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Invasive management of acute coronary syndrome: Interaction with competing risks

Anthony (Ming-yu) Chuang [a,b,*,1], David G. Hancock [a,b,1], Amera Halabi [a,b,1], Matthew Horsfall [a,b,1], Julian Vaile [a,b,1], Carmine De Pasquale [a,b,1], Ajay Sinhal [a,b,1], Dylan Jones [a,b,1], Richard Brogan [b,1], Derek P. Chew [a,b,1]

[a] School of Medicine, Flinders University of South Australia, Adelaide, Australia
[b] Department of Cardiovascular Medicine, Southern Adelaide Local Health Network, Adelaide, Australia

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ABSTRACT

Background: The aim of this study was to characterise the interaction between ACS- and non-ACS-risk on the benefits of invasive management in patients presenting with acute coronary syndrome (ACS).
Methods: Consecutive patients admitted to a tertiary hospital's Cardiac Care Unit in the months of July–December, 2003–2011 with troponin elevation (>30 ng/L) were included. "ACS-specific-risk" was estimated using the GRACE score and "non-ACS-risk" was estimated using the Charlson-Comorbidity-Index (CCI). Inverse-probability-of-treatment weighting was used to adjust for baseline differences between patients who did or did not receive invasive management. A multivariable flexible parametric model was used to characterise the time-varying hazard.
Results: In total, 3057 patients were included with a median follow-up of 9.0 years. Based on CCI, 1783 patients were classified as 'low-non-ACS risk' (CCI ≤ 1; invasive management 81%; 12-month mortality 5%), 820 as 'medium-non-ACS risk' (CCI 2–3; invasive management 68%; 12-month mortality 13%), and 468 as 'high-non-ACS risk' (CCI ≥ 4; invasive management 47%; 12-month mortality 29%). After adjustment, invasive management was associated with a significant reduction in one-year overall-mortality in the 'low-risk' and 'medium-risk' groups (HR = 0.38, 95%CI:0.26–0.56; HR = 0.46, 95%CI:0.32–0.67); but not in the 'high-risk' group (HR = 1.02, 95%CI:0.67–1.56). The absolute benefit of invasive management was greatest with higher baseline ACS-risk, with a non-linear interaction between ACS- and non-ACS-risk.
Conclusions: There is a complex interaction between ACS- and non-ACS-risk on the benefit of invasive management. These results highlight the need to develop robust methods to objectively quantify risk attributable to non-ACS comorbidities in order to make informed decisions regarding the use of invasive management in individuals with numerous comorbidities.

1. Introduction

Acute Coronary Syndrome (ACS) represents one of the most common hospital presentations, with significant short-term and long-term morbidity and mortality, and frequently occurs in patients with a large number of comorbidities [1–6]. Current clinical guidelines universally recommend invasive management with angiogram, and subsequent percutaneous coronary intervention if appropriate, as treatment of choice for 'suitable' patients with ACS [7–10]. However, these recommendations are based on large-scale randomised controlled trials (RCTs) [11–14], which were performed on highly selected patient groups that differ significantly from those patients commonly seen in clinical practice with high burdens of comorbidity [15]. Defining the suitability of patients with complex comorbidity for invasive management has not been adequately explored and this decision is left to clinical discretion. This is especially relevant given the invasive nature of angiography, its relative contraindications, and the variable risks from this procedure in patients with different combinations of comorbidities [9].

Abbreviations: ACS, Acute coronary syndrome; CCI, Charlson comorbidity index; CI, Confidence interval; cTnT, Cardiac troponin-T; GRACE, Global Registry of Acute Coronary Events; HR, Hazard ratio; ICD, International Classification of Diseases; IPTW, Inverse probability of treatment weighting; MI, Myocardial infarction; NNT, Number needed to treat; RCT, Randomised control trial; TIMI, Thrombolysis in Myocardial Infarction.

