E/e' in relation to outcomes in ST-elevation myocardial infarction

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Abstract
Background: Myocardial infarction (MI) is a high-risk condition especially when filling pressure is raised, and earlier reports have suggested that E/e' is associated with poor outcome. However, whether E/e' predicts risk better than LVEF, which is the current standard of practice, is not known. We investigated this question in the largest and most rigorous study of MI patients so far.

Methods and Results: We studied 660 patients with ST-elevation MI (STEMI) treated with primary percutaneous coronary intervention and related E/e' to short-term mortality (in-hospital death), as well as long-term events at 2 years comprising (a) a composite of MI, stroke, heart failure, and death, and (b) death alone. Short-term models were adjusted for age, sex, and LVEF. Long-term models were adjusted for age, sex, diabetes, revascularization procedure, history of MI, hypertension, renal function, drugs on discharge, and LVEF. Elevated E/e'> 15 indicated higher risk of short-term events (n = 19:7.0% (95% confidence interval 3.4-10.8%) vs. 1.0% (0.3 - 2.3%); adjusted odds ratio 3.7 (1.3-10.5)). While elevated E/e' was also associated with long-term outcomes (n = 103 composite events: 15.9% (11.9% – 21.4%) vs 6.8% (5.2% – 8.7%), P < .001; n = 38 death events: 6.0% (3.9% – 9.5%) vs 2.0% (1.3% – 3.2%), P = .001), E/e' was rendered nonsignificant for long-term outcomes by multivariable adjustment (p = ns for both). LVEF, on the contrary, was a highly significant predictor in the adjusted long-term model.

Conclusion: E/e' is associated with poor outcome in STEMI, but LVEF is a stronger predictor of long-term risk.

Keywords
E/e', echocardiography, filling pressure, myocardial infarction
1 | INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) remains a high-risk cardiovascular event despite therapeutic advances such as primary percutaneous coronary intervention (PCI).\(^1\) Mortality in the acute phase is largely secondary to loss of pumping strength, which leads to congestive heart failure (CHF), shock, and arrhythmias originating from the left ventricle. Cardiovascular mortality postdischarge, however, comprises a number of different components. Real-world data have shown these to primarily be re-infarction, stroke, CHF, and sudden cardiac death.\(^2\) While scoring systems such as TIMI and GRACE have been validated for risk prediction, echocardiography is also performed routinely as depressed left ventricular (LV) ejection fraction (LVEF) during the index admission identifies patients at risk of late mortality (≥40 days postdischarge).\(^3\) Elevated LV filling pressure is also an important risk indicator in STEMI,\(^4\) and CHF indeed accounts for a significant proportion of both short-term and long-term deaths.\(^5\)

This begs the question of whether echocardiographic measures of LV filling pressure may be valuable risk predictors in STEMI, especially E/e’ which seems especially attractive as it is both directly influenced by myocardial function\(^5,6\) and predictive of adverse LV remodeling post-MI.\(^7\) Unfortunately, contemporary reports associating E/e’ with outcomes post-MI have yielded conflicting results. Firstly, a link between E/e’ and in-hospital death remains unproven.\(^8\) Secondly, the relationship between E/e’ and long-term outcomes is controversial: While initial data showed that E/e’ was a very strong predictor of poor outcome 13 months post-MI in n = 250 patients,\(^9\) a larger study performed by the same authors, which controlled better for residual confounding, showed E/e’ to be nonsignificant, once key covariates such as age and LVEF were entered into the model (n = 388).\(^10\)

On this background, we performed the largest study so far relating E/e’ to outcomes in STEMI. We compared utility of adding E/e’ to clinical covariates and LVEF in sequential testing. In order to achieve a satisfactory sample size, we analyzed 2-year follow-up data after STEMI admission.

