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REVIEW

Outcomes of Coronary Artery Bypass Grafting in Patients With Poor Myocardial Viability: A Systematic Review and Meta-Analysis of the Last Decade

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Objectives Our objective is to assess whether the presence of myocardial viability is a predictor of mortality among patients undergoing coronary artery bypasss grafting (CABG) through a systematic review meta-analysis.

Methods Comprehensive review of EMBASE and PubMed in accordance with PRISMA guidelines, including studies of patients undergoing CABG with assessment of myocardial viability and recorded long-term mortality, age and sex. Studies were restricted to the last decade, and data were stratified by imaging modality (magnetic resonance imaging [MRI] or nuclear medicine). Random-effects model for assessing pooled effect, heterogeneity assessment using Chi-square and I^2 statistics, publication bias assessed by funnel plots and Egger's test.

Results Meta-analysis of contemporary data (January 2010 to October 2020) yielded 3,621 manuscripts of which 92 were relevant, and 6 appropriate for inclusion with 993 patients. Pooled analysis showed that patients with non-viable myocardium undergoing CABG are at 1.34 times the risk of mortality compared to those with viable myocardium (95% CI 1.01–1.79, p=0.05). Subgroup analysis of the MRI or nuclear medicine modalities was not statistically significant and there was no confounding by age or sex in meta-regression. There was significant heterogeneity in imaging modality and diagnostic criteria, but heterogeneity between study findings was low with an I^2 statistic of 29%. The risk of publication bias was moderate on the Newcastle-Ottawa Scale), but not statistically significant (Egger's Test coefficient=1.3, 95%CI -0.35–2.61, p=0.10).

Conclusions There is a multitude of methods for assessing cardiac viability for coronary revascularisation surgery, making meta-analyses fraught with limitations. Our meta-analysis demonstrates that the finding of non-viable myocardium can not be used draw conclusions for risk assessment in coronary surgery.

Keywords Coronary artery bypass grafting • Myocardial viability

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Introduction

Ischaemic heart disease (IHD) is the leading cause of mortality worldwide and is responsible for 8.9 million or 16% of all annual deaths [1]. Myocardial viability assessment is crucial to prognostication, as patients with poor viability, or irreversible ischaemic changes, may have a significantly higher rate of mortality and adverse cardiovascular events. Methods for detecting viability are rapidly evolving and are beginning to identify patients who stand to benefit from revascularisation [2]. The emerging consensus from these viability assessment techniques is that intervention may not confer survival benefit [3–19]. This is reflected in global guidelines [20,21], which recommend careful consideration through multidisciplinary discussion and case-based evaluation of percutaneous and surgical treatment strategies for patients with non-viable myocardium.

Whilst coronary artery bypass grafting (CABG) in patients with non-viable myocardium can be undertaken safely [18,22–28], non-viable myocardium may be a significant predictor of mortality and correlated with worse functional recovery and higher rates of adverse events [18,19]. However, the risks of intervention in these patients remains poorly delineated. Our objective is to assess whether the presence of myocardial viability is a predictor of mortality among patients undergoing coronary artery bypass graft (CABG) through a systematic review meta-analysis. We focussed on contemporary evidence from the last decade, where viability has been assessed by newer methods of cardiac magnetic resonance imaging (CMR), single photon emission computed tomography (SPECT) or 18-F fluorodeoxyglucose positron emission tomography (18F-FDG PET) before undergoing CABG.

Methods

Search Strategy and Study Eligibility

This systematic review and meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [29] and registered on PROSPERO (CRD42020218178) prior to screening. A comprehensive search strategy for full-text English language articles in EMBASE and PubMed from 1 January 2010 to 27 October 2020 was developed with an institutional librarian using the search terms listed in Appendix 1, with terms detecting coronary artery bypass grafting combined with terms for viability scans. These included cardiac MRI, stress echocardiography, positron emission tomography (PET) and SPECT. All authors independently reviewed all searched studies using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) [30], an online platform for systematic reviews.

