Peer Review File

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Comment 1: The reference papers in the Introduction section are outdated. Recent studies and review papers should be cited [J Cardiol. 2019;74:95-101].

Reply 1: We thank the reviewer for their comment. We have updated some of the references, particularly relating to the prevalence and annual incidence of ACS.

Changes in the text:
We have added the following references:
2. AIHW. Heart, stroke and vascular disease—Australian facts. Canberra: AIHW 2021.
3. Sanchis-Gomar F, Perez-Quilis C, Leischik R, et al. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med 2016;4:256.
5. Nadlacki B, Horton D, Hossain S, et al. Long term survival after acute myocardial infarction in Australia and New Zealand, 2009-2015: a population cohort study. Med J Aust 2021;214:519-25
9. Saito Y, Kobayashi Y. Percutaneous coronary intervention strategies in patients with acute myocardial infarction and multivessel disease: Completeness, timing, lesion assessment, and patient status. J Cardiol 2019;74:95-101

We have removed the following references:
> Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006;333:1091.
> Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362:2155-65

Comment 2: The rate of 0-VD is very high (i.e. 24%), probably indicating that a lot of MINOCA patients were included into the database. What are the possible underlying mechanisms? This reviewer wonders the definition of NSTEMI and the robustness of the dataset. Also, the definition of dyslipidemia should be provided.

Reply 2: We acknowledge that the rate of 0-VD seems relatively high. Firstly, we would like to clarify that all stenoses were assessed and reported visually by the performing Cardiologist, with data from these reports immediately collected and entered into the CADOSA registry by trained researchers. The 0-VD group was then independently audited by the research team to confirm that all patients classified as 0-VD truly had no severe lesions, as defined by our study (70% or above in epicardial vessels, 50% in the left main). In addition to MINOCA (defined as absence of any coronary artery stenosis ≥50% severity), these 0-VD cases would therefore have included cases where the culprit lesion was associated with angiographic severity of 50-69%. Other non-atherosclerotic causes of NSTEMI (e.g. spontaneous coronary dissection) would also have been captured in this group. We have included a brief paragraph acknowledging and discussing this finding in our discussion (outlined below).

All CADOSA definitions are consistent with the American College of Cardiology CathPCI Registry, National Cardiovascular Data Registry (NCDR). We have included a sentence in the methods section stating this (line 82). We have included the requested definitions of NSTEMI and dyslipidemia in the manuscript as requested by the reviewer in methods, Line 82.

Changes in the text:
Line 82: …including for NSTEMI and each traditional cardiovascular risk factor (12). NSTEMI was defined as a typical rise and fall in cardiac biomarkers with ST-segment depression or t-wave abnormalities and/or ischaemic symptoms. Dyslipidemia was defined as a documented history of dyslipidemia diagnosed and/or treated by a physician. Hypertension was defined as a history of hypertension being actively treated, a blood pressure greater than 140mmHg systolic or 90mmHg diastolic or current use of anti-hypertensive pharmacologic therapy. Smoking was defined as a confirmed history of smoking at any time in the past. Diabetes was defined as a documented history of diabetes including a need for anti-diabetic agents, or a fasting blood sugar >7mmol/L. Family history was defined as any blood relative with a history of angina, AMI or sudden cardiac death at an age less than 55 years.

Discussion paragraph beginning at line 235:
Interestingly, we also identified that almost a quarter of NSTEMI patients had 0-VD, with most appropriately treated medically, consistent with a lack of evidence to support percutaneous stenting of non-severe plaques (23). The cohort of 0-VD patients would have included, but would not be limited to, patients with myocardial infarction with nonobstructive coronary arteries (MINOCA), defined as patients with an AMI but with no obstructive lesion >50% in severity and no clinically apparent diagnosis (27). The prevalence of MINOCA amongst cohorts of patients with AMI has been estimated to be approximately 6% (28) but is more frequent in NSTEMI, where it rises to 8-10% (29,30). In addition, the 0-VD group in our study also included patients with at worst angiographically moderate stenoses of 50-69% severity. Finally, other non-atherosclerotic causes of NSTEMI, such as coronary vasospasm or spontaneous coronary dissection would also have been captured. This is reflected by the lower prevalence of traditional risk factors for atherosclerosis, younger age and female predominance (57.6%) that we observed in the 0-VD group. Taken together, the relatively high prevalence of 0-VD in our study highlights the heterogenous basis of NSTEMI and underscores the necessity that future research addresses the fundamental pathophysiological mechanism in each individual patient.