2 | METHODS

2.1 | Patients and data sources

The study was based on prospectively acquired clinical registries combined with administrative data as follows. Patients were originally identified in an Interventional Cardiology Procedural Registry as having successfully undergone percutaneous coronary intervention (PCI) for ST-elevation MI at a single tertiary center (National Heart Centre Singapore). Angiographic and echocardiographic data were extracted from digital sources. Linkage to outcome events was performed using 2 main data sources: firstly, registries at Singapore National Registry of Diseases Office (NRDO) were used to analyze myocardial infarction, ischemic stroke, and death events. Secondly, claims data at Ministry of Health were used to analyze admissions with heart failure. Data were subsequently anonymized before being made available by NRDO to our biostatistician (FG). Detailed information about databases including their audited accuracy is available as an online supplement (Appendix S1).

All cases admitted between 1 August 2007 and 31 December 2010 were considered for inclusion. We excluded patients that (a) had not undergone echocardiography within a week of PCI and (b) had neither Singapore citizenship nor permanent residency. We counted only the first recorded admission meeting these criteria if more than 1 existed. The study had ethics approval from SingHealth Centralized Institutional Review Board which was granted with waiver of requirement for patient consent. It was nonexperimental in design and did not violate the Declaration of Helsinki.

2.2 | Echocardiography

Measurements were derived according to guidelines as recommended by the American Society of Echocardiography.\(^11,12\) In brief, LVEF was derived from end-diastolic volume (EDV) and end-systolic volume (ESV) using the following formula: LVEF = (EDV-ESV)/EDV; with EDV and ESV measured as recommended by biplane Simpson’s method. Mitral inflow including E-wave velocity and deceleration time was interrogated using pulsed-wave Doppler in the apical 4-chamber view, with the Doppler beam aligned parallel to the direction of flow and the sample volume at the leaflet tips. Spectral tissue Doppler imaging was performed in the apical 4-chamber view and e’ derived from the basal septum. E/e’ was computed by dividing transmural E-wave velocity by e’. We defined as abnormal an E/e’ ≥ 15, in line with current echocardiographic guidelines\(^13\) which propose that values above this threshold identifies elevated LA pressure,\(^14\) an appropriate assumption given that the prevalence of elevated LA pressure is high in a population of STEMI cases.\(^15\)

2.3 | Clinical outcomes

The primary short-term outcome was all-cause death during the index admission. The primary long-term outcome was time postdischarge to a composite outcome comprising (i) myocardial infarction, (ii) ischemic stroke (iii) admission with CHF, and (i) all-cause death. The secondary long-term outcome was time postdischarge to all-cause death alone. Long-term outcome analyses were based on events up to 24 months postdischarge. Short- and long-term models were nonoverlapping such that outcome events were counted only once: in-hospital deaths were not included in long-term survival analyses, which began at the time of discharge. This was due to the fact that ongoing medical treatments were felt to be important confounders in long-term analyses, and robust data for medications were only available at the time of discharge.
2.4 | Statistical analysis

Short-term outcomes were analyzed using logistic regression while adjusting for age, sex, and LVEF. Long-term outcomes were analyzed in Cox regression models adjusted for age, sex, diabetes, revascularization procedure, history of myocardial infarction, hypertension, renal function, treatment with beta blockers, ACE inhibitors or angiotensin receptor blockers, statin, clodipogrel, and for LVEF. Information about drugs was taken at the time of discharge for all drugs studied. All analyses were performed using Stata v. 13 (College Station, Texas, USA). Risk is reported as proportions for short-term events and as cumulative incidence (based on analysis of person-years) for long-term events.

3 | RESULTS

3.1 | Population characteristics

We identified n = 660 patients that met inclusion criteria, comprising 555 males (84%) and 105 females (16%), with a mean age of 59 ± 12 years. Median length of stay was 4 days (inter-quartile range: 3-5). There were 184 patients (28%) with elevated E/e’; this subgroup was significantly older, with a higher prevalence of smoking, diabetes, hypertension, dyslipidemia, chronic kidney disease, and peripheral vascular disease (Table 1). On the contrary, a similar proportion of patients with raised E/e’ had a prior history of myocardial infarction and revascularization, and prescription of cardioprotective therapeutics did not differ in this subgroup (antiplatelet drugs, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, and diuretics) (Table 1). Patients with elevated E/e’ differed in terms of echocardiographic findings: LV dimensions were larger and LVEF was lower (Table 2).

