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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.

Table 2
Operative variables and outcomes.

	AST ≤ 90 ($n = 755$)	AST > 90 ($n = 49$)	*P*-value
Operation Details			
Off-pump	2.8% (21)	2.0% (1)	1.000
Number of bypassed vessels	3.3 (0.8)	3.1 (0.7)	0.134
Left internal mammary artery graft	98.1% (741)	93.9% (46)	0.079
Right internal mammary artery graft	5.8% (44)	10.2% (5)	0.213
Radial artery graft	22,6% (171)	34.7% (17)	0.080
Saphenous vein grafts	93.9% (709)	89.8% (44)	0.229
Operation time (minutes)	215 (220)	229 (247)	0.037
Cardiopulmonary bypass time (minutes)	91 (25)	99 (44)	0.609
Cross-clamp time (minutes)	59 (20)	59 (29)	0.362
Post-operative outcomes			
Composite morbidity	16.4% (124)	40.8% (20)	<0.001
Stroke	0.9% (7)	4.1% (2)	0.100
Renal failure	2.1% (16)	4.1% (2)	0.301
Ventilation >24 h	11.9% (90)	32.7% (16)	<0.001
Deep sternal wound infection	0.4% (3)	0.0% (0)	1.000
Return to theatre	4.6% (35)	10.2% (5)	0.089
New atrial fibrillation	21.3% (161)	34.7% (17)	0.034
Perioperative myocardial infarction	12.2% (66)	27.8% (10)	0.018
hs-TnT >140 ng/L	86.5% (475)	86.1% (31)	1.000
New ECG and/or echocardiographic changes	12.6% (94)	25.0% (12)	0.026
Operation to discharge (days)	8.1 (5.8)	8.5 (4.3)	0.073
Total mortality	2.3% (17)	12.2% (6)	0.002
Mortality at 30 days	0.9% (7)	10.2% (5)	<0.001
Mortality after 30 days	1.3% (10)	2.0% (1)	0.502

AST = aspartate aminotransferase; hs-TnT = high-sensitivity troponin T.

Results from the receiver-operative characteristics analyses are listed in Table 3. Post-operative AST levels were associated with 30-day mortality (c-statistic 0.762, 95% CI 0.609–0.915, $P = 0.002$), composite morbidity (c-statistic 0.573), ventilation > 24 h (c-statistic 0.615) and peri-operative MI (c-statistic 0.594). Hs-TnT was associated with long-term mortality (c = 0.637), composite morbidity (c = 0.708), renal failure (c = 0.659), ventilation >24 h (c = 0.732), return to theatre (c = 0.644) and perioperative MI (c = 0.575).

Table 4 shows the variables with $P < 0.10$ in multivariable analyses. Female sex, CCS Class IV angina and operation time were independent predictors of AST >90 U/L. 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, $P = 0.002$). If post-operative complications was introduced into the model, AST >90 U/L remained an independent predictor of 30-day mortality (OR 7.61, 95% CI 1.69–34.8, $P = 0.008$).

Post-operative AST, as a continuous parameter when hs-TnT was adjusted for, independently predicted 30-day mortality (OR 1.14, 95% CI 1.04–1.25, $P = 0.004$) and long-term mortality (HR 1.08, 95% CI 1.01–1.16, $P = 0.031$) but not composite morbidity (OR 1.03, 95% CI 0.962–1.10, $P = 0.409$). Hs-TnT as a continuous parameter predicted