Inclusion and Exclusion Criteria

We included all original studies of human adult subjects who underwent CABG with assessment of myocardial viability and recorded long-term mortality. In studies with both surgical and percutaneous coronary revascularisation, only the subset of patients with CABG were included. Myocardial viability assessment had to be done prior to surgical intervention. Studies needed to report specific numbers with an assessment of distribution (95% confidence intervals, standard deviation, or interquartile range). In studies with serial follow-up of the same cohort, the study with the longest follow-up and most complete data were used for main analysis. We excluded patients who underwent concurrent left ventricular (LV) reduction surgery (septal myectomy) or revascularisation by percutaneous coronary artery intervention. Patients who only had stress or exercise electrocardiograms (ECG) or resting echocardiograms were also excluded. Conference abstracts, case reports and editorials were excluded. Final analysis was undertaken to predict all-cause mortality, or cardiovascular mortality if all-cause mortality was not available.

Data Extraction and Quality Assessment

Each study was reviewed for eligibility by two of the study team members independently, with discrepancies and final selection achieved by unanimous consensus. We contacted the corresponding authors at least twice if specific data were not reported. References within review articles were also searched to ensure that all articles meeting eligibility criteria have been included. Endnote x9.0.1 (Thomas Reuters 1998–2001) was used for organising all references. For each study, two of the authors independently performed data extraction through a standard form (Table 1), and verified quality assessment using the Newcastle-Ottawa Scale [30]. All authors reviewed data once extracted, and discrepancies were resolved through unanimous consensus.

Statistical Analysis

The raw and adjusted (covariates per each study design and analysis) rates for all the primary outcome of mortality (all-cause or cardiovascular) were recorded where possible. Data was stratified by imaging modality to allow sub-group analysis. Mortality, age, and gender were consistently extracted from each report. Patients were subdivided based on viability determined by the individual study defined criteria. A random-effects model was used for analysis to pool data to address the heterogeneity in imaging modalities and viability definitions. Analysis was undertaken for all outcomes using pooled relative risk estimates. Heterogeneity was evaluated using Chi-square and I^2 statistics. Publication bias was evaluated by visual assessment of funnel plots, and the effect of small studies was evaluated by Egger's test. Influence analysis was performed to determine the effect of individual studies, and cumulative analysis to assess the impact of publication year. Significance level was predetermined to be $p<0.05$. Data was analysed using Stata v15.2 (StataCorp LLC, College Station, TX, USA).

Results

A search of PubMed and EMBASE (Appendix Table 1) yielded 3,621 manuscripts (Figure 1). After full text review of

Table 1 Description of 6 included studies from 2010-2020 on myocardial viability and outcomes after CABG.

Author	Year	Type	Modality	Assessment of Non-Viability	Median Follow-Up (Months)	Age ± SD	Sex (% Male)	Death in Viable	Death in Non-Viable	RR (95% CI)	Weight
Gerber, B. et al. [34]	2012	Cohort	MRI	Extent of Scar assessed by LGE	48	66±10	87%	18/61	5/18	0.92 (0.52, 1.62)	17.3%
Lee, S. et al. [31]	2016	Cohort	MRI	Extent of Scar assessed by LGE	113	64±9	72%	3/53	19/93	3.61 (1.12, 11.63)	5.4%
Kancharla, K. et al. [35]	2016	Cohort	MRI	Extent of Scar assessed by LGE	100	63.2±11.5	72%	15/52	49/133	1.28 (0.79, 2.07)	21.6%
Li, S. et al. [37]	2017	Cohort	SPECT 18FDG-PET	18FDG-PET <50% (metabolism) and/or SPECT <50% (perfusion)	12	67.2±10.1	79%	3/60	8/55	2.91 (0.81, 10.42)	4.7%
Liu, Y. et al. [38]	2018	Cohort	18FDG-PET	Ratio of viable to total myocardium ≤10%	32	54.8±12.5	83%	3/23	5/30	1.28 (0.34, 4.80)	4.3%
Panza, J. et al. [39]	2019	RCT	SPECT DSE	SPECT: ≤11 viable segments DSE: ≤5 segments	125	61.2±9.2	88%	144/244	38/54	1.19 (0.97, 1.46)	42.8%
Cao, J. et al. [36]	2020	Cohort	PET	Ratio of viable to total myocardium ≤10%	36	59±8	Unknown	3/75	5/35	3.57 (0.90, 14.11)	4.1%