3.2 | Predictors of outcome

In short-term models, there were 19 in-hospital death events. These occurred more commonly in patients with elevated vs. normal E/e’: 7.0% (95% confidence interval (CI95) 3.4%-10.8%) vs. 1.0% (CI95 0.3%-2.3%; adjusted odds ratio (OR) 3.7 (CI95 1.3-10.5). P = .014; Table 3). In long-term models, there were 103 composite outcome events and 38 long-term all-cause death events. Analyses of long-term outcomes demonstrated higher risk of suffering a composite outcome in patients with elevated E/e’: 15.9% (CI95 11.9%-21.4%) vs. 6.8% (CI95 5.2%-8.7%); unadjusted HR 2.3 (CI95 1.6-3.4), P < .001; Table 4). The effect size was smaller after adjusting for key clinical confounders: HR 1.6 (CI95 1.0-2.5; P = .036). Incorporating LVEF into the model for composite outcomes rendered the effect of E/e’ nonsignificant: HR 1.4 (CI95 0.9-2.2; P = .170). Of note, LVEF in the final model had a P-value of <.001. Risk of all-cause death was also higher in patients with elevated E/e’: 6.0% (CI95 3.9%-9.5%) vs 2.0% (CI95 1.3%-3.2%); unadjusted hazard ratio (HR) 2.9 (CI95 1.5-5.5, P = .001). After multivariable adjustment, however, hazard ratio of E/e’ for all-cause death straddled the null at 1.9 (CI95 0.9-3.9), P = .093.

4 | DISCUSSION

While considerable progress has been made in STEMI care, mortality and morbidity remain high, and risk stratification is important. While filling pressure has been shown to be an important predictor of poor outcome in MI, earlier reports seeking to connect E/e’ to clinical outcomes have yielded mixed results. The present study found an association between E/e’ and in-hospital death in patients with STEMI. There was also an association with long-term risk of composite outcome events, as well as with death, which was noted in unadjusted analyses. However, after rigorous adjustment for confounding, E/e’ no longer predicted long-term outcome events independently. In contrast, LVEF was related to long-term outcomes while retaining a very high degree of statistical significance in the fully adjusted model.

4.1 | Short-term risk

The present study is the first to find a relationship between short-term risk of death post-STEMI and E/e’ done shortly after admission. These results confirm and extend findings made in the only previously published study with a similar design where Naqvi et al analyzed n = 59 STEMI patients and reported that short-term adverse composite endpoint events were indeed predicted by E/e’ (3 deaths, 7 CHF events, 4 episodes of ventricular tachycardia, and 1 patient requiring emergency surgical revascularization). In the present study, mortality was found to peak early: 19 in-hospital deaths occurred vs. a total of only 38 deaths during 2 years postdischarge. This is in keeping with previous reports where the risk of death in STEMI has been shown to be especially high in the acute phase. Accurate prediction of mortality risk is thus especially important in the acute phase of STEMI, introducing the possibility of targeting at-risk patients, for example, with specific measures to prevent deaths from ventricular arrhythmias. One example is implantation of an implantable cardioverter-defibrillator (ICD). Clinical practice guidelines recommend that the decision to implant an ICD is deferred for 40 days post-STEMI, based on neutral results of 2 randomized controlled trials where patients were enrolled very early post-MI on the basis of LV ejection fraction (DINAMIT, IRIS). It is attractive to note that E/e’ added incrementally to the prediction of in-hospital mortality by LVEF in the present study. Naturally, the model was based on 19 in-hospital deaths, and as such, adjustment for confounders was limited. This is important as patients at highest risk of arrhythmia commonly have comorbidities which put them at risk of nonarrhythmic death too. However, the same applies to using LVEF: patients with low LVEF are also at high risk of nonarrhythmic death, something that may help to explain the neutral results of
The number of long-term outcome events in the present study was larger than in any previous publication in this field, which enabled us to adjust coefficients for a range of potential confounders. This enabled us to adjust coefficients for a range of potential confounders. This is
Table 2: Echocardiographic data for study population

