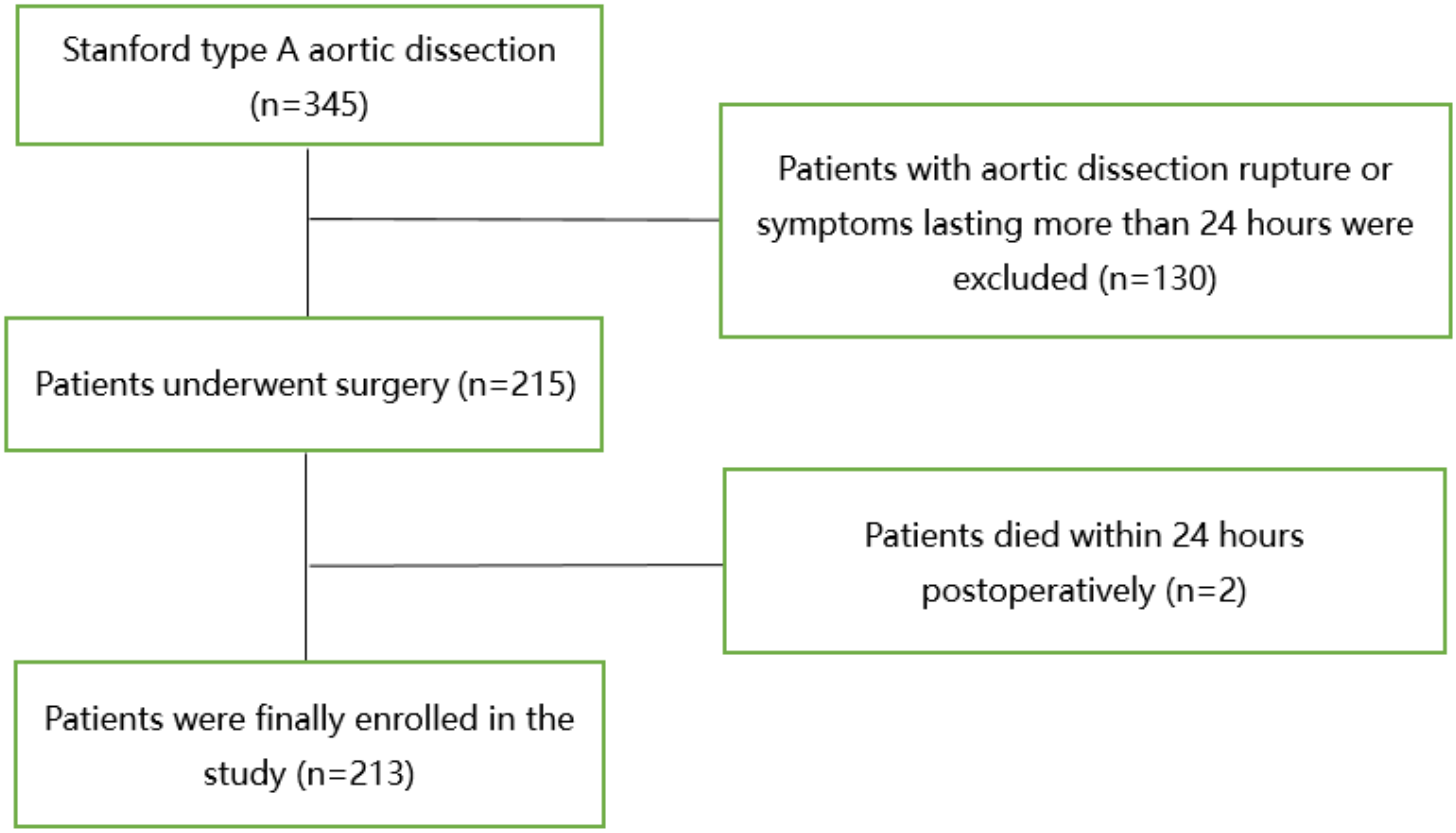


**Figure 1**

Flow diagram of the screening and enrollment of study patients.

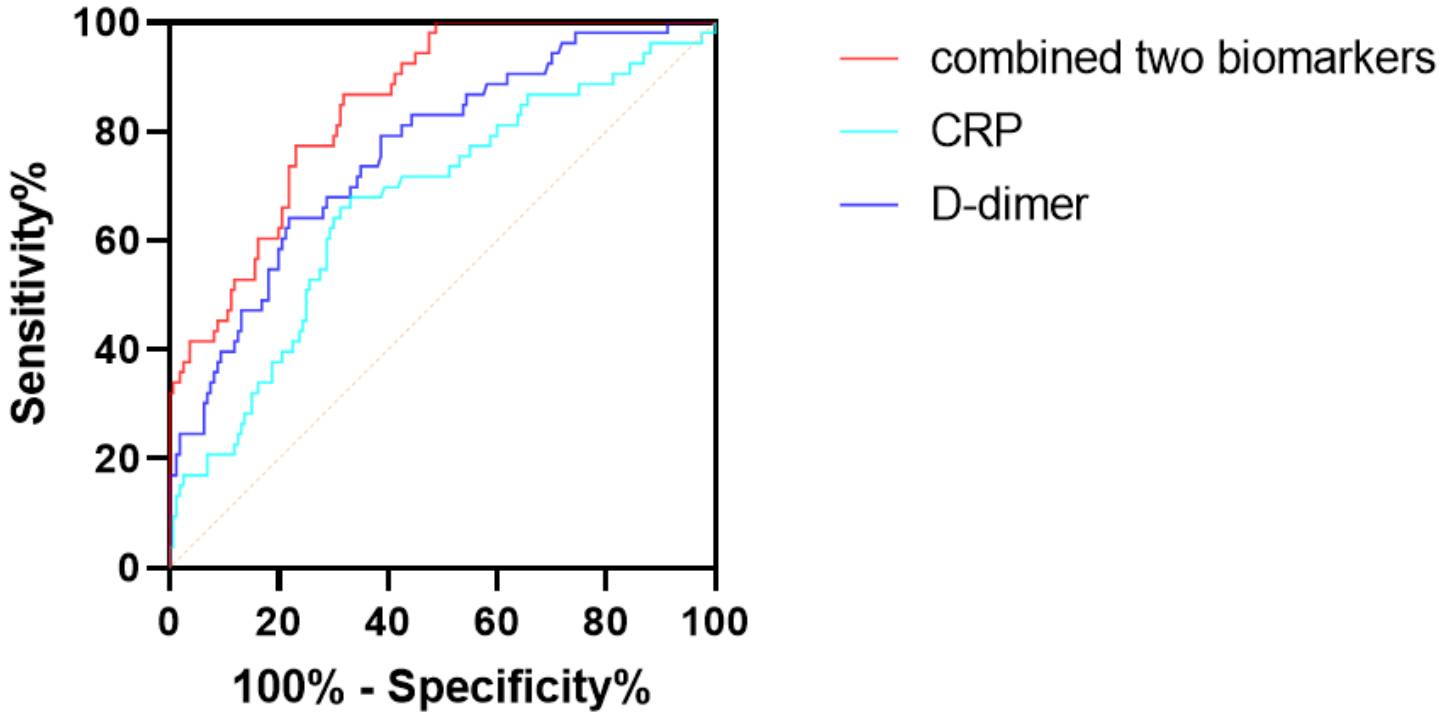


**Figure 2**

Receiver operating characteristic (ROC) curves of D-dimer, CRP and combination of these two biomarkers for adverse postoperative outcomes.

## Supplementary Files

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- data.xlsx