Abbreviations: CI, confidence intervals; DSE, dobutamine stress echocardiogram; FDG-PET, Fluorodeoxyglucose positron emission tomography; LGE, late gadolinium enhancement; m, months; MRI, magnetic resonance imaging; RR, risk ratio; SD, standard deviation; SPECT, single photon emission computed tomography.

two authors, 92 (Supplementary File, References S1–S92) articles relevant to assessing myocardial viability following revascularisation were found. Upon full text review each by two independent reviewers, 14 were excluded as abstracts from conference, 27 recording non-mortality outcomes, 18 for non-surgical revascularisation, 9 for not assessing any revascularisation, 6 for retrospective review, 6 for no appropriate control, 4 for analysis of the same study, and 1 for a separate report on the same study population, resulting in 7 articles appropriate for analysis, presented in Table 1. There were 993 patients, with range of median age of 54.8–67.2 years, follow-up of 12–125 months, and risk ratio for predicting mortality of 0.92–3.61.

Meta-Analysis

Pooled risk ratios predicting mortality after CABG with non-viable myocardium with weightage of pooled mean are listed in Table 1 and shown through forest plots in Figure 2. Six (6) of the seven studies had higher risk of mortality with non-viable myocardium, of which only one was statistically significant (OR 3.61, 95%CI 1.12–11.63) [31]. The most contemporary report of the Surgical Treatment for Ischemic Heart Failure (STITCH) trial by Panza et al. had the largest study with a subset of 298 patients followed up to a median of 125 months and found no change in risk of mortality by extent of myocardial viability (RR 1.19, 95%CI 0.97–1.46).

Pooled analysis demonstrated 1.34-times the risk of mortality with non-viable myocardium (95% CI 1.01–1.79, p=0.05) compared to viable myocardium. In meta-regression analysis, neither age (RR 1.02, 95%CI 0.76–1.36, p=0.85) nor male sex (RR 1.01, 0.83–1.22, p=0.92) were correlated with mortality and were the only variables consistently collected through all seven studies. Subgoup analyses were undertaken by method of viability assessment: magnetic resonance imaging (MRI) or nuclear medicine (18FDG-PET and SPECT). Non-viability on MRI was not correlated with mortality (RR 1.34, 95%CI 0.76–2.37, p=0.31). Nuclear medicine scans showed a trend for correlation between non-viable myocardium and mortality, but this was not significant at a p=0.05 level (RR 1.52, 95%CI 0.92–2.51, p=0.10). Forest plots for combined and subgroup analyses are shown in Figure 2.

Heterogeneity Assessment

To assess the variation in study outcomes between studies, we performed an inter-study heterogeneity assessment shown in Table 2. In pooled analysis, there was evidence of mild heterogeneity on I^2 statistic (29%, 95%CI 0-69%), but not on chi-squared analysis (χ^2=8.44, p=0.21). In subgroup analysis, assessment using I^2 statistic showed moderate heterogeneity in MRI Studies (I^2=54%, 95%CI 0–87%) and mild in nuclear medicine analyses (I^2=28%, 95%CI 0–73%), but Chi-square analysis did not show significant heterogeneity in the MRI (χ^2=4.20, p=0.12) or nuclear medicine (χ^2=4.14, p=0.25) subgroups [32].