| Measure                                      | All N = 660 | E/e' < 15 N = 476 | E/e' ≥ 15 N = 184 | P-Value |
|----------------------------------------------|-------------|------------------|------------------|---------|
| Left ventricular dimensions                 |             |                  |                  |         |
| Inter-ventricular septal thickness (cm)      | 1.07 ± 0.23 | 1.05 ± 0.21      | 1.12 ± 0.28      | <.01    |
| Left ventricular end-diastolic diameter (cm)| 4.81 ± 0.68 | 4.76 ± 0.65      | 4.95 ± 0.73      | <.01    |
| Posterior wall thickness (cm)               | 1.03 ± 0.26 | 1.01 ± 0.26      | 1.06 ± 0.24      | .08     |
| Left ventricular end-diastolic volume (mL)  | 134 ± 43    | 131 ± 40         | 142 ± 49         | .02     |
| Left ventricular end-systolic volume (mL)   | 75 ± 39     | 70 ± 35          | 85 ± 47          | <.01    |
| Left ventricular mass (g)                   | 189 ± 58    | 184 ± 56         | 203 ± 63         | <.01    |
| Contractile function                        |             |                  |                  |         |
| Left ventricular ejection fraction (%)      |             |                  |                  |         |
| Left ventricular dysfunction (ejection < 40%)| 388 (60.7%) | 260 (56.5%)      | 128 (71.5%)      | <.01    |
| Peak systolic velocity, s' (cm/s)           | 0.07 ± 0.02 | 0.07 ± 0.02      | 0.06 ± 0.02      | <.01    |
| Regional wall motion abnormalities          | 524 (79.4%) | 382 (80.3%)      | 142 (77.2%)      | .19     |
| Diastolic function                          |             |                  |                  |         |
| Trans-mitral E-wave/ A-wave                 | 1.59 ± 7.99 | 1.27 ± 3.3       | 2.39 ± 14        | .14     |
| Mitral valve deceleration time (ms)         | 187 ± 51    | 190 ± 48         | 179 ± 58         | .02     |
| Basal septal early-diastolic relaxation velocity, e' (cm/s) | 0.06 ± 0.02 | 0.07 ± 0.02 | 0.04 ± 0.01 | <.01 |
| Indices of filling pressure                 |             |                  |                  |         |
| LA volume (mL)                              | 45.5 ± 15.4 | 14.1 ± 34.8      | 50.4 ± 17.3      | <.01    |
| E/e'                                         | 13.6 ± 7.1  | 10.6 ± 2.3       | 21.6 ± 8.9       | <.01    |
| Valvular heart disease                      |             |                  |                  |         |
| At least moderate mitral regurgitation      | 27 (4.1%)   | 15 (3.1%)        | 12 (6.5%)        | .08     |
| At least moderate aortic stenosis*          | 4 (0.7%)    | 1 (0.2%)         | 3 (1.6%)         | .07     |

Note: All data are shown as n (%) or median (inter-quartile range) as appropriate. Significance testing performed by Fisher’s exact test.

