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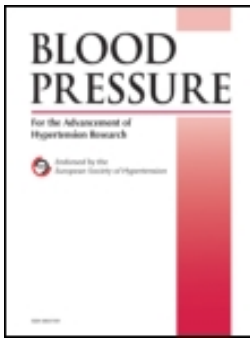
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ORIGINAL ARTICLE

C-reactive protein, not cardiac troponin T, improves risk prediction in hypertensives with type A aortic dissection

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Abstract

Background: The aim of the study was to evaluate prognostic role of inflammatory biomarkers, cardiac troponin T (cTnT) and D-dimer in type A acute aortic dissection (AAD) and to examine whether they might help in risk stratification beyond values of International Registry of Acute Aortic Dissection (IRAD) score. **Methods:** Baseline biomarkers were determined in 54 consecutive predominantly hypertensive patients with type A AAD and evaluated for in-hospital mortality. **Results:** After multivariable adjustment, the independent predictors of outcome were age (OR = 1.09; 95% CI 1.02–1.18), treatment strategy (OR = 0.11; 95% CI 0.02–0.06) and C-reactive protein (CRP) either as binary (OR = 7.06; 95% CI 1.34–37.36) or continuous variable (OR = 1.10; 95% CI 1.01–1.21). cTnT did not independently influence mortality. Receiver-operating characteristic (ROC) curve analysis showed significant link between CRP and outcome (area under the ROC curve, AUC = 0.79; $p < 0.01$). Values of CRP > 9.8 mg/l had 83% sensitivity and 80% specificity for predicting in-hospital mortality. Addition of CRP to IRAD score improved prediction of short-term outcome, AUC increased from 0.74 to 0.89 ($p = 0.004$). **Conclusion:** Admission CRP has independent prognostic value in type A AAD and the addition of CRP to IRAD score improved discriminative capacity of in-hospital mortality irrespective of symptom duration and treatment strategy.

Key Words: Aortic dissection, C-reactive protein, D-dimer, troponin T, mean platelet volume, mortality

Introduction

Type A acute aortic dissection (AAD) is one of the most feared complications of hypertension and a highly lethal medical emergency (1). Besides early diagnosis and surgical treatment, there is growing interest in bedside risk assessment for in-hospital death. In addition to the validated International Registry of Acute Aortic Dissection (IRAD) score (comprising age, abrupt onset of chest pain, hypotension/shock/tamponade, kidney failure, pulse deficit and abnormal ECG), a routine clinical biomarker would be a valuable tool in early stratification of patients with type A AAD (2). C-reactive protein (CRP) is a simple marker widely used in clinical practice. The major part of CRP is synthesized by

hepatocytes driven by interleukin 6 (IL-6), and genes associated with chronic inflammation (including IL-6 production) are up-regulated in type A AAD (3). Vessel wall inflammation in patients with acute aortic syndromes has been associated with high risk for disease progression (4) and prognostic role of CRP in broad spectrum of acute aortic diseases was shown (5–9). The prognostic implication of cardiac troponins, although proved to be strong predictors of outcome in the acute coronary syndromes, has not been comprehensively studied in acute aortic syndromes (10,11). Therefore the objective of the present study is to answer whether admission CRP, cardiac troponin T (cTnT), D-dimer and any of the inflammatory biomarkers examined (white blood

cells, WBC, fibrinogen, mean platelet volume, MPV, as indicator of platelet function) can independently predict short-term outcome in patients with type A AAD. Besides, we wanted to examine which biomarker might help in risk stratification beyond values of IRAD score. To the best of our knowledge, this is the first report that analyzed admission CRP, cTnT, D-dimer, MPV, WBCs and fibrinogen together in the setting of type A AAD and short-term mortality.

Methods

We retrospectively studied 54 consecutive patients with Stanford type A AAD admitted to the University Hospital between January 2006 and December 2013. One patient with type A AAD was excluded during the period of the study due to concomitant bronchopneumonia. The diagnosis of AAD was based on symptom onset, patient history, imaging (contrast enhanced computed tomography, transthoracic echocardiography) and/or autopsy. The diagnosis of hypertension was in accordance with the European Society of Cardiology / European Society of Hypertension 2013 guidelines (12).