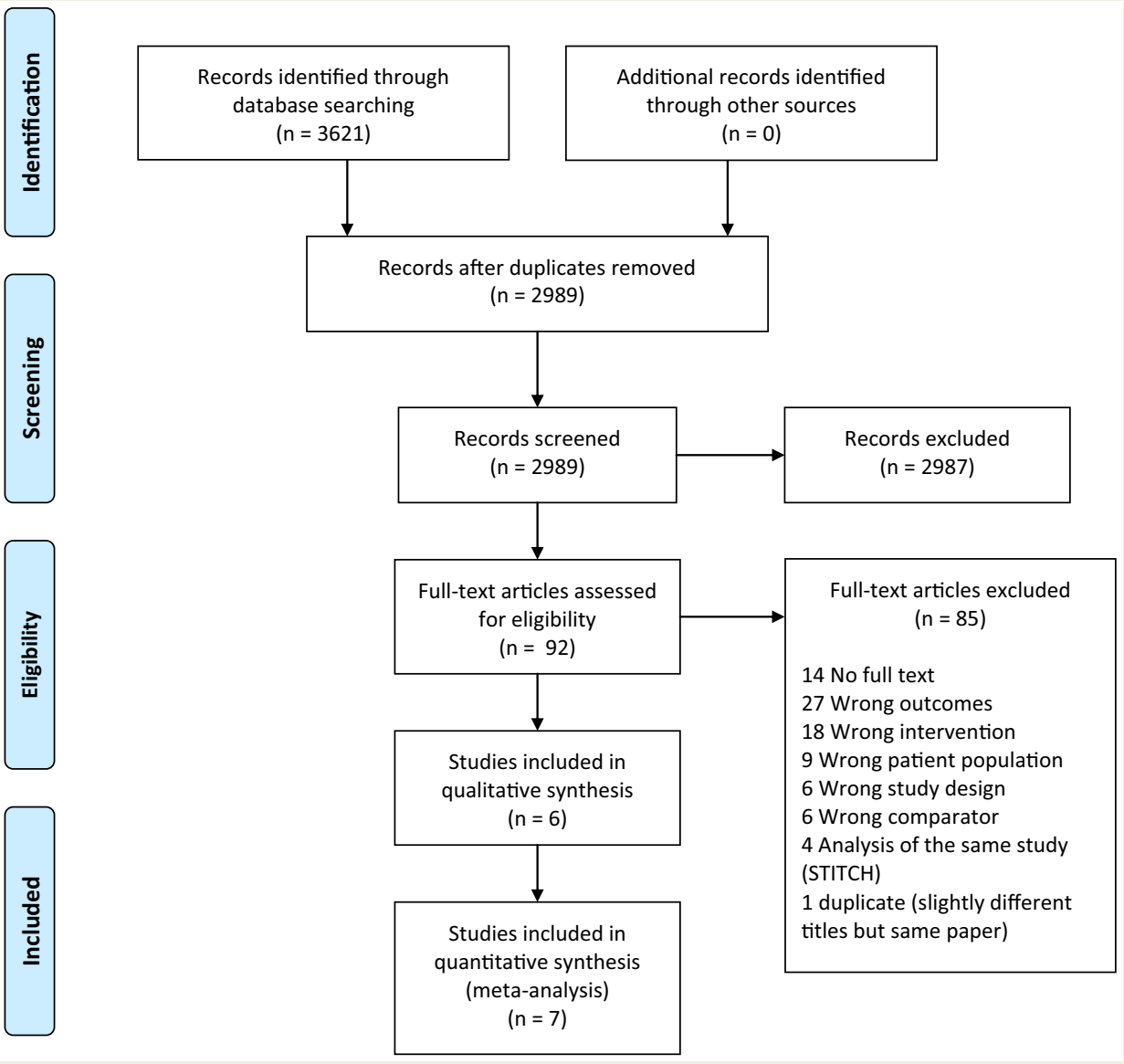

Figure 1 After employing the search strategy, studies were filtered using the Preferred Reporting for Systemic Reviews (PRISMA) guidelines [29]. A total of 3,621 studies were filtered, of which 632 duplicates were removed. Of these, 2,987 were excluded as they did not assess adult patients undergoing myocardial viability assessment by either cardiac magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), stress echocardiography or 18-F fluorodeoxyglucose positron emission tomography prior to coronary artery bypass grafting. Amongst the remaining 92 studies, 6 had the exposure and outcome of interest, which were included in the meta-analyses.

Publication Bias Assessment and Sensitivity Analysis

The risk of publication bias was assessed using the Newcastle-Ottawa Scale [33], which showed risk of bias to be low in one study, and moderate in six studies (Table 3). Publication bias was assessed using visual inspection of a Funnel plot, Egger's test and Influence analysis (Figure 3). Visual assessment of the funnel plot demonstrates smaller studies were more likely to have a larger effect size (points in the bottom right part of pyramid), but a plot of Egger's Test did not demonstrate any statistical evidence of bias (coefficient for risk of bias=1.3, 95%CI -0.35, 2.61, p=0.10). Cross correlation with influence analysis, where the pooled risk was re-calculated by omission of individual studies, is shown in Figure 3c. The omission of the study by Panza et al. [5] generated the greatest effect on the estimate, however no omission led to a change in pooled estimate of greater than 0.25 units in magnitude.

Discussion

Our meta-analysis of contemporary data (January 2010 to October 2020) demonstrates the following key findings.

