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Original Article

Predicative value of preoperative C-reactive protein for postoperative adverse cardiac events in patients undergoing major abdominal surgery

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Abstract: Background: The occurrence of adverse cardiac events always disturbs the successful recovery, personal and economic life of patients undergoing major abdominal surgery. This study aimed to gain further insight into potential predicators for adverse cardiac events after major abdominal surgery. Methods: 246 patients who scheduled to undergo selective major abdominal surgery were eligible to enter this study. The clinical data, preoperative laboratory tests, the characteristics before the surgery, comorbidities and operation-related information were all recorded in details. The study end-point was defined as the occurrence of adverse cardiac events within 30 postoperative days. Results: Of all the 246 enrolled patients, 51 (51/246, 20.7%) were diagnosed with adverse cardiac events within 30 days after the operation. The univariate analysis and multiple logistic regress analysis suggested that C-reactive protein (CRP) level was the only preoperative predicator for postoperative adverse cardiac events after major abdominal surgery (OR: 3.93, 95% CI: 1.82-8.57, P=0.011). The sensitivity and specificity of CRP for the adverse cardiac events predication were respectively 72.0% and 72.5% with the area under the curve (AUC) of 0.766 (95% CI: 0.690-0.843, P<0.001) by receiver operating characteristic (ROC) analysis. Conclusions: The preoperative CRP concentration was an independent predicative factor for adverse cardiac events after major abdominal surgery.

Keywords: C-reactive protein, predication, adverse cardiac events, major abdominal surgery

Introduction

Great improvements of postoperative care, surgical techniques and anaesthesia management have been achieved during the decades, however, the incidence of postoperative complications after major abdominal surgery was reported to be 11-28% [1, 2]. The occurrence of cardiac or non-cardiac postoperative complications always disturb the successful recovery, personal and economic life of patients undergoing major abdominal surgery. Perioperative mortality and morbidity rates are always accompanied with major abdominal surgery, and adverse cardiovascular events play important role in the causes of death [3]. Among those elderly patients (≥60 years) with adverse cardiovascular events, the perioperative mortality rate can be as high as 2.8-5.8% [4]. About one third of deaths during the perioperative period after emergency general surgery were associated with adverse cardiac events [5, 6]. During the past decades, researchers and doctors have focused themselves on the involved mechanisms and potential preoperative predicative biomarkers of postoperative complications. C-reactive protein (CRP), synthesized by the liver, is an acute phase reactant produced in situations of infection and inflammation. Serum levels of CRP is significantly increased within 6 hours after the surgery and the peak value is reached about 48 h after the surgery. Serum concentration of CRP could effectively reflect the acute inflammatory intensity. Previous studies have revealed that increased CRP level is a significant risk factor for postoperative septic complications and the increase of CRP levels place before the onset of the clinical symptoms [7]. CRP level in patients with coronary heart disease is also reported to be an effective marker for the assessment of vascular inflammation activity and acute coronary

Table 1. Univariate analysis of potential predicative factors for postoperative adverse cardiac events after major abdominal surgery

