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Association of Critical Value With 28-Day Mortality After Cardiac Surgery

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ABSTRACT

Objective: The emergence of critical values gives a warning to the medical safety of hospitalized patients, especially Cardiosurgery Intensive Care Unit (CSICU) patients. The aim of this study was to investigate the association between early postoperative critical values and the prognosis of patients after cardiac surgery.

Methods: Clinical data of the patients were obtained from the Cardiac Critical Care Clinical Database of the Cardiovascular Intensive Care Unit of Nanjing First Hospital. A total of 1,598 consecutive patients undergoing cardiac surgery were enrolled in this retrospective cohort study, during the period from July 2019 to December 2020. According to whether critical value occurred within 7 days after cardiac surgery, patients were divided into two groups: the critical value group and control group. COX regression and survival analysis were performed to analyze the clinical data of the two groups. The area under the receiver operating characteristic curve (ROC) was used to assess the critical value's predictive value and determine the optimal cutoff value.

Results: With patients in the critical value group, the 28-day mortality after cardiac surgery was 21.98%, significantly higher than that of the control group ($P < 0.05$). Logistic regression analysis revealed the APACHE II score (Adjusted HR-1.11, 95% CI-1.043-1.185) and critical value group (Adjusted HR-13.57, 95% CI-6.714-27.435) were independent predictors of 28-day mortality after cardiac surgery. The ROC curve showed that the critical value case model (AUC = 0.748 ± 0.052, $P < 0.05$) could effectively predict the 28-day mortality, and the optimum cutoff was 1 case (sensitivity 52.63%, specificity 95.70%).

Conclusions: One or more reported cases of critical values in the early postoperative period could be an independent risk factor for 28-day mortality in patients undergoing cardiac surgery. The predictive model based on critical value might be effective in clinical therapy and risk stratification.

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INTRODUCTION

Critical value (panic value) refers to a physiological state that can be life threatening. Patients will be in danger without timely and effective intervention. But the prognosis of the patients would be significantly improved once valid treatment is received [Expert Consensus 2013]. As one of the "core systems" for medical safety in medical institutions at different levels, the critical value reporting system was subsumed into a patient safety goal by the former Ministry of Health in China in 2007. Previous investigations indicate there was no established criterion of critical values in healthcare, due to differences in organization, number of patients, specialties, and clinical requirements [AlSadah 2019]. Thus, the aim of this study was to assess the predictive value and clinical significance of the current "critical value system" by evaluating the correlation between critical values during the early period after cardiac surgery and the prognosis.

METHODS

Study design: This single center, retrospective, cohort study was conducted at the Department of Critical Care Medicine of Nanjing First Hospital. The inclusion criterion was adult patients, who underwent cardiac surgery from July 2019 to December 2020. Patients who lacked laboratory values or lost 28-day follow up were excluded. In addition, false positive critical values also were excluded, due to laboratory errors. A total of 1,598 consecutive patients were enrolled in the study, of which 91 patients had critical values within 7 days after cardiac surgery (5.7%). The total number of critical values was 188. Included patients were divided into a critical value group and control group, according to the occurrence of critical value within 7 days after surgery.

COX regression analysis was performed to explore the risk factors for 28-day mortality. COX regression analysis was used to evaluate the association between all the covariates that had statistical differences with the prognosis of the patients after cardiac surgery. The area under the receiver operating characteristic curve (ROC) of the 2 models and the Youden index, which was used to determine the optimal cutoff value, also were computed to assess the effect of critical values during the early postoperative stage on the prognosis of cardiac surgery patients.