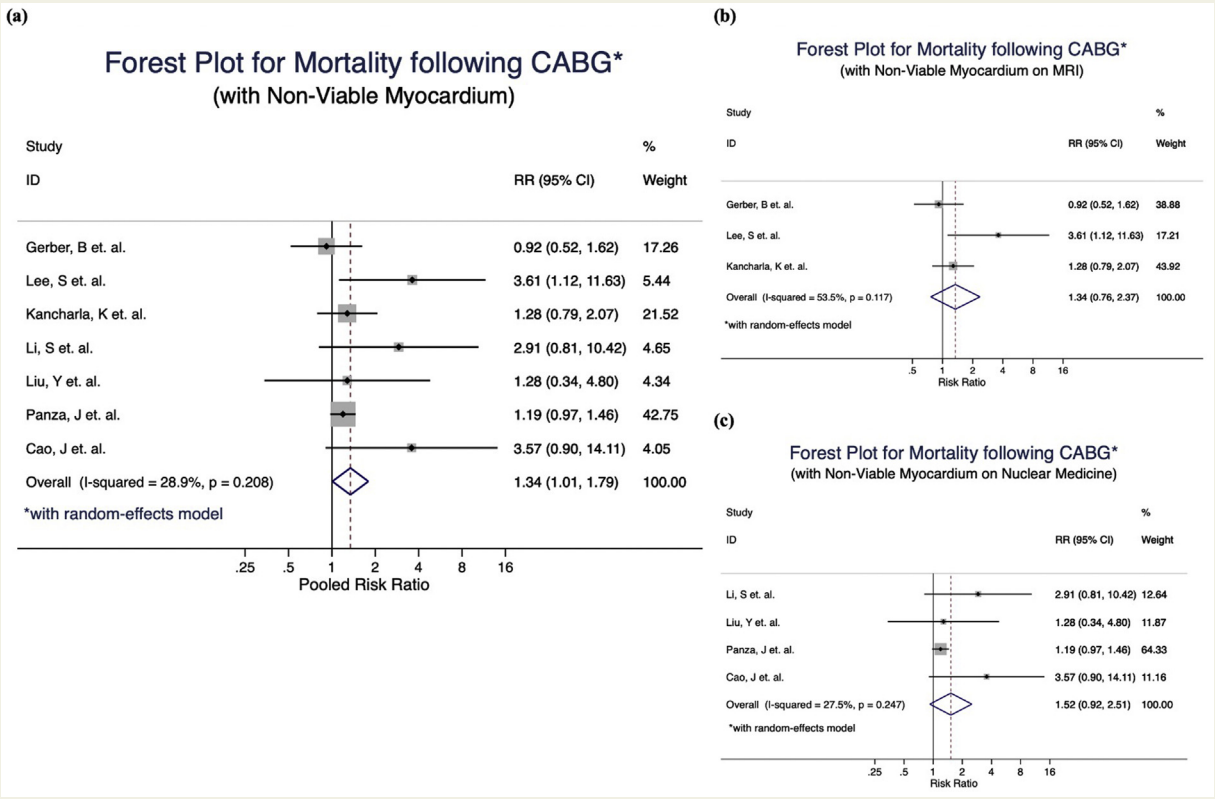

Figure 2 Forest plots assessing a random effects model to assess risk ratios for mortality following CABG with non-viable myocardium, assessed in (a) the combined cohort, (b) MRI studies and (c) Nuclear Medicine (18-FDG PET and SPECT) imaging.
Abbreviations: CABG, coronary artery bypass graft; ID, identification; RR, risk ratio; CI, confidence interval.

Firstly, there is significant heterogeneity in the modalities and diagnostic criteria for assessing myocardial viability, rendering any pooled analysis difficult and fraught with bias. Second, using this heterogenous criteria in patients undergoing CABG, those with non-viable myocardium detected prior to surgical revascularisation are at 1.34 times the risk of mortality compared to those with viable myocardium (95% CI 1.01–1.79, p=0.05). Third, subgroup analysis of the MRI or nuclear medicine modalities was not statistically significant and there was no confounding by age or sex in meta-regression analysis. Fourth, despite the difference in imaging modality and criteria, the heterogeneity between study findings was low with an I^2 statistic of 29%. The risk of bias from seven studies was overall moderate, but there was no statistical evidence of publication bias.