Table 3: Risk of short-term events in relation to E/e' ≥ 15

| Model 1 (unadjusted) | Model 2 (adjusted) | Model 3 (adjusted) |
|----------------------|--------------------|--------------------|
| OR (95% CI)          | P-Value            | OR (95% CI)        | P-Value            | OR (95% CI)        | P-Value |
| Short-term mortality 660 | 19                 | 6.0 (2.2–15.9)      | <.0001             | 4.8 (1.7–13.3)      | .003    | 3.7 (1.3–10.5) | .014 |

Note: Odds ratios (OR) are shown of E/e' ≥ 15 for predicting early outcome events with 95% confidence interval (CI). Model 1 provides an unadjusted estimate of the risk of short-term mortality in relation to E/e' ≥ 15. Estimates were adjusted for age and sex in model 2, and for age, sex, and LVEF in model 3.
model.\(^{21,22}\) Several problems can arise as the EPV ratio decreases. Firstly, if many factor variables act to create small subgroups where few or no outcome events occur, this causes a state of "statistical separation"; the outcome variable is able to separate one or more of the predictor variables.\(^{23}\) Fortunately, this did not occur in the present analysis. Secondly, analyses run on small or moderate-sized data sets can give rise to inaccurate coefficients due to optimism, "finite sample bias."\(^{24}\) However, simulations have shown that this does not primarily relate to the EPV ratio, as finite sample bias does not reduce to zero even when EPV is very large (EPV ratio > 100).\(^{25}\) A number of simulation studies to establish a lower limit for EPV ratio in statistical modeling have yielded conflicting results. Courvoisier et al.\(^{26}\) investigated the correctness of estimates in models based on simulated data and found that the EPV ratio is in fact less important than the structure of the data itself. While Peduzzi et al. found more stable estimates when the EPV ratio was at least 10,\(^{27}\) Vittinghoff & McCulloch found that observational research can relax that requirement when conducted to analyze causal influences, as models remain accurate when EDV ratio is below 10. Instead, they argued that models built for prediction need a higher EPV ratio of \(\geq 20.28\).

The present study found that LVEF remained very highly significant in the final model, but not \(E/e'\). While patients who develop CHF post-STEMI often have raised filling pressures, this is not always the case. One way to interpret our findings is that CHF deaths may be a relatively more important problem during the admission—at which time at-risk patients can be identified by raised \(E/e'\)—whereas death events may occur in poor LVEF patients over the first 2 years postdischarge irrespective of whether they had elevated filling pressure or not at the time of the initial STEMI. Future work in this area will benefit from more granular data on mortality, which will show whether the death events identified by LVEF are different to those associated with raised \(E/e'\).

### 5 | LIMITATIONS

In addition to limitations related to sample size discussed in detail above, an important consideration is the fact that the population under study constitutes a subset of STEMI admissions where primary PCI was successfully performed. Secondly, as the national level data used in this report do not incorporate global risk scores, we were unable to compare echocardiographic indices (LVEF, \(E/e'\)) against, for example, TIMI or GRACE score. Nonetheless, echocardiography may be viewed as complementary to such global risk scores, in that LVEF is traditionally used to identify patients at risk of remote SCD post-STEMI, and this should be viewed as the main rationale for the present study. Thirdly, while we were able to analyze levels of biomarkers such as cardiac troponin T and CK-MB, Singapore Myocardial Infarction Registry does not collect data on NT-proBNP, which is therefore not included in the present report.

### 6 | CONCLUSION

In conclusion, in the largest study population and most rigorous analysis to date, we found that \(E/e'\) is a stronger predictor of in-hospital death than LVEF, but that the relationship between \(E/e'\) and adverse outcome events at 2 years was rendered nonsignificant once LVEF was entered into the model. While these results suggest that \(E/e'\) may help to identify STEMI patients at highest risk of death in the acute phase, our data do not support an independent role of \(E/e'\) in predicting long-term outcome in STEMI.

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### CONFLICT OF INTERESTS

Authors report no relationships that could be construed as a conflict of interest.

### AUTHOR CONTRIBUTIONS

All authors made important contributions in terms of concept and design of the study, and associated analysis. All authors helped to draft the article and performed critical revision. All authors gave approval to final manuscript version. Data were acquired by SBT, WRL, NH, MRA, JMF, JY, SHE, and ZPD. Preliminary statistical analyses were performed by AS and SBT, and final models including survival...
analyses were run by FG. Work done with government agencies in Singapore was facilitated by MYC and KKY.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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