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Post-operative aspartate aminotransferase levels independently predict mortality after isolated coronary artery bypass grafting

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ABSTRACT

Background: Since troponins have become widely available, the roles of other less specific biomarkers for myocardial necrosis following coronary artery bypass grafting (CABG) have been seldom studied. Aspartate aminotransferase (AST) may not only be released from the heart but also from the liver or skeletal muscle. We assessed whether post-operative AST levels were associated with mortality and morbidity after contemporary (CABG).
Method: Patients undergoing isolated CABG during July 2010–June 2012 at Auckland City Hospital were included if they had a post-operative AST measurement within 48 h ($n = 804$ of 818). The prognostic utility of 2× upper limit of normal of AST (>90 U/L) pre-specified for adverse outcomes was assessed.
Results: Median post-operative AST level was 37 U/L (lower quartile 30, upper quartile 48). In multivariable analysis, including baseline characteristics, AST >90 U/L was independently associated with 30-day mortality (OR 12.0, 95% CI 2.99–47.9, $P < 0.001$), long-term mortality (OR 12.0, 95% CI 1.69–34.8, $P < 0.001$) and composite morbidity (OR 3.31, 95% CI 1.56–7.02, $P = 0.002$). AST as a continuous parameter remained an independent predictor for 30-day and long-term mortality when hs-TnT was adjusted for but not for composite morbidity. Independent predictors of AST >90 U/L included female sex, unstable angina and operation time.
Conclusion: Increase in AST levels within 48 hours of CABG was a strong independent predictor of 30 day mortality. Although AST increase is not specific to myocardial necrosis, it remains useful for prognosis in cardiac surgery.

1. Introduction

Cardiac troponins are the recommended biomarkers for diagnosing myocardial infarction (MI), including type 5 MI, which is associated with coronary artery bypass grafting (CABG) [1]. Over the last decade, studies of cardiac biomarkers for type 5 MI have therefore focused on troponins, with a paucity of literature about older biomarkers such as aspartate aminotransferase (AST). This has occurred in part because troponins have superior sensitivity, specificity and prognostic value in this context [2–5]. However, one contemporary study reported post-operative AST levels independently predicted early and late mortality after CABG [6], but this finding has not been reproduced in other recent studies [7–9]. Whether AST levels are related to post-operative complications has not been previously studied. Older studies from our centre identified a cutpoint for AST twice the upper limit of normal (ULN) to be associated with myocardial damage after cardiac surgery [10,11]. We therefore assessed the prognostic utility of this cutpoint for post-operative AST levels to predict mortality and morbidity after CABG and compared AST with high-sensitivity troponin T (hs-TnT).

2. Methods

Ethics approval was attained from the ethics committee of our institution's research office. The study involved patients who underwent isolated CABG without concomitant valve surgery from July 2010 to June 2012 at Auckland City Hospital. Patients were included if they had AST levels measured within 48 h after CABG, which was routinely performed in the cardiovascular intensive care unit. Where several measurements were taken the highest level was recorded. The normal reference range for AST is <45 U/L. This was compared to hs-TnT levels routinely measured 12–24 h after surgery, which has a 99% upper reference limit (URL) of 14 ng/L.

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Clinical pre-, peri- and post-operative data were collected from computerised records retrospectively.

Definitions for pre-operative characteristics are as follows. Angina and dyspnea were graded using the Canadian Cardiovascular Society Classification (CCS) and the New York Heart Association Functional Classification (NYHA), respectively. Critical pre-operative state involved patients who required inotrope, ventilator and/or intra-aortic balloon pump (IABP) support during the hospital admission prior to surgery. Hypertension referred to a previous formal diagnosis, being prescribed medications to reduce blood pressure or any measurement of over 140/90 mmHg pre-operatively. Stroke was defined as neurological deficit that persisted over 24 h as a result of disturbance of cerebral blood supply. Peripheral vascular disease included claudication, ankle brachial index <0.9, imaging evidence of >50% stenosis in any peripheral artery, a peripheral vascular intervention or amputation for arterial insufficiency. Chronic respiratory diseases included a previous formal diagnosis, use of inhaled corticosteroids for respiratory symptoms or forced expiratory volume in 1 s (FEV1) <80% on spirometry. The number of major coronary vessels with >50% stenosis was recorded. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet and Renal Disease equation and the last serum creatinine measurement pre-operatively. EuroSCORE I and II were calculated to estimate operative risk [12,13]. The type and number of bypass grafts and duration of operation, cardiopulmonary bypass and aortic cross-clamps were recorded.

Mortality data were obtained from New Zealand's national registry up until 30 June 2014. Five post-operative complications as defined by the Society of Thoracic Surgeon's (STS) score and their composite were determined, including permanent stroke (acute neurological deficit >24 h due to cerebral blood supply disturbance), renal failure (new dialysis requirement or increase of creatinine to >4.0 mg/dL and >3 times last pre-operative level), prolonged ventilation >24 h, deep sternal wound infection and return to theatre for any reason [14]. Peri-operative MI was defined according to the Third Universal Definition for type 5 MI [1], including troponin increase to more than 10 times the 99th percentile URL of the assay and new signs of infarction on ECG, echocardiogram, coronary angiogram or magnetic resonance imaging. The pre-specified outcomes for analyses were 30-day mortality, long-term mortality during follow-up and composite morbidity.