Parameters	All (n=246)	Cardiac events (n=51)	No cardiac events (n=195)	*P*-value
Age (year)	50.8 (20-78)	59.4 (20-78)	48.5 (24-67)	0.025*
Gender				
Male	103 (41.9%)	23 (45.1%)	80 (41.0%)	
Female	143 (58.1%)	28 (54.9%)	115 (59.0%)	0.60
ASA physical status				
I	127 (51.6%)	26 (51.0%)	101 (51.8%)	
II	77 (31.3%)	14 (27.5%)	63 (32.3%)	
III	42 (17.1%)	11 (21.6%)	31 (15.9%)	0.59
RCRI				
I	125 (50.8%)	24 (47.1%)	101 (51.8%)	
II	93 (37.8%)	16 (31.4%)	77 (39.5%)	
III	28 (11.4%)	11 (21.5%)	17 (8.7%)	0.034*
BMI (kg/m^2)	20.5 (16.4-37.8)	21.2 (16.4-35.3)	20.3 (17.0-37.8)	0.37
Heart rate	71.8 (47-110)	73.1 (51-103)	71.5 (47-110)	0.65
Blood pressure (mmHg)				
Systolic	120.1 (90-174)	126.3 (98-174)	118.5 (90-155)	0.11
Diastolic	69.6 (56-100)	67.6 (56-90)	70.1 (62-100)	0.33
Preoperative biomarkers				
BNP (pg/ml)	44.4 (6.8-1756.3)	87.3 (14.5-1756.3)	33.2 (6.8-465.1)	0.003*
cTnT (ng/L)	9.9 (4.5-17.8)	12.5 (5.8-17.8)	9.2 (4.5-16.4)	0.024*
CRP (mg/l)	4.1 (0.4-24.4)	6.6 (0.4-24.4)	3.4 (0.6-12.3)	0.012*
IL-6 (pg/ml)	18.7 (7.6-54.3)	26.1 (10.5-54.3)	16.3 (7.6-41.4)	0.031*
TNF-α (ng/L)	16.4 (1.5-87.3)	14.7 (1.5-77.5)	16.8 (3.3-87.3)	0.55
Serum creatinine (mg/dl)	0.8 (0.3-3.7)	1.2 (0.6-3.7)	0.7 (0.3-2.1)	0.041*
Urea (mmol/l)	6.0 (1.8-8.9)	6.6 (1.8-8.9)	5.8 (2.1-7.8)	0.25
Types of surgery				
Gastric-oesophageal	29 (11.8%)	7 (13.7%)	22 (11.3%)	
Gastric bypass	23 (9.3%)	6 (11.8%)	17 (8.7%)	
Colorectal	125 (50.8%)	26 (51.0%)	99 (50.8%)	
Hepatic	15 (6.1%)	4 (7.8%)	11 (5.6%)	
Pancreatic	33 (13.4%)	6 (11.8%)	27 (13.8%)	
Other	21 (8.5%)	2 (3.9%)	19 (9.7%)	0.78
Comorbidities				
Diabetes	24 (9.8%)	7 (13.7%)	17 (8.7%)	0.28
COPD	29 (11.8%)	8 (15.7%)	21 (10.8%)	0.33
Coronary artery disease	47 (19.1%)	15 (29.4%)	32 (16.4%)	0.036*
Dilated cardiomyopathy	18 (7.3%)	8 (15.7%)	10 (5.1%)	0.010*
Arterial hypertension	111 (45.1%)	24 (47.1%)	87 (44.6%)	0.75
Congestive heart failure	17 (6.9%)	4 (7.8%)	13 (6.7%)	0.77
Prior myocardial infarction	30 (12.2%)	8 (15.7%)	22 (11.3%)	0.65
Peripheral artery disease	17 (6.9%)	3 (5.9%)	14 (7.2%)	0.75
Atrial fibrillation	31 (12.6%)	8 (15.7%)	23 (11.8%)	0.46
Duration of surgery (min)	132.6 (78-233)	166.1 (86-233)	123.8 (78-185)	0.021*
Duration of anesthesia (min)	153.4 (94-274)	188.2 (102-274)	144.3 (94-210)	0.029*
Estimated blood loss (ml)	199.3 (50-500)	245.3 (70-500)	187.3 (50-400)	0.034*

ASA, American Society of Anesthesiologists; RCRI, Revised Cardiac Risk Index; BMI, Body Mass Index; BNP, B-type natriuretic peptide; cTnT, cardiac troponin T; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; COPD, chronic obstructive pulmonary disease. *P*-values were calculated by Chi-square test, Fisher exact test or Student's t-test. *P value<0.05.

events predication [8]. However, whether CRP levels can serve as a predicator for adverse cardiac events after non-cardiac surgery remains unclear. In this regard, this study aimed at gain further insight into potential predicative biomarkers for adverse cardiac events after major abdominal surgery.

Material and methods

Patients

This study protocol was approved by the Medical Institutional Ethics Committee of Jiangsu province. Those patients who scheduled to undergo selective major abdominal surgery in Taizhou People's Hospital from March, 2012 to March, 2015 were eligible to enter this study. All patients included offered written informed consent. Those patients who required emergency surgery or had no signed informed consent were excluded.

Methods

In the morning on the 1 day before the surgery, fasting blood samples were extracted from all the patients and then stored at room temperature. The inflammatory cytokines including CRP, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were determined in the blood samples using enzyme-linked immunesorbent assays (ELISA), following the manufacturers' instructions (R&D Systems, Minneapolis, MN, USA). B-type natriuretic peptide (BNP), cardiac troponin T (cTnT), creatinine and urea were also detected from the obtained preoperative blood samples.

All the participants were assessed for cardiac risk factors by the same expert in cardiology and an anesthesiology resident before the surgery who were blinded to this study. The clinical data, preoperative laboratory tests, the characteristics before the surgery, comorbidities and information correlated to the operation were all noted in details. During a month after the operation, the expert in cardiology and anesthesiology resident assessed all enrolled patients for adverse cardiac events by utilizing clinical and instrumental methods combined with biochemical markers. The study end-point was defined as the occurrence of adverse cardiac events within 30 postoperative days. The evaluation of Revised Cardiac Risk Index (RCRI), cardiovascular comorbidities and postoperative adverse cardiac events were all according to the updated American College of Cardiology (ACC)/ American Heart Association (AHA) Task Force guidelines [9].