Data collection: All data retrospectively were collected from the Cardiac Critical Care Clinical Database of Cardiovascular Intensive Care Unit in Nanjing First Hospital. Clinical data, including demographic characteristics, APACHE II

Table 1. Items and definitions of critical value

Item	Definition
WBC↑	Leukocyte count>30×10^9/L
WBC↓	Leukocyte count <1.0×10^9/L
PLT↑	Platelet count >700×10^9/L
PLT↓	Platelet count <20×10^9/L
Hb↓	Hemoglobin<50g/L
PT↑	Prothrombin time >20 second (Patients undergoing anticoagulant therapy were excluded)
APTT↑	Activated partial prothrombin time >70 second (Patients undergoing anticoagulant therapy were excluded)
K^+↑	Serum potassium >6.5mmol/L
K^+↓	Serum potassium <2.5mmol/L
Glu↑	Glucose>22.0mmol/L
Glu↓	Glucose <2.7 mmol/L
Ca^{2+}↓	Serum calcium <1.5mmol/L
CVB^+	Positive central venous catheter blood culture
PVB^+	Positive peripheral blood culture
pH↑	Arterial blood gas pH>7.6
pH↓	Arterial blood gas pH<7.1

WBC, white blood cell; PLT, platelet; Hb, hemoglobin; PT, prothrombin time; APTT, activated partial prothrombin time; K+, potassium; Glu, glucose; Ca^{2+}, calcium; CVB, central venous catheter blood culture; PVB, peripheral blood culture; pH, potential of hydrogen

Table 2. Classification and definitions of cardiac surgery

Classification	Definition
CABG	On-pump CABG; off-pump CABG; minimally invasive left chest incision CABG; ventricular aneurysm resection plus CABG; coronary endarterectomy plus CABG
Valve surgery	MVR; MVP; AVR; AVP; TVP; TVR; combined valvular surgery
Major vascular surgery	David procedure (aortic root replacement with aortic valve preservation); Bentall procedure (composite graft replacement of the aortic valve, aortic root, and ascending aorta, with re-implantation of the coronary arteries into the graft); Wheat procedure (replacement of aortic valve and ascending aorta with preservation of aortic sinus)
Sun's procedure	The Sun's procedure is a treatment of type A aortic dissection that integrates total aortic arch replacement using a tetra furcated graft with implantation of a specially designed frozen elephant trunk in the descending aorta. Some patients underwent Sun's procedure combined with CABG or valve surgery simultaneously.
Combined operation	Two or more CABG, valve surgery, and major vascular surgery performed at the same time
Others	The numbers of congenital heart disease surgery, cardiac tumor resection, pericardiectomy and heart transplantation were very few in the study, so the operations described above fall into this category.

CABG, coronary artery bypass grafting; MVR, mitral valve replacement; MVP, mitral valve plasty; AVR, aortic valve replacement; AVP, aortic valve plasty; TVP, tricuspid valvuloplasty; TVR, tricuspid valve replacement

score, Euro SCORE (European System for Cardiac Operative Risk Evaluation), duration of cardiac surgery, surgical procedures, mean arterial pressure (MAP) at ICU admission, PO2/FIO2 at ICU admission, and vasopressor use were recorded for outcome comparison.

Clinical outcome: The primary outcome of this study was 28-day mortality after cardiac surgery.

Diagnosis of critical value: The diagnosis of critical values was based on the criteria published by the Expert Consensus on the Clinical Application of Critical Values in Critical Care Diseases (Adults) [Expert Consensus 2013]. All the critical values and warning ranges after calibrating laboratory instrument parameters are listed in Table 1. (Table 1)

Classification of cardiac surgery: The classification of various cardiac operations included in this study are listed in Table 2. (Table 2)

Statistical analysis: SPSS software package version 22.0 was used for statistical analysis. Continuous variables are reported as mean ±SD when normally distributed and as median (interquartile range [IQR]) when not normally distributed. Categorical variables were presented as numbers and percentages. Proportions for categorical variables were compared using the $\chi 2$ test or Fisher's exact test. To evaluate which variables were associated with the 28-day mortality, Cox proportional hazards regression analysis was performed and hazard ratio (HR) with a 95% confidence interval (CI) was calculated. The receiver operating characteristic curve (ROC) was used to evaluate the prognostic value of correlation factors. A *P*-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics: Of the 1598 patients who underwent cardiac surgery, 1507 patients (94.31%) were in the control group, and 91 patients (5.69%) were in the critical value group. (Table 3) The median age of the patients in the critical value group was 63.53±12.35 years, older than the 60.79±12.3 years of the control group ($P = 0.04$). The critical value group had higher APACHE II scores (15.33±5.15 vs. 11.79±3.31, $P < 0.01$), SOFA scores (7.15±2.72 vs. 5.46±2.00, $P < 0.01$), and longer operation time (342.0±111.0 min vs. 257.4±78.1 min, $P < 0.01$). There were no statistical differences in mean arterial pressure (MAP), PO2/FIO2 at ICU admission and vasopressor use between the two groups ($P > 0.05$ for all). Among all study patients, critical values occurred