Measurements of hematological variables were performed with the Beckman Coulter Hematology Analyser and fibrinogen was determined by Clauss method and high sensitivity CRP by immunoturbidimetric method (Olympus, Ireland). cTnT was measured using the Elecsys assay (F. Hoffmann-La Roche Ltd, Basel, Switzerland). A value of 0.01 ng/ml (the lowest level of detection) was chosen to define an elevated cTnT level (13). All biomarkers were measured on admission. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

The investigation was performed in accordance with the ethical standards in the Declaration of Helsinki, was approved by the University Hospital Ethical Review Board and informed consent approval was not required for the study under the Croatian law.

Differences between the groups were determined by *t*-test, Mann-Whitney test and Kruskal-Wallis test for continuous variables and by chi-square test for categorical variables. Correlations were performed using the Pearson or Spearman tests. Analysis of normality was performed with the Kolmogorov-Smirnov test. Non-normally distributed variables included admission systolic and diastolic blood pressure, heart rate, CRP, D-dimer, hemoglobin and time from symptom onset to admission. Receiver-operating characteristic (ROC) analyses were calculated for ability of CRP, IRAD score alone and in combination with admission CRP to predict in-hospital mortality. Multivariate logistic regression analysis was performed to find significant independent predictors of in-hospital mortality and results were expressed as odds ratios (OR) and their associated 95%

confidence intervals (CI). CRP was entered in multivariate analysis both as binary and continuous variable. The value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Statistica, version 6.0 (StatSoft, Tulsa, Oklahoma) and MedCalc® Version 11.3.1.0.

Results

Baseline characteristics of the study population according to in-hospital mortality are shown in Table I. The mean age of the 54 patients was 69 ± 14 years; 34 (63%) patients were men and 50 (93%) patients had a history of hypertension. The antihypertensive drugs that the patients had been taking prior to admission were as follows: 43% ACE inhibitors/angiotensin receptor blockers, 20% calcium channel blockers, 28% β -blockers, 19% diuretics. Thirty-seven percent of patients did not take any antihypertensive therapy before the admission. On admission, 20% of patients had elevated systolic blood pressure (SBP > 140 mmHg), 45% had normal SBP and 35% had low SBP (< 100 mmHg). The median onset of symptoms before admission was 2.3 h (interquartile range 1.0–6.0 h). Thirty-two patients (59%) underwent emergency surgical repair, and the others were treated conservatively or died shortly after admission in the emergency department before receiving surgical repair. There was no significant difference in age between subgroups of patients treated surgically or under conservative treatment ($p = 0.12$). During in-hospital stay, 24 (44%) patients died. The causes of death included hemopericardium with tamponade, aortic rupture and multiple organ failure (four patients did not undergo autopsy due to family request). Non-survivors were older (77 vs 62 years; $p < 0.001$) and less frequently received surgery (29% vs 83%; $p < 0.01$). CRP levels were significantly higher in non-survivors, while D-dimer values, fibrinogen, WBCs and MPV were comparable in both groups (Table I). D-dimer was elevated (> 500 ng/ml) in 52 (96%) patients and increased with the anatomical extension of disease ($p = 0.01$). On admission elevated cTnT levels (≥ 0.01 ng/ml) were detected in 18 (33%) of individuals (mean cTnT = 0.04 ng/ml, range = 0.01–0.18 ng/ml). These patients were older (75 vs 65 years; $p = 0.015$), with higher values of IRAD score (3.8 vs 3.0; $p = 0.02$) and CRP (23.3 vs 8.3 mg/l; $p = 0.001$), with a trend towards higher creatinine (123 vs 108 $\mu\text{mol/l}$; $p = 0.06$), lower hemoglobin levels (130 vs 138 g/l; $p = 0.07$) and lower admission systolic blood pressure (107 vs 129 mmHg; $p = 0.09$). The variables associated with in-hospital mortality in the univariate analysis were age, treatment strategy (surgical vs conservative treatment), cTnT and CRP entered either as binary (CRP > 9.8 mg/l) or continuous variable (Table II).