Statistical analysis

SPSS19.0 (SPSS, Inc.) was used for data analysis in this present study. Categorical data are presented as number (n) and percentage (%), while continuous data presented as mean and range. Chi-square test or Fisher exact test was used for independent categorical data. Student's t-test was utilized for the comparison of continuous variables between groups. Receiver operating characteristic (ROC) curve analysis were plotted to evaluate the predicative value of CRP for adverse cardiac events and establish the cut-off value. Potential independent predictive factors for adverse cardiac events were analyzed by using multiple logistic regression analysis. All statistical tests were bilateral probability and $P<0.05$ was considered significant.

Results

Patient characteristics and postoperative adverse cardiac events

A total of 246 patients with a mean age of 50.8 years (20-78 years) were eligible to be included in this study participation with signed informed consent. Male patients occupied 103 of them (41.9%) and a majority of the enrolled patients underwent colorectal surgery (125/246, 50.8%). Of all the 246 enrolled patients, 51 (51/246, 20.7%) were diagnosed with adverse cardiac events within 30 days after the operation. In the 51 patients diagnosed with adverse cardiac events, 21 were with cardiac breathlessness, 9 with heart failure, 8 with angina pectoris, 5 with myocardial infarction, 5 with hypertensive urgency and 3 with cardiac exitus.

Univariate analysis for adverse cardiac events

The results from univariate analysis of potential predicators for adverse cardiac events (see **Table 1**) revealed that those patients with an older age, a higher levels of RCRI, a longer duration of surgery and anesthesia, a more estimated blood loss were more likely to result in adverse cardiac events ($P<0.05$). Compared to those without cardiac events, the levels of cTnT,

Table 2. Multiple logistic regression analysis for postoperative adverse cardiac events after major abdominal surgery

	Adverse cardiac events		
Variables	OR	95% CI	*P* value
Age	1.87	0.71-4.68	0.20
RCRI	1.12	0.38-2.98	0.87
cTnT	0.47	0.19-1.24	0.33
BNP	2.23	0.78-7.12	0.09
CRP	3.93	1.82-8.57	0.011*
IL-6	1.05	0.41-2.69	0.84
Serum creatinine	0.61	0.28-2.01	0.59
Coronary artery disease	1.04	0.93-1.12	0.43
Dilated cardiomyopathy	2.26	0.58-6.67	0.19
Duration of surgery	1.45	0.61-3.34	0.36
Duration of anesthesia	1.38	0.43-4.41	0.60
Estimated blood loss	1.14	0.39-3.36	0.67

RCRI, Revised Cardiac Risk Index; cTnT, cardiac troponin T; BNP, B-type natriuretic peptide; CRP, C-reactive protein; IL-6, interleukin-6; CI: Confidence Interval; OR, Odds Ratio. **P* value<0.05.

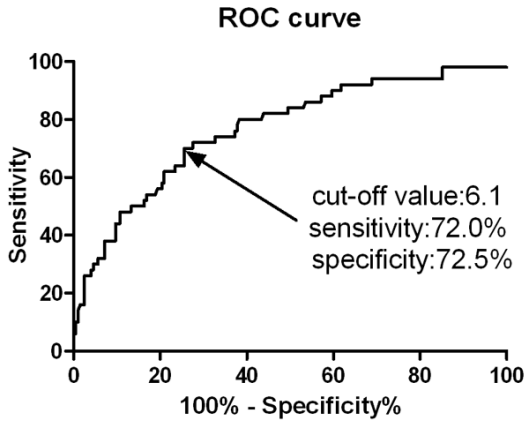

Figure 1. Predicative value of C-reactive protein (CRP) for postoperative adverse cardiac events by receiver operating characteristic (ROC) curve analysis.

BNP, CRP, IL-6 and serum creatinine from preoperative blood samples were significantly increased in patients with adverse cardiac events (P<0.05). Furthermore, the comorbidities including coronary artery disease and dilated cardiomyopathy also correlated with the occurrence of postoperative adverse cardiac events closely (P<0.05).

Multiple logistic regression analysis for postoperative adverse cardiac events

Considering the variables mentioned above as potential predicators for postoperative adverse cardiac events, a multiple logistic regression analysis was conducted. As shown in **Table 2**, CRP level was the only preoperative variable predicator for postoperative adverse cardiac events after major abdominal surgery (OR: 3.93, 95% CI: 1.82-8.57, P=0.011).

Predicative value of preoperative CRP level for adverse cardiac events

The ROC curve analysis was conducted to assess preoperative CRP level as a predicative biomarker for adverse cardiac events. As shown in **Figure 1**, the results from ROC curve yielded a cut-off value of 6.0 mg/L, a sensitivity of 72.0%, a specificity of 72.5% with the area under the curve (AUC) of 0.766 (95% CI: 0.690-0.843, P<0.001). The original data was uploaded as the Supplementary data.