Table 3. Baseline clinical characteristics of the study patients

	Critical value group (*N* = 91)	Control group (*N* = 1507)	Statistical value	*P*-value
Gender (male/female)	63/28	921/576	χ^2=2.783	0.25
Age (years)	63.53±12.35	60.79±12.3	t=2.057	0.04
APACHE II score	15.33±5.15	11.79±3.31	t=9.512	<0.01
Euro score	7.15±2.72	5.46±2.00	t=7.67	<0.01
Hypertension	62	1029	χ^2=0.001	0.98
Diabetes mellitus	45	710	χ^2=0.188	0.67
Emergency operation	39	680	χ^2=0.673	0.25
Operation time (min)	342.0±111.0	257.4±78.1	t=9.752	<0.01
MAP (mmHg)	78.38±7.92	78.96±6.38	t=-0.828	0.41
Received vasoactive drugs, n (%)	83 (91.21%)	1322 (87.72%)	χ^2=0.981	0.32
PO2/FIO2 (mmHg)	357.23±149.57	353.12±129.9	t=0.291	0.77
Type of surgery, n (%)*				
CABG	14 (3.13%)	433 (96.87%)		
Valve surgery	26 (4.45%)	558 (95.55%)		
Major vascular surgery	8 (5.71%)	132 (94.29%)	χ^2=41.389	0.00
Sun's procedure	19 (17.43%)	90 (82.57%)		
Combined operation	16 (9.52%)	152 (90.48%)		
Others	8 (5.33%)	142 (94.67%)		
28-day mortality, n (%)	20 (21.98%)	18 (1.19%)	χ^2=159.685	0.00

%*: Percentage of critical value reports among patients undergoing similar procedures

Table 4. Cox Model to identify independent predictors for 28-day mortality

	B	SE	Wald	df	*P*-value	HR	95% CI
APACHE II score	0.106	0.033	10.505	1	0.001	1.112	1.043-1.185
Critical value group	2.608	0.359	52.749	1	0.000	13.572	6.714-27.435

CI, confidence interval; HR, hazard ratio

in 14 (3.13%) patients after coronary artery bypass grafting, 26 (4.45%) patients after valve surgery, 8 (5.71%) patients after major vascular surgery, 19 (17.43%) patients after Sun's procedure, 16 (9.52%) patients after the combined operation, and 8 (5.33%) patients after other operations. The types of surgery between the two groups were significantly different ($P < 0.05$). Moreover, patients in the critical value group were noted to have a 28-day mortality rate of 21.98%, markedly higher than 1.19% in the control group ($P < 0.05$).

Multivariable Cox analysis for 28-day mortality after cardiac surgery: In the multivariable Cox proportional hazards model, critical value group, age, operation time, APACHE II scores, SOFA scores, and type of surgery were analyzed as variables known to influence 28-day mortality. We assigned values to different operations: CABG=1, valve surgery=2, major vascular surgery=3, Sun's procedure=4, combined operation=5, others=6.

Results of COX regression analysis: overall assignment test $\chi2$=188.863 (P = 0.00), likelihood ratio test $\chi2$=76.811 (P = 0.00), an overall test of the model was statistically significant ($P < 0.05$). The test results for each parameter showed that APACHE II scores and critical value group were independent predictors of 28-day mortality. (Table 4) In contrast, age (P = 0.05), operation duration (P = 0.554), Euro score (P = 0.201), and type of surgery (P = 0.591) did not show statistical differences between the two groups (residual $\chi2$=6.146, P = 0.188).