These findings have some implications for clinical practice. At present, studies are beginning to quantify the benefits of intervention stratified by myocardial viability [3–19], with emerging trends demonstrating that patients with

Table 2 Assessment of Heterogeneity made in the combined, MRI and Nuclear medicine cohorts, described using distribution of pooled risk ratio, Chi-square statistic, H statistic and I Squared percentage.

Assessment	Combined		MRI Only		Nuclear Medicine	
	Value (95% CI)	P-value	Value (95% CI)	P-value	Value (95% CI)	P-value
Pooled Risk Ratio	1.34 (1.01,1.79)	0.05	1.34 (0.76-2.37)	0.31	1.52 (0.92-2.51)	0.10
Chi Squared (χ^2)	8.44	0.21	4.30	0.12	4.14	0.25
H Statistic	1.2 (1.0-1.8)		1.5 (1.0-2.7)		1.2 (1.0-1.9)	
I^2 Percentage	29 (0-69)		54 (0-87)		28 (0-73)	

Abbreviations: CI, confidence interval; MRI, magnetic resonance imagine.

Table 3 Risk of Bias Assessment using Newcastle-Ottawa Scale. Each study was assessed using their selection criteria, comparability and outcome, with points allocated as described by Wells et al. [33]. Assessment of bias was made as either High (red), Moderate (orange) or Low (light green), with an overall rating.