Table I. Baseline characteristics of patients with type A acute aortic dissection.

Variables	All (n = 54)	Survived (n = 30)	Died (n = 24)	p-value
Demographics				
Age, years	69 ± 14	62 ± 12	77 ± 13	< 0.001
Male gender, n (%)	34 (63)	20 (67)	14 (58)	0.729
History				
Hypertension, n (%)	50 (93)	26 (87)	24 (100)	0.182
Diabetes mellitus, n (%)	5 (9)	2 (7)	3 (13)	0.754
Dyslipidemia, n (%)	18 (33)	10 (33)	8 (33)	0.772
Smoking, n (%)	25 (46)	16 (53)	9 (39)	0.376
Clinical characteristics				
Time to admission, h	2.3 (1–6)	2.8 (1–5)	2 (1–6.5)	0.732
Admission SBP, mmHg	115 (90–134)	113 (90–130)	120 (91–148)	0.588
Admission DBP, mmHg	70 (60–80)	70 (60–80)	75 (60–95)	0.196
Heart rate, per min	65 (59–79)	64 (60–75)	72 (55–80)	0.993
Aortic diameter, mm	48.7 ± 6.7	48.6 ± 7.5	48.8 ± 5.6	0.923
LV ejection fraction, %	56 ± 6.5	57 ± 6.6	55 ± 6.4	0.425
Surgical treatment, n (%)	32 (59)	25 (83)	7 (29)	< 0.001
IRAD score	3.3 ± 1.2	2.8 ± 1.2	3.8 ± 1.1	0.004
Laboratory parameters				
CRP, mg/l	9.15 (4.1–17)	5.0 (2.5–8.5)	15.7 (10.8–21.4)	< 0.001
D-dimer, µg/ml	4.3 (1.6–5.1)	3.7 (0.9–5.4)	4.5 (3.8–5.2)	0.241
cTnT, ≥ 0.01 ng/ml	18 (33)	7 (23)	11 (46)	0.092
Fibrinogen, g/l	3.6 ± 1.4	3.4 ± 1.1	3.7 ± 1.7	0.519
WBC, × 10 ⁹ /l	12.4 ± 4.8	11.8 ± 4.2	13.2 ± 5.5	0.334
Platelet count, × 10 ⁹ /l	194 ± 64	191 ± 62	199 ± 67	0.641
MPV, fl	8.4 ± 1.0	8.3 ± 1.0	8.5 ± 1.0	0.548
Hemoglobin, g/l	137 (124–147)	138 (126–147)	137 (123–147)	0.690
eGFR, mL/min	57 ± 14	59 ± 10	54 ± 18	0.186

SBP, systolic blood pressure; DBP, diastolic blood pressure; LV, left ventricular; IRAD, International Registry of Acute Aortic Dissection; CRP, C-reactive protein; cTnT, cardiac troponin T; WBC, white blood cells; MPV, mean platelet volume; eGFR, estimated glomerular filtration rate. Categorical variables are presented as absolute (relative) frequencies and continuous variables as mean ± standard deviation or median (interquartile range). Differences between the groups are determined by *t*-test or Mann-Whitney test for continuous variables and by chi-square test for categorical variables.

After multivariable adjustment for age, gender, treatment strategy, time to admission, CRP and cTnT, the independent predictors of in-hospital mortality were age, treatment strategy and CRP either as binary or continuous variable (Table II).

ROC curve analysis showed a significant link between CRP and mortality among patients with AAD (AUC = 0.79; $p < 0.01$) (Figure 1A). Values of CRP > 9.8 mg/l had 83% sensitivity and 80% specificity for predicting in-hospital mortality. Mean values of IRAD score were 3.3 ± 1.2 , being significantly higher in non-survivors compared with survivors (3.8 vs 2.8; $p = 0.004$). IRAD score weakly correlated with CRP ($r = 0.29$; $p = 0.03$), but not with D-dimer ($p = 0.78$). CRP levels positively correlated with the

time after onset of symptoms ($r = 0.34$; $p = 0.01$). After adjustment for IRAD score, treatment strategy and time of onset of symptoms, CRP remained independent predictor of in-hospital mortality (OR = 8.24; 95% CI 1.40–48.39; $p = 0.019$). When CRP values were incorporated into IRAD score, better discriminative ability for in-hospital mortality was obtained, i.e. the area under ROC curve (AUC) increased from 0.74 to 0.89 ($p = 0.004$) (Figure 1B).