2.1. Statistical analyses

We pre-specified dividing patients into two groups based on a cutpoint of 90 U/L, i.e. twice the ULN, for analyses. Mann–Whitney *U* test and Fisher's exact test were used for univariate analyses for continuous (presented as mean/standard deviation) and categorical variables (percentage/frequency), respectively. Kaplan–Meier curves and log-rank (Mantel–Cox) test was used for univariate longitudinal analyses. Receiver-operative characteristics analysis was used to calculate c-statistic and 95% confidence interval (95% CI). Multivariable analyses incorporated variables with $P < 0.10$ in univariate analyses, using logistic regression to calculate odds ratios (OR) for cross-sectional outcomes and Cox proportional hazards regression used to calculate hazards ratios (HR) for mortality. AST and hs-TnT as continuous parameters, and separately AST >90 U/L were included in the multivariable models for outcomes. All tests were two-tailed with significance level set at 0.05. Statistical software used were SPSS (Version 17.0, SPSS Inc., Chicago, IL, USA) and Prism (Version 5, GraphPad Software, San Diego, CA, USA).

3. Results

A total of 818 patients underwent isolated CABG during the two-year study period, of which 804 had post-operative AST measurements within 48 h included in the study, 555 (69.0%) of whom had AST in the normal range <45 U/L. Median post-operative AST levels was 37 U/L (lower quartile 30, upper quartile 48).

Table 1 presents the baseline characteristics for subjects with post-operative AST≤ and >90 U/L. Those with AST >90 U/L ($n = 49$, 6.1%) had a higher proportion of women (40.8% vs. 19.2%, $P = 0.001$) and higher prevalence of CCS class IV angina (51.0% vs. 36.7%, $P = 0.049$).

Operative and post-operative data are shown in Table 2. AST >90 U/L was associated with longer operation time (229 vs. 215 min, $P = 0.037$). In univariate analyses for outcomes, AST >90 U/L was associated with 30-day mortality (OR 12.1, 95% CI 3.70–39.8, $P < 0.001$), composite morbidity (OR 3.51, 95% CI 1.92–6.40, $P < 0.001$), ventilation > 24 h (OR 3.58, 95% CI 1.90–6.77, $P < 0.001$), peri-operative MI (OR 2.78, 95% CI 1.28–6.02, $P = 0.01$) and new atrial fibrillation (OR 1.96, 95% CI 1.06–3.62, $P = 0.032$).

Fig. 1 illustrates survival over a mean follow-up of 2.8 ± 0.6 years. Patients with AST >90 U/L had significantly greater long-term mortality (HR 19.8, 95% CI 3.36–117, $P < 0.001$). One-year survival was 87.3% for patients with AST >90 U/L compared to 98.0% for patients AST <90 U/L. Most of the difference was within the first month.

Table 1
Baseline characteristics.

	AST ≤ 90 ($n = 755$)	AST > 90 ($n = 49$)	*P*-value
Demographics			
Age, years	64.6 (10.0)	62.6 (10.0)	0.165
Female	19.2% (145)	40.8% (20)	0.001
Ethnicity			0.634
Caucasian	54.6% (412)	51.0% (25)	
Maori or Pacific	24.6% (186)	22.4% (11)	
Other	20.8% (157)	26.5% (13)	
BMI, kg/m^2	29.0 (5.3)	30.3 (6.3)	0.244
Presentation			
Angina CCS class IV	36.7% (277)	51.0% (25)	0.049
Dyspnoea NYHA class IV	4.0% (30)	6.1% (3)	0.446
Recent myocardial infarction within 6 weeks	49.5% (374)	51.0% (25)	0.883
Critical pre-operative state*	9.4% (71)	12.2% (6)	0.457
Inpatient operation	79.3% (599)	81.6% (40)	0.855
Past Medical History			
Myocardial infarction	66.0% (498)	73.% (36)	0.349
Percutaneous coronary intervention	10.7% (81)	14.3% (7)	0.475
Coronary artery bypass grafting	1.2% (9)	4.1% (2)	0.141
Congestive heart failure	5.7% (43)	2.0% (1)	0.511
Atrial fibrillation	7.9% (60)	2.0% (1)	0.167
Diabetes	38.4% (290)	34.7% (17)	0.652
Diabetes on insulin	10.9% (82)	8.2% (4)	0.810
Hypercholesterolaemia	91.5% (691)	93.9% (46)	0.790
Hypertension	71.0% (536)	61.2% (30)	0.149
Current smoker	14.0% (106)	24.5% (12)	0.059
Stroke	6.5% (49)	4.1% (2)	0.762
Peripheral vascular disease	11.3% (85)	6.1% (3)	0.348
Chronic respiratory disease	17.2% (130)	10.2% (5)	0.241
Dialysis	3.2% (24)	0.0% (0)	0.391
Investigations			
Left main stem >50% stenosis	43.7% (330)	46.9% (23)	0.659
Three-vessel disease	82.1% (620)	67.3% (33)	0.014
Ejection fraction			0.133
Normal (>50%)	71.4% (539)	63.3% (31)	
Mild impairment (40–50%)	14.3% (108)	10.2% (5)	
Moderate impairment (30–40%)	9.1% (69)	16.3% (8)	
Severe impairment (<30%)	5.2% (39)	10.2% (5)	
Estimated GFR (mL/min)	79.3 (28.6)	78.4 (29.5)	1.000
EuroSCORE I	4.4% (4.8%)	4.6% (6.4%)	0.539
EuroSCORE II	2.5% (2.9%)	3.2% (4.7%)	0.575

AST = aspartate aminotransferase; BMI = body mass index; CCS = Canadian Cardiovascular Society Classification; NYHA = New York Heart Association Functional Classification.
* Critical pre-operative state involved patients who required inotrope, ventilator and/or intra-aortic balloon pump (IABP) support during the hospital admission prior to surgery.