ROC Curve analysis: As shown in Figure 2, the area under the ROC curve of the 2 models had statistical difference (area under the ROC curve of APACHE II model= 0.684±0.044, P = 0.00; area under the ROC curve of critical

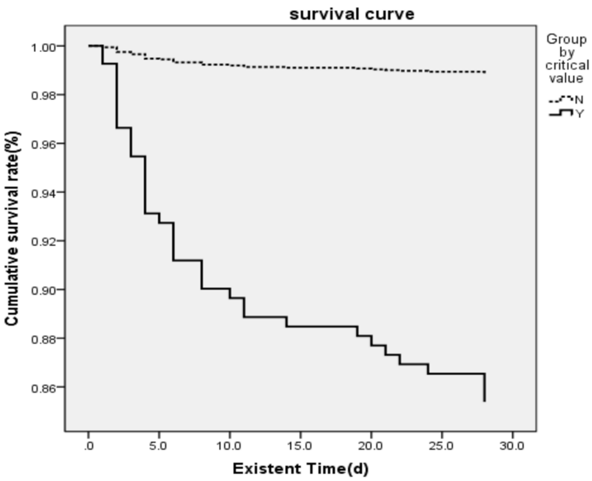

Figure 1. Postoperative 28-day survival curve, according to critical value group

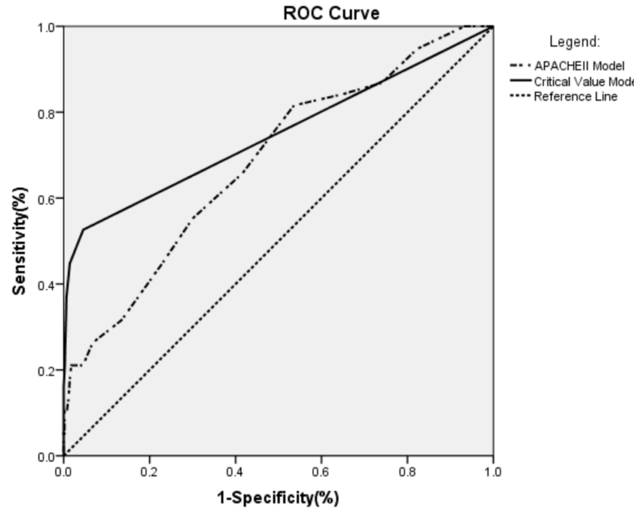

Figure 2. Receiver operating characteristic (ROC) curves of APACHE II model and critical value model

value model= 0.748±0.052, P = 0.00). (Figure 2) Further, Z-test was performed on the area under the ROC curve of both groups (Z-value=21.02248, $P < 0.05$), which was statistically significant, suggesting that the critical value model could predict the prognosis better than the APACHE II score model. Using the Youden index, the threshold critical value of 1 case was found to best predict 28-day postoperative mortality in patients following cardiac surgery. This cutoff value gave 52.63% sensitivity and 95.70% specificity.

DISCUSSION

Recently, the critical value notification system has become one of the important initiatives to implement medical quality control and treatment level in hospitals of all levels all over the world. The importance of critical value management has been emphasized in multiple versions of Patient Safety Objectives promoted by the Chinese Physicians Association in recent years. According to the National Patient Safety Objectives in the United States, the requirement for critical value management is the same [Chinese Medical Doctor Association 2019; The Joint Commission 2019]. However, there are significant differences between different countries in the identification and notification management for critical values, resulting in various effects on clinical work [Lippi 2016]. Some domestic publications have addressed that the categories of critical values were basically consistent in different medical institutions. Nevertheless, there are significant differences in the critical value thresholds [Zeng 2013; Ye 2017]. Although previous studies have set critical value thresholds by considering the ages and diseases of relevant patients through analyzing big data of laboratory results, there is a lack of making corresponding clinical evaluation [Du 2018; Tan 2019].