* Corresponding author at: Flinders University, Flinders Drive, Bedford Park, South Australia 5042, Australia.
E-mail address: anthony.chuang@sa.gov.au (A.(M.) Chuang).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Previous studies assessing the benefits of invasive management in patients with high comorbidity burdens have shown mixed results [4, 16–19]. One of the primary limitations affecting the interpretation of these studies is the lack of an objective score for modelling comorbidity burden and thus risk attributable to non-ACS conditions. While multiple scores have been proposed to quantify ACS related-risk (e.g. Global Registry of Acute Coronary Events [GRACE] score, Thrombolysis in Myocardial Infarction [TIMI] score, HEART risk scores) [20], there are currently a limited number of tools to specifically quantify non-ACS risk. Therefore, treatment decisions in ACS are currently based on the objective assessment of a patient's ACS risk (complemented by validated tools such as the GRACE score), but are highly subjective when assessing a patient's non-ACS or competing risk.

The development of an objective approach to accurately quantify non-ACS (competing) comorbidity burden has important implications for rationalising treatment decisions in a robust and objective manner. Therefore, we sought to characterise the interaction between ACS and non-ACS risk and their temporal impact on the benefits of invasive management in ACS, using a flexible parametric model and propensity score with inverse probability of treatment weighting (IPTW).

2. Methods

2.1. Study population

The study population was drawn from a registry database, which collected data prospectively for all consecutive patients admitted to the Cardiac Care Unit of a tertiary public hospital in South Australia in the months July to December over a 9-year time period (2003−2011). Patients were excluded from the analyses if no cardiac troponin-T (cTnT) testing was performed, or if they did not have an elevated cTnT (i.e. cTnT ≤ 30 ng/L). Furthermore, patients were excluded if death occurred within 7 days of presentation to avoid the inclusion of patients who may have died before angiography could be offered or where angiography would unlikely to have altered outcomes. All other patients were included regardless of final diagnoses.

Patient data was linked with hospital International Classification of Diseases, version 10 Australian Modified (ICD-10 AM) primary and secondary diagnosis codes. Trained independent coding professionals, applying standardized audited protocols, used medical record clinical documentation, imaging and pathology data to classify primary and secondary diagnoses for each clinical presentation. All diagnostic codes for patients transferred between hospitals were interrogated to ensure that all suitable cases were identified. Comorbidities were identified by examining available hospitalization records from the preceding 10 years. Deaths were identified through hospital records and the state death registry. The Human Research Ethics Committee of the South Australian Department of Health approved this study and the study complies with the Declaration of Helsinki.

2.2. Group definitions and outcomes

In this cohort study, we employed the GRACE score to estimate ACS risk and Charlson Comorbidity Index (CCI) to estimate competing non-ACS risk. The CCI was originally developed as a prognostic index in patients admitted to a general medical service, then later adapted to coded diagnostic data as a measure of comorbidity burden predicting long-term mortality [21]. While it has been validated in the context of ACS-related mortality [22, 23], its discriminatory power is modest and it was not designed as a measure of non-ACS risk per se. However, we chose to use CCI because of its ease of application, prior validation, and lack of other available tools. Of note, prior MI also contributes 1 point to the CCI, but is not a factor considered in the GRACE score. Hence, CCI were calculated for each patient based on their primary and secondary diagnoses using ICD-10 codes, and classified into three competing risk groups: 1) low non-ACS risk [CCI = 0–1], 2) medium risk [CCI = 2–3], and 3) high risk [CCI ≥ 4]. For calculation of GRACE scores, a cTnT cut-off equivalent to high-sensitivity troponin-T of 29 ng/L was used (i.e. 30 ng/L).

The primary outcome was overall (all-cause) mortality given its patient relevance and the high competing risk profile of the patient cohort. The composite endpoint of all-cause mortality or recurrent myocardial infarction (MI) is also reported. In-hospital recurrent MI was adjudicated based on a documented recurrent rise and/or fall in troponin by two clinicians. Late MI was determined by a readmission with an ICD-10 AM code for myocardial infarction (I21–I25). Patients were followed-up for a minimum of 5 years from their first presentation and then were censored at the time of last known follow-up. The primary intervention assessed was angiography (i.e. invasive management). The decision for invasive management and all subsequent management was made at the treating physician's discretion, independent of this study.