Study	Selection			Comparability	Outcome		Overall
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Exposed vs unexposed cohorts	Assessment of outcome	Adequacy of follow up	
Gerber, B. et al. [34] (2012)	LOW	LOW	LOW	MODERATE	MODERATE	MODERATE	MODERATE
Lee, S. et al. [31] (2016)	LOW	LOW	LOW	HIGH	MODERATE	MODERATE	MODERATE
Kancharla, K. et al. [35] (2016)	LOW	LOW	LOW	HIGH	MODERATE	MODERATE	MODERATE
Li, S. et al. [37] (2017)	LOW	LOW	LOW	MODERATE	MODERATE	MODERATE	MODERATE
Liu, Y. et al. [38] (2018)	LOW	LOW	LOW	MODERATE	MODERATE	MODERATE	MODERATE
Panza, J. et al. [39] (2019)	LOW	LOW	LOW	LOW	MODERATE	MODERATE	LOW
Cao, J. et al. [36] (2020)	LOW	LOW	LOW	MODERATE	MODERATE	MODERATE	MODERATE

myocardial viability have improved survival, and those with non-viable myocardium may not benefit from CABG compared to medical therapy alone [17]. However, we cannot offer a benefit-to-risk assessment for these patients, as the risks of surgical revascularisation in these patients are not known. The bulk of evidence comes from small subset analyses (<200 patients) of studies not powered to assess outcomes post coronary artery bypass grafting, with significant heterogeneity in the assessment of viability. Our meta-analysis mitigates some of these shortcomings by generating a large, pooled analysis (n=993), attempts to adjust for heterogeneity through a random-effects model, and demonstrates that nonviable myocardium may be a predictor of mortality post CABG. We demonstrate that there remains a multitude of methods for assessing cardiac viability for coronary revascularisation surgery, making meta-analyses fraught with limitations. Our meta-analysis demonstrating 1.34-times higher risk of mortality in patients with non-viable myocardium does not validate myocardial viability assessment in coronary surgery but suggests that there is emerging data that warrants further validation prior to clinical translation.

The strengths of this paper are as follows. The analyses are selective for patients who underwent CABG, thereby providing specific surgical risk assessment. Restricting papers to the last decade ensures that the multiple imaging modalities to assess myocardial viability, such as FDG-PET, SPECT, low dose dobutamine stress echocardiography and cardiac magnetic resonance imaging (CMR), are all contemporary and free from changes in technology. The selected papers have clear definitions on viability quantification. Our analysis did not show significant evidence of heterogeneity (I^2=29%), despite the differences in the viability assessment protocols. This possibly suggests that there is no significant signal or effect on outcomes of CABG, based on each of the viability assessment methods used. However, our attempt at subgroup analysis to compare different modalities of viability assessment did not show any statistically significant results, likely due to the small number of studies, demonstrating the need for a larger number of studies for each modality.

These findings have some limitations. Our meta-analyses cannot mitigate the significant limitations in underlying data, which include the selection and measurement biases within study and publication biases across studies. All except one of the studies to date are without randomisation, with an inherently high risk of bias and confounding by indication. The random-effect estimates do not address the significant heterogeneity in imaging modality or myocardial viability assessment and does not validate one strategy over another. It also does not address the lower number of patients (n=993) from seven studies. Outcomes are reported using crude risk ratio rather than adjusted analyses, as controlling for potential confounders was not possible due to the lack of variables consistently recorded in all seven studies. The funnel plot demonstrates visual evidence of publication bias, albeit not statistically significant and cannot be more thoroughly