Discussion

In this study, we investigated the prognostic impact of baseline inflammatory biomarkers together with

Table II. Predictors of in-hospital mortality in type A acute aortic dissection.

Variables	Univariate model		Multivariate model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.10 (1.04–1.17)	0.0008	1.09 (1.02–1.18)	0.014
Surgical treatment	0.08 (0.02–0.30)	0.0002	0.11 (0.02–0.60)	0.011
CRP	1.11 (1.03–1.20)	0.0082	1.10 (1.01–1.21)	0.040
CRP (> 9.8 mg/l)	20.00 (4.94–80.89)	0.0001	7.06 (1.34–37.36)	0.021
TnT (≥ 0.01 ng/ml)	2.78 (0.9–8.93)	0.080	–	–

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; TnT, cardiac troponin T.

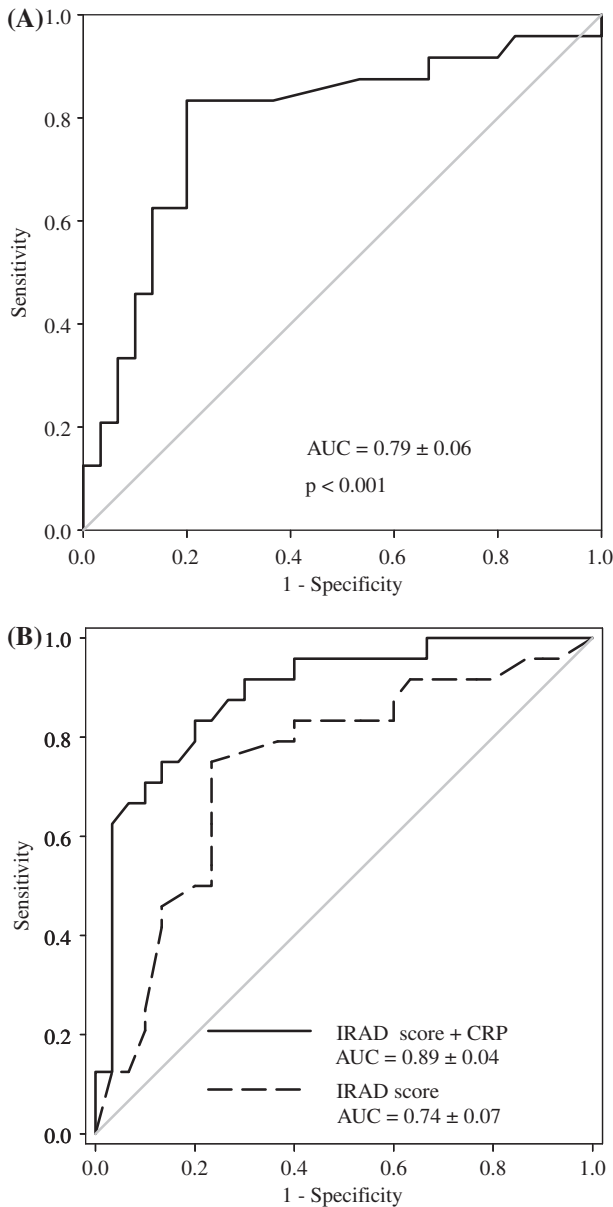


Figure 1. Receiver-operating characteristic curves (ROC) for ability of: (A) C-reactive protein (CRP); (B) International Registry of Acute Aortic Dissection (IRAD) score alone and in combination with CRP to predict in-hospital mortality in type A acute aortic dissection. AUC, area under the ROC curve.

cardiac troponin T and D-dimer in predominantly hypertensive patients with type A acute aortic dissection. Only the initial CRP was an independent predictor of short-term mortality. In addition, CRP improved the prognostic value of IRAD score.