Comment 3: Table 1 and 2 look somewhat redundant. Either (probably Table 1) may be shown as a supplemental material.

Reply 3: We thank the reviewer for their comment. The rationale behind having table 1 and 2 as separate tables is to point out both the differences between each group by number of severe vessels involved, and then by the presence or absence of MVD. We think there is value in having both data sets available, especially now the 0-VD has a greater focus in the discussion at the reviewer's recommendation. In particular, we point to the fact that the 0-VD group is the only group to have a majority of female patients, and that it has a significantly lower proportion of traditional atherosclerotic risk factors.

Our preference would be to keep both tables in the text, or to combine them into one table with 2 panels. However, if the reviewer and editorial board believe that this detracts from the paper, we would be prepared to make table 1 the supplementary table and retain table 2 in the main manuscript.

Changes in the text:
No changes made at this stage.

Comment 4: How were coronary artery stenoses analyzed? Does this depend on eye-ball assessment at local physicians?

Reply 4: All stenoses were assessed and reported visually by the performing Cardiologist as part of standard clinical practice. As the CADOSA registry is part of clinical quality registry data collection in our state, coronary artery stenosis values were extracted in real-time by

trained researchers from the medical records. In the vast majority of cases, stenotic severity is reported as a quantitative value or range. If quantitative data was not provided in the clinical angiogram report, the authors reviewed the angiogram images to determine the stenosis severity and assign it a quantitative severity. We have added two sentences clarifying this in paragraph 2 of the methods section.

Changes in the text:
Line 105-106: 'Patient characteristics, including traditional risk factors for atherosclerosis, were extracted from the clinical record.'

Line 109-111: 'Lesion severity was determined by experienced operators using visual assessment and all lesions were described quantitatively as part of standard clinical practice.

Comment 5: As mentioned by the authors, the lack of data on staged PCI in the present study is a major limitation. Only culprit lesion may be treated by primary PCI during the index hospitalization. For the sake of readers, the authors should describe how common staged PCI procedures are in Australia in MI/NSTEMI.

Reply 5: This is a good question. Unfortunately, the data on this is limited, in keeping with the general dearth of published data on the prevalence and treatment of MVD in NSTEMI. In our recent review of the evidence for multi-vessel revascularization in NSTEMI, we found that all contemporary studies were retrospective and either only looked at in-patient management or did not specify the proportion of inpatient and outpatient 'staged' procedures (Ther adv Chronic Dis 2020.11:2040622320938527). We have added a sentence highlighting this in the Discussion, Line 190.

We do have limited data on the rate of repeat PCI procedures in our cohort. This only applies to those patients with MVD who had PCI in the initial procedure (546). Of these patients, 38 (7.0%) had a second PCI procedure, 22 (4.0%) during the index admission, and 16 (2.9%) underwent an additional PCI procedure as an outpatient, on average 15± 21 days beyond discharge. Of patients having a second procedure, 32 (84.2%) were planned and 31 (81.6%) were non-culprit interventions. No patients in the entire cohort underwent 3 procedures in 90 days, excluding a further procedure in these 546 patients, or two PCI procedures in the 1016 patients with MVD who had an initial diagnostic angiogram. Whether the second procedure represents complete revascularization is unclear.

Changes in the text:
Results, Line 180-186: 'With respect to staged procedures, 546 patients with MVD had PCI during their initial procedure. In this cohort, repeat procedures were performed in 38 (7.0%) patients, 21 (4.0%) during the index admission and 16 (2.9%) beyond discharge at an average of 15±21days. Of patients having a second procedure, 32 (84.2%) were planned and 31 (81.6%) were non-culprit interventions. No patient in the entire studied cohort had three procedures within 90 days, thus excluding 1016 patients with MVD who had an initial coronary angiogram without PCI.'

Discussion, Line 210-216: 'We have shown a small number of patients with MVD undergoing PCI in their index procedure had a second PCI procedure, either during the index admission or within 90 days of discharge. Most of these procedures were planned interventions on non-culprit lesions. The overall numbers are small in keeping with a paucity of evidence supporting non-culprit intervention in NSTEMI. However, whether the second procedure represented complete revascularization is unclear. This is an area requiring further examination in future trials with data pertaining to both real world practice elsewhere and outcomes lacking.'