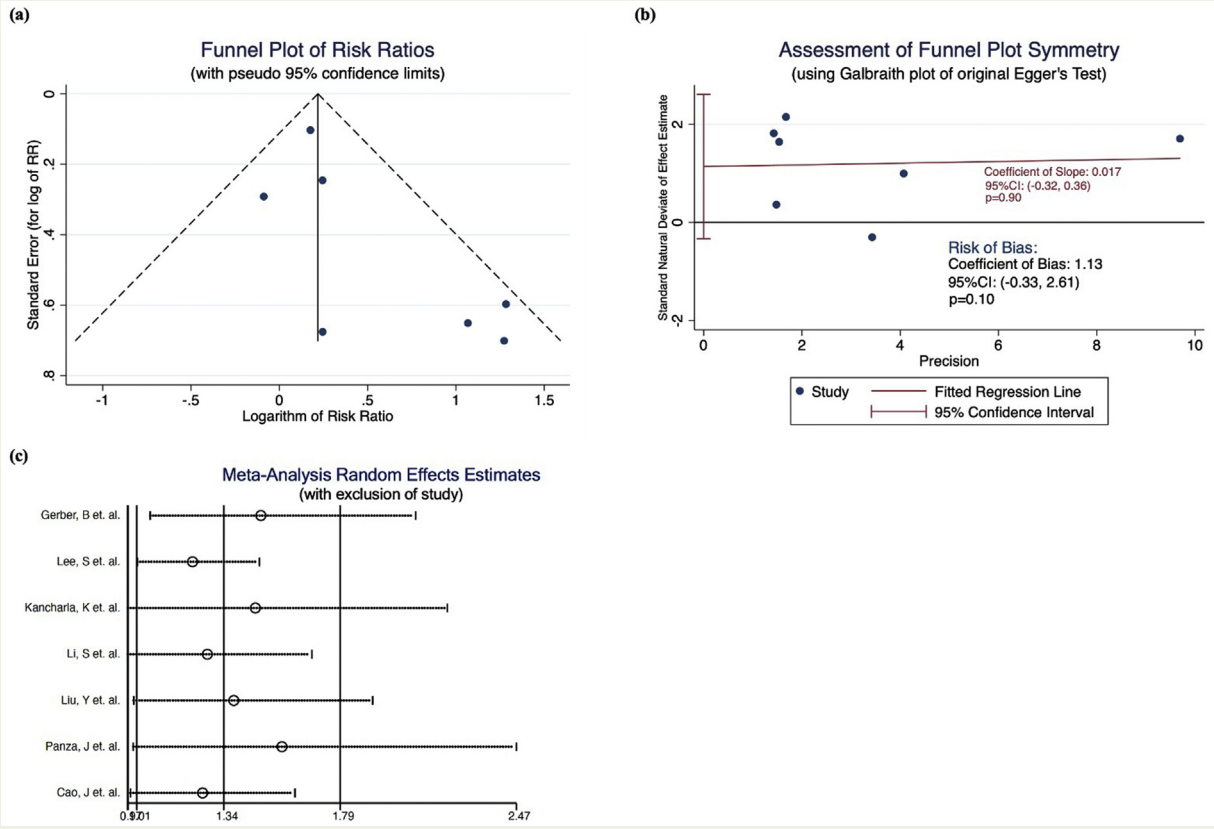

Figure 3 Graphs to demonstrate influence and publication bias: (a) Funnel plot used for visual assessment of publication bias, with each study's logarithm of effect size (x axis) plotted against the inverse of their respective standard error (y axis). (b) The corresponding Galbraith plot of the Egger's test showed coefficients for slope risk of bias (c) Influence analysis demonstrating change in pooled effect estimates on omission of individual studies. The study omitted is described in the y axis and the effect estimate (circle) with 95% confidence intervals (bar) are plotted on the x axis.
Abbreviations: log, logarithm of effect size; CI, confidence interval.

examined due to the small number of studies. Even though we have restricted analysis to the last decade to minimise the effect of evolving technology or outcomes, the more recent studies (2017 and onward) appear to show favourable outcomes in those with myocardial viability. This may suggest significant heterogeneity in viability assessment with technological advancements, improvements in medical therapy, or changing clinical practices for patients with non-viable myocardium. Moreover, the variation in threshold for binary definition for viability may not adequately reflect the clinical spectrum of viability.

Conclusions

There is a multitude of methods for assessing cardiac viability for coronary revascularisation surgery, making meta-analyses fraught with limitations. Our meta-analysis demonstrates that the finding of non-viable myocardium cannot be used draw conclusions for risk assessment in coronary surgery.

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Appendices. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2021.12.016.

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