2.3. Biomarker measurements and invasive management

The indication and timing for cTnT testing was clinically determined and independent of this study. All troponin samples were analysed using 4th generation cardiac troponin-T assay (Roche Diagnostics: lower limit of detection: 10 ng/L; 99th percentile upper reference limit in a normal population (no acute disease): 10 ng/L; lowest concentration with a CV < 10%: 30 ng/L). In the patients with multiple troponin measurements during the index hospital admission, the highest value was chosen irrespective of time from presentation. Invasive management was defined as the performance of coronary angiography during the index (initial) admission with or without percutaneous coronary intervention. The indication and timing for invasive management was clinically determined.

2.4. Statistical analysis

To mitigate potential bias caused by missing data, we used multiple imputation by chained equations to create 10 datasets from 20 iterations; the resultant model estimates for each variable were combined using Rubin's rules. Observed baseline differences in recorded variables between patients that underwent invasive management and those that did not were controlled for with propensity score analysis [24, 25]. Propensity scores for the likelihood of invasive management were generated by using a doubly robust augmented inverse probability of treatment weighting estimator that included the following covariates: age in years, gender, GRACE score, CCI, known congestive cardiac failure, known coronary artery disease, known hypertension, known diabetes, known chronic obstructive pulmonary disease, known chronic kidney disease, previous coronary artery bypass graft, ST-elevation myocardial infarction presentation, known peripheral arterial disease, known atrial fibrillation and maximum in-hospital cTnT. The balance of covariates between the weighted groups was assessed using standardized differences and by comparing the distribution of propensity scores and covariates in our unadjusted and IPTW-adjusted analyses.

To estimate the treatment effect of invasive management and its temporal pattern, a Royston and Parmar (RP) flexible parametric model with time-varying covariates and restricted cubic splines (varying spline knots) was utilised [26, 27]. The selection of the number of internal spline knots in the RP model was guided by optimizing the Akaike information criterion. The analyses were performed in patient cohorts subdivided on their non-ACS risk category (low, medium and high risk). The proportional hazards scale was used in the RP model to facilitate comparison of the hazard ratios (HRs) observed. Estimates are reported as HRs with corresponding 95% confidence intervals (95% CI). Interactions between invasive management, ACS risk and non-ACS risk were assessed by including interaction terms (CCI and GRACE score) in the flexible parametric model. The absolute benefit associated with invasive management was explored by inputting various levels of GRACE score and CCI into the flexible parametric model. The numbers needed to treat (NNT) to prevent one death were calculated from the absolute difference in estimated mortality at 12 months with and without invasive management. Continuous variables were tested for normal distribution and were reported either as means ± standard deviation or as medians with 25th and 75th percentiles. Categorical variables were reported as frequencies and proportions. Baseline characteristics were compared using Pearson's chi-square test for categorical variables and analysis of variance or Mann-Whitney-Wilcoxon for continuous variables, where appropriate. All reported *P*-values were 2-sided, and statistical significance was set at $P < 0.05$. All analyses were performed using STATA 14.1 (College Station TX, USA).

3. Results

3.1. Patient characteristics

Cohort selection is outlined in Fig. 1. Three thousand and fifty-seven eligible patients were included in the analysis with a median follow-up period of 9.0 years (interquartile range: 7.0–15.5 years). There were 1786 patients in the low non-ACS risk group [CCI = 0–1], 810 in the medium risk group [CCI = 2–3], and 461 in the high risk group [CCI ≥ 4]. The clinical characteristics of patients in each of these groups are presented in Table 1. Within these risk groups, 81.4% (1454/1786), 54.7% (553/810), and 48.4% (223/461) underwent coronary angiography respectively (Table 1 and Supp Table 1). The observed 12-month mortality rates were 5% (n = 81), 13% (n = 109), and 29% (n = 136).

3.2. Inverse probability of treatment weighting

Baseline characteristics among included patients that were or were not selected for angiogram are presented in Supp Table 2. Significant differences were observed in all measured characteristics between groups (i.e. standardized differences >10%). As expected, patients selected for angiogram were on average younger (mean age 63.9 versus 73.3), with fewer comorbidities (mean CCI 1.63 versus 2.54) and had lower ACS-risk (median GRACE score 103.8 versus 126.4). After inverse probability of treatment weighting, the distribution of baseline characteristics was highly comparable (i.e. standardized differences of <10%)

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