While inflammatory biomarkers and cardiac troponins are well studied in acute coronary syndromes, their prognostic role in acute aortic diseases is less clear (14,15). CRP is a simple marker widely commercially available and used in daily routine clinical practice. According to our results, admission CRP proved to be adequately sensitive and specific for prediction of in-hospital outcome in type A AAD. Furthermore, CRP release is temporally correlated with time after the onset of symptoms.

Schillinger et al. (5) demonstrated prognostic role of admission CRP in patients with symptomatic thoracic or abdominal aortic aneurysm. The majority of the study patients had the onset of symptoms before admission more than 8 h, and in 24% of them no data on the beginning of symptoms were available. Our results show that CRP elevation is time dependent, what was considered in final multivariate model. In a study by Wen et al. (6), CRP predicted hospital death among patients with acute aortic dissection. In an entire patient group (including both type A and B AAD), baseline CRP was associated with short-term mortality. However, when type A and B AAD were analyzed separately, CRP was no longer a predictor of adverse outcome. Sakakura et al. (7) found that peak but not admission CRP values were strong predictors for adverse long-term events in type B acute aortic dissection. In a study by Okina et al. (8), the CRP pattern obtained during hospitalization could provide information regarding cardiovascular outcomes in patients with both type A and B acute aortic dissection assigned to medical treatment. Patients who underwent emergency surgery or died within few days post admission were not included in that study. The behavior of CRP was prospectively studied in 47 medically treated patients with type A and B aortic dissection and intramural hematoma (9). Re-elevation or delayed recovery of CRP levels during hospital stay corresponded with intramural events.

Hence, previous studies investigated heterogeneous groups of patients in the broad spectrum of acute aortic diseases. Our study included a cohort of consecutive patients with type A AAD irrespective of treatment approach, CRP was measured on admission, taking into consideration, regarding outcome analysis, treatment strategy, time of onset of symptoms, admission cTnT and IRAD score. The findings of this study confirm that CRP has independent prognostic role in type A acute aortic dissection on top of the validated IRAD score.

Del Porto et al. (16) found a significant increase in CRP and proinflammatory cytokines in AAD patients compared with controls and suggested that this is evidence for an important role of immunological pathways in type A AAD. Genes associated with chronic inflammation are up-regulated in type A AAD (3), and vessel wall inflammation found in patients with acute aortic syndromes was associated with high risk for disease progression (4). Thus, it seems that inflammation might play a significant role in the pathogenesis along with prognosis of acute aortic dissection.

In line with our results, recent studies did not show independent prognostic value of D-dimer regarding in-hospital mortality in patients with type A AAD (6,17,18). Conversely, Ohlmann et al. (19) identified D-dimer as independent predictor of mortality among patients with AAD but without subgroup

analysis concerning types of AAD. Sodeck and co-workers (20) showed that pre-operative NT-proBNP predicts outcome in patients undergoing surgery in type A acute aortic dissection.

We believe that this is the first time the prognostic role of admission cTnT was investigated in patients with type A AAD. The subgroup with increased cTnT values, according to clinical characteristics and laboratory parameters on presentation, represented a population at greater risk of worse hospital outcome. However, in line with previous report that measured admission cardiac troponin I levels in type A AAD (21), in our study cTnT was not an independent predictor of mortality.

The main limitation of this single center study focused on in-hospital mortality and multimarker approach is the relatively small sample size, which can only be overcome by a multicenter study.

In conclusion, our data show that CRP taken at the time of admission has independent prognostic value in risk stratification of patients with type A acute aortic dissection. The addition of CRP to IRAD score improved discriminative capacity of in-hospital mortality irrespective of symptom duration and treatment strategy. Admission cardiac troponin T did not independently influence mortality but was associated with the severity of disease, renal function and inflammation.

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Disclosure: The authors declared no conflict of interest.

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