Comment 6: In the Ethical statement section, the authors describe that "individual consent for this retrospective analysis was waived", while in the Discussion section (in the first paragraph),

they say “This prospective, contemporary registry study found that~”. This reviewer wonders if the present analysis was done in a retrospective or prospective manner.

Reply 6: We apologize for any confusion. This analysis was performed retrospectively. However, the data was collected prospectively. We have altered the wording of the relevant sentences in the methods and discussion as shown below:

Changes in the text:
Abstract, Line 43: Data was analysed retrospectively.

Methods, Line 93-94: ‘Data is collected prospectively, in real time, by trained data officers ensuring high quality data.’

Methods, Line 99-101: ‘Consecutive patients presenting with NSTEMI to three tertiary hospitals in Adelaide, South Australia, between the 1st of January 2012 and the 31st of December 2016 were prospectively enrolled into the database.’

Discussion, line 193-194: ‘This retrospectively analysed contemporary registry study found that the prevalence of MVD in patients undergoing coronary angiography for NSTEMI was 42%.’

Comment 7: In-hospital mortality is extremely low (i.e. 0.9%) compared with other previous studies [Circulation. 2017;136:1908-19, Circ J. 2017;81:958-65]. Such a low mortality rate is unrealistic, so the authors should delve into this issue.

Reply 7: We thank the reviewer for their comment and acknowledge the low rate of inpatient mortality demonstrated in our study.

The reviewer cites two contemporary studies, both showing higher rate of mortality associated with NSTEMI. Puymirat et al. showed a 6-month mortality associated with NSTEMI of 6.3% in 2015, down from 6.9% in 2010. Ozaki et al. reported data from a large Japanese registry including over 11,000 NSTEMI patients and showed an inpatient mortality rate with NSTEMI of 2.0%. Given that our study also reports inpatient mortality only, the data from Ozaki et al. is more relevant and comparable to our own. We believe that our low mortality rate of 0.9% relates to the fact that our study only includes NSTEMI patients who underwent coronary angiography. This excludes a number of patient groups who would have been deemed inappropriate for angiography on the basis of being high-risk or having poor prognosis due to advanced age, frailty or other comorbid conditions (e.g. end-stage kidney disease and contraindications to dialysis; dementia; nursing home level of care; active malignancy). It also potentially means that our study would have included fewer cases of Type 2 MI, as our practice is increasingly not to refer these patients to invasive angiography. It is therefore not surprising that an angiogram-based NSTEMI registry like ours would have a lower inpatient mortality rate than an all-comers registry.
By comparison to our study, the data from Ozaki et al. relates to patients who actually underwent PCI. As mentioned above, a large proportion of our included patients had 0-VD, very few of whom had PCI, and these were associated with the lowest mortality rate. Similarly, a sizeable proportion of our studied patients with CAD received medical management, which may imply relative clinical stability.

Finally, we had a relatively young cohort of patients in comparison to Ozaki et al. and Puymirat et al., which would also be expected to associate with lower inpatient mortality.

As the reviewer has suggested, we have included a paragraph in the discussion examining this issue.

Changes in the text:

Discussion paragraph beginning at line 252:

Unsurprisingly, we have demonstrated inpatient mortality increases significantly with the number of severely stenosed vessels. However, it should be noted that the inpatient mortality rate we observed is lower than that described in previous studies of NSTEMI cohorts, in part due to a younger population (31,32). Furthermore, as our study only included patients undergoing angiography, it likely excluded many elderly, frail or co-morbid patients who would likely have been deemed inappropriate for coronary angiography because of their high risk, poor quality of life or poor prognosis. Inclusion of these patients in an all-comers registry would have almost certainly resulted in a higher mortality rate. As a comparison, one recent study that included all patients presenting with NSTEMI, only 80% of whom underwent angiography, reported 30-day inpatient mortality of 6.29% (32). Another study included not only patients undergoing angiography but also required them to have undergone PCI (31), thus excluding patients with 0-VD. This would explain their higher inpatient mortality rate of 2.0%, given that patients with 0-VD have a more favorable inpatient prognosis, as revealed by our own data.