Critical values must be proactively reported, with timely and accurate intervention for the safety of patients. Therefore, it is impossible to evaluate the impact of critical value on the prognosis of patients through prospective cohort study. However, the existence of critical value may be the cause of condition aggravation or the indicators of disease outcome [Expert Consensus 2013]. To some extent, critical values are closely associated with the development and poor prognosis of organ injury. Therefore, we concluded that the critical value might be an optimal prognosis assessment index. The aim of this retrospective cohort study was to evaluate the prognosis ability of critical value in cardiac surgery patients and make clinical evaluation on the effectiveness of the current critical value management system.

Univariable associations between risk factors and postoperative 28-day mortality are shown in Table 3. In this study, we demonstrated no statistical significances in gender, circulation, and oxygenation at ICU admission between the two groups. The mean operation time significantly was longer in the group of patients, who had critical values after cardiac surgery ($P < 0.05$). Patients in the critical value group were more likely to get higher APACHE II scores and Euro scores ($P < 0.05$). Similarly, there also were differences in mortality and surgery classification between the two groups. A growing number of clinical studies have shown that age is associated with cardiovascular outcomes after surgery. APACHE II scores and Euro scores comprehensively reflect the basic organ function and acute physiological state of the patients. The duration of operation indicates the impact of the surgery on the patients as well as the degree of its influence. However, the predictive value of these factors mentioned above on the prognosis of the patients still is controversial [Daniels 2020; Atalay 2019; Raut 2020; Luthra 2015].

Among patients who underwent various categories of cardiac surgery, there were differences in the occurrence of early postoperative critical value. Listed from high to low: Sun's procedure (17.43%), combined operation (10.12%), major vascular surgery (5.71%), other surgery (5.33%), valve surgery (4.45%), and coronary surgery (3.13%). This finding showed that the incidence of critical values varies with the complexity of the procedure and its impact on the cardiac structure, consistent with current clinical consensus.

The COX survival analysis showed that APACHE II scores and critical value group served as independent predictors of 28-day mortality after cardiac surgery after excluding relevant confounding factors. In contrast, the risk of death was 13.57 times higher for the patients in the critical value group than those in the control group. Further by comparative analysis of ROC curves, we found that the critical value model had a higher predictive value than the APACHE II score model for 28-day mortality in patients after cardiac surgery. Moreover, one or more critical values in the early postoperative period showed accurate predictive value (sensitivity 52.63%, specificity 95.70%) for 28-day postoperative mortality.

Patients often susceptibly suffered from complications, such as acid-base imbalance, internal environment disorder and massive bleeding, after undergoing thoracotomy and cardiopulmonary bypass. The postoperative critical value system is conducive to enact rapid treatment and improve the prognosis of patients. However, so far, most studies have focused more on critical value boundary rather than the correlation between the critical value system and mortality of patients [Schapkaitz 2015], especially for patients undergoing heart surgery. Our research attempted to evaluate the correlation and had defined the best cutoff value related to 28-day mortality in the study population. This study result may provide other relevant researchers with the reference to optimize clinical practices.

However, this study has certain limitations. First, the study was carried out in a single center with some deficiency. Only patients undergoing cardiac surgery were included in the study, which may lead to selection bias and limit the research conclusions' applicability to other critically ill patients. Second, this study was a retrospective study, and the predictive value of the critical value model needs to be further validated and optimized by prospective trials. Lastly, we only used the 28-day postoperative mortality as the primary outcome and did not further analyze the relevance with other adverse states (ie. complications, sequelae, etc.), which was also a follow-up study direction.

CONCLUSIONS

In conclusion, under the current "critical value system" and warning range, one or more critical value cases in the early postoperative period of cardiac surgery are independent risk factors for 28-day mortality, which has a greater prognostic value in cardiac surgical populations. The predictive model based on critical value might be effective in clinical therapy and risk stratification for patients undergoing cardiac surgery.

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