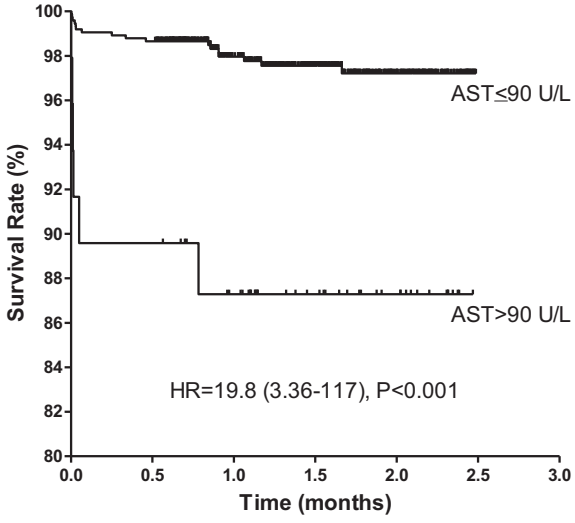

Fig. 1. Kaplan–Meier survival curve by AST group.

Table 3
Receiver-operative characteristics analyses.

Outcome	AST C-statistic	Hs-TnT C-statistic
30-day mortality	**0.762 (0.609–0.915)**	0.649 (0.452–0.845)
Long-term mortality	0.580 (0.491–0.670)	**0.637 (0.507–0.768)**
Composite morbidity	**0.573 (0.518–0.628)**	**0.708 (0.656–0.760)**
Stroke	0.615 (0.464–0.766)	0.635 (0.455–0.814)
Renal failure	0.445 (0.313–0.576)	**0.659 (0.506–0.811)**
Ventilation >24 h	**0.615 (0.555–0.676)**	**0.732 (0.675–0.788)**
Deep sternal wound infection	0.584 (0.170–0.999)	0.694 (0.232–1.000)
Return to theatre	0.479 (0.380–0.578)	**0.644 (0.549–0.739)**
Perioperative myocardial infarction	**0.594 (0.524–0.664)**	**0.575 (0.505–0.644)**

All figures are c-statistic with 95% CI.
Bolded = significant findings.
AST = aspartate aminotransferase; hs-TnT = high-sensitivity troponin T.

Table 4
Multivariable analyses.

AST >90 U/L	Odds ratio	95% Confidence interval	*P*-value
Female	2.67	1.44–4.96	0.002
CCS Class IV	1.71	1.04–2.81	0.023
Left internal mammary graft	0.338	0.173–0.662	0.002
Operation time (per 10 min)	1.18	1.06–1.31	0.001
30-day mortality	**Odds ratio**	**95% Confidence interval**	***P*-value**
Female	4.41	1.25–15.6	0.021
Maori/Pacific ethnicity	6.47	1.70–24.7	0.006
NYHA Class IV	11.2	2.71–45.7	0.001
AST >90 U/L	12.0	2.99–47.9	<0.001
AST (per 10 U/L increase)	1.14	1.04–1.24	0.004
hs-TnT (per 100 ng/L increase)	1.02	0.978–1.05	0.429
Long-term mortality	**Hazards ratio**	**95% Confidence interval**	***P*-value**
Peripheral vascular disease	3.24	1.14–9.19	0.027
Left internal mammary graft	0.171	0.039–0.753	0.020
Ventilation > 24 h	3.39	1.30–8.84	0.0.012
Return to theatre	4.24	1.48–12.1	0.007
AST >90 U/L	4.07	1.52–10.9	0.005
AST (per 10 U/L increase)	1.08	1.00–1.15	0.037
hs-TnT (per 100 ng/L increase)	1.00	0.970–1.03	0.987
Composite morbidity	**Odds ratio**	**95% Confidence interval**	***P*-value**
CCS Class IV	1.48	0.949–2.31	0.084
Critical pre-operative state*	2.29	1.24–4.22	0.008
Diabetes on insulin	2.11	1.15–3.86	0.015
Current smoker	2.02	1.15–3.54	0.008
Previous coronary artery bypass grafting	4.44	1.09–18.1	0.038
Left main stem >50% stenosis	1.62	1.05–2.50	0.029
Ejection fraction impaired <40%	3.30	2.00–5.47	<0.001
eGFR (per mL/min)	0.991	0.983–0.998	0.019
AST >90 U/L	3.31	1.56–7.02	0.002
AST (per 10 U/L increase)	1.03	0.962–1.10	0.409
hs-TnT (per 100 ng/L increase)	1.09	1.05–1.13	<0.001

AST = aspartate aminotransferase; CCS = Canadian Cardiovascular Society Classification; eGFR = Estimated glomerular filtration rate; hs-TnT = high-sensitivity troponin T; 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.

composite morbidity ($P < 0.001$) but not 30-day mortality ($P = 0.429$) or long-term mortality ($P = 0.987$).