Discussion

Previous studies have reported that the occurrence of perioperative adverse cardiac events might result in the prolonged hospital stay, elevated incidence of non-cardiac adverse events, increased morbidity and mortality [10, 11]. The mortality of patients who suffered from perioperative myocardial infarction can be as high as 15% to 25% and approximately only 35% can survive from the attack of perioperative cardiac arrest [12]. Essential accurate preoperative assessment of risk factors for perioperative cardiac events in major abdominal surgery is recommended because these patients are not always assessed for their cardiac status and it may result in some emergency situations [13]. However, no optimal detector has be used to accurately predict the preoperative cardiac risk stratification and prepare for counteraction so far.

In this present study, the combined incidence of postoperative adverse cardiac events was 20.7%, a little higher than other reports [13, 14], which might be the result of a relatively high-risk cohort. Our study pointed out that the age, RCRI, duration of surgery and anesthesia, estimated blood loss, preoperative biomarkers (cTnT, BNP, CRP, IL-6 and serum creatinine) and some comorbidities (coronary artery disease and dilated cardiomyopathy) were all potential risk factors for postoperative adverse cardiac events. Results from a single-center study proposed that medical history, surgery type, patient condition and physical examination were significant preoperative risk comprising

factors for adverse cardiac events [3]. Another prospective study conducted in a single-center cohort formulated that the RCRI was an effective parameter for the estimate of cardiac events as it incorporated many clinical factors including medical history of stoke, coronary disease, renal dysfunction, surgery risk and medications, etc [15]. RCRI was validated as an effective evaluation tool for perioperative risk for adverse cardiac events during the patients undergoing non-cardiac surgery [16]. This is consistent with our finding that a higher levels of RCRI was more likely to result in adverse cardiac events. However, in contrast to the results as described by previous studies [17], preoperative RCRI evaluation did not predict postoperative adverse cardiac events in our present study supported by the results of multiple logistic regression analysis. The discrepancy may ascribe to the differences in the sample size, inclusion and exclusion criteria. The differences in surgery types and surgical techniques may also be possible explanations. Preoperative BNP was reported to be a better predictor of adverse cardiac events compared to other evaluations in patients after abdominal surgery [13], which was in support with our results.

The multiple logistic regression analysis demonstrated that preoperative CRP levels were the only predicative factor for adverse cardiac events after major abdominal surgery. Preoperative CRP has been reported to be a prognostic predicator for postoperative outcomes of patients underwent cardiac surgery by previous studies [18, 19]. Results from a prospective study of 295 patients with non-cardiac surgery showed that postoperative CRP levels were predicative for the cardiovascular outcomes 1 year after the surgery [20]. However, another prospective study revealed that postoperative CRP was with no close correlation with clinical outcomes in patients undergoing cardiac surgery [21]. A close association was also found between an elevation of early postoperative CRP concentration with the long-term postoperative major adverse cerebral and cardiovascular events during those patients with cardiac surgery [22]. The cut-off value of preoperative CRP at 3 mg/L was considered as a significant risk for postoperative cardiovascular events [23], which was inconsistent with our value of 6.0 mg/L. The sensitivity and specificity of CRP for the adverse cardiac events predication were respectively 72.0% and 72.5% with the AUC of 0.766 (95% CI: 0.690-0.843, P<0.001) by ROC curve analysis. A significant positive correlation between morbidity of cardiovascular diseases and preoperative CRP concentration has been demonstrated both in patients with coronary artery disease and animal experiments [24, 25]. The involved explanations for the predicative value of CRP for adverse cardiac event was a more complex problem than expected. The important roles of CRP in inflammatory complement cascade, neutrophil attraction and activation, vasoconstriction of the coronary vessels [26], clot formation, pro-coagulant agent, endothelial dysfunction and inducing cell adhesion molecules [27], reducing the blood flow and triggering the vasospasm of coronary artery [28] may be possible explanations. Moreover, the accurate preoperative or postoperative CRP threshold levels to effectively predicate the adverse outcomes and involved mechanisms still require more and further investigations.

Study limitations

This study has some limitations. First, this is a single-center analysis with a relatively small cohort of patients. Second, we have concluded the predicative value of CRP for postoperative adverse cardiac events, however, the involved mechanisms still remain unclear. Last, we have no idea whether the reduction of CRP by specific treatment strategy could consequently affect adverse cardiac events.

Disclosure of conflict of interest

None.

Authors' contribution

YX L, HL X participated in the conception and design, data collection, statistical analysis and wrote the manuscript. GZ X participated in the conception and design and data collection.

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