4. Discussion

The novel finding of our study is that elevated AST levels independently predicts 30-day mortality and long-term mortality after isolated CABG even when adjusted for hs-troponin. It was also independently associated with composite morbidity after adjustment for baseline variables.

AST is an enzyme that catalyses aspartate and α-ketoglutarate to oxaloacetate and glutamate, and is mainly found in the liver, followed by the heart and other organs including skeletal muscle, brain and kidneys. AST peaks around 24–36 h post-operatively after CABG, and remains elevated for 3–5 days [15,16]. The wide tissue distribution impairs its specificity for myocardial damage and therefore MI diagnosis. However, AST might be a prognostic indicator in cardiac surgery because non-cardiac sources of AST rise such as liver or skeletal muscle can also reflect impaired cardiac function, ischaemia and decreased tissue perfusion. We routinely measure AST after cardiac surgery because of earlier work published from our centre showing AST's correlation with myocardial damage and prognosis in this context [10,11].

A few studies have found AST to be independently associated with mortality after CABG [6,17]. However, other smaller and underpowered studies did not find an independent association [7–9]. Early studies showed that AST levels remained normal in the majority of patients after CABG [18,19]. One study found 71.8% of patients having AST <50 U/L post-operatively, similar to the 68.9% of patients having normal AST <45 U/L in our study [6].

Although AST >90 U/L predicted both 30-day and long-term mortality in our study, the main difference in mortality was in the first 30 days, whereas late mortality was not significantly different. Similar results have been reported in other studies [6,17]. This was true even after adjusting for post-operative complications including ventilation >24 h and return to theatre, as well as hs-TnT, suggesting its prognostic value for early mortality has a different pathophysiology.

The optimal cutpoint for AST rise for predicting mortality after CABG would be expected to differ from that for hs-troponin. The recent third universal definition for type 5 MI, which involves dual criteria of elevated biomarkers, preferably troponin, with new signs of infarction on electrocardiogram, echocardiogram, coronary angiogram or cardiac magnetic resonance imaging and arbitrarily set the biomarker threshold at 10 times 99th percentile URL [1]. This threshold is supported by a subsequent study using high-sensitivity troponin T of >140 ng/L, i.e., 10 times 99th percentile URL with ECG and/or echocardiographic criteria [20]. Other studies of isolated troponin rise in CABG have found much higher optimal cutpoints of 50–160 times [21,22]. Our study's cutpoint of AST >90 U/L is 2 times the ULN and independently predicted 30-day and long-term mortality. Other studies have reported lower thresholds of 3–6 times ULN for AST [6,7,17].

Our results also show that AST independently predicted composite morbidity in our study although not after hs-TnT adjustment. AST >90 U/L was also associated with higher rates of ventilation >24 h, new atrial fibrillation and MI.

4.1. Limitations

This is a single-centre retrospective study. We did not have serial AST data for a significant proportion of patients to assess the dynamic profile of post-operative AST levels, and did not measure AST pre-operatively. Other liver enzymes were not routinely measured for assessment of liver damage causing the elevation of AST. Duration of follow-up was short given that this was a contemporary cohort, and other outcomes during follow-up were not obtained.

5. Conclusion

Post-operative AST levels predict mortality and morbidity after CABG. AST is a useful prognostic biomarker for adverse outcomes after CABG even though it is not specific for myocardial damage.

Conflict of interest

TW, RS, TR and GG have no conflicts to declare.

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