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ORIGINAL CONTRIBUTION

Major adverse cardiac event rates in moderate-risk patients: Does prior coronary disease matter?

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Abstract

Background: Despite negative troponins and nonischemic electrocardiograms (ECGs), patients at moderate risk for acute coronary syndrome (ACS) are frequently admitted. The objective of this study was to describe the major adverse cardiac event (MACE) rate in moderate-risk patients and how it differs based on history of coronary artery disease (CAD).

Methods: A secondary analysis of the HEART Pathway implementation study was conducted. This prospective interrupted time-series study accrued adults with possible ACS from three sites (November 2013–January 2016). This analysis excluded low-risk patients determined by emergency providers' HEART Pathway assessments. Non–low-risk patients were further classified as high risk, based on elevated troponin measures or ischemic ECG findings or as moderate risk, based on HEAR score ≥ 4, negative troponin measures, and a nonischemic ECG. Moderate-risk patients were then stratified by the presence or absence of prior CAD (MI, revascularization, or ≥70% coronary stenosis). MACE (death, myocardial infarction, or revascularization) at 30 days was determined from health records, insurance claims, and death index data. MACE rates were compared among groups using a chi-square test and likelihood ratios (LRs) were calculated.

Results: Among 4,550 patients with HEART Pathway assessments, 24.8% (1,130/4,550) were high risk and 37.7% (1715/4550) were moderate risk. MACE at 30 days occurred in 3.1% (53/1,715; 95% confidence interval [CI] = 2.3% to 4.0%) of moderate-risk patients. Among moderate-risk patients, MACE occurred in 7.1% (36/508, 95% CI = 5.1% to 9.8%) of patients with known CAD versus 1.4% (17/1,207, 95% CI = 0.9% to 2.3%) in patients without known prior CAD ($p < 0.0001$). The negative LR for 30-day MACE among moderate-risk patients without prior CAD was 0.08 (95% CI = 0.05 to 0.12).

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Conclusion: MACE rates at 30 days were low among moderate-risk patients but were significantly higher among those with prior CAD.

KEYWORDS
acute coronary syndrome, chest pain, heart disease, HEART Pathway, risk stratification

INTRODUCTION

Patients presenting to the emergency department (ED) with acute chest pain are challenging for emergency providers.[1–8] Chest pain evaluations are high stakes, because a missed diagnosis of acute coronary syndrome (ACS) can lead to poor patient outcomes and medicolegal consequences.[9] In addition, overly conservative approaches of admitting and testing patients with chest pain can lead to ED and hospital crowding.[10,11] To address this diagnostic dilemma, recent multidisciplinary efforts have developed guidelines, best practices, and diagnostic pathways to improve care for patients with chest pain.[12–16] These efforts have transformed the care of patients with acute chest pain in the ED setting. Ten years ago, standard practice was to admit and stress test virtually all adult patients with chest pain, which was inefficient and costly.[17–19] Now, the standard of care is based on validated diagnostic pathways that safely identify patients who can be sent home without objective cardiac testing (OCT; stress testing, coronary computed tomography angiography, or invasive coronary angiography).[12–14,20–22] For example, the History, Electrocardiogram (ECG), Age, Risk factors, and Troponin (HEART) Pathway is a well-validated accelerated diagnostic protocol (ADP) that has been successfully implemented and has demonstrated safe reductions in health care utilization outcomes, such as hospitalizations, length of stay, and OCT.[12,13,23]

While the application of the HEART Pathway has reduced unneeded testing and hospitalizations among low-risk chest pain patients, only 35% to 45% of patients with chest pain are determined to be low risk (<1% risk of 30-day death, myocardial infarction [MI], or coronary revascularization).[12,13,23] Most of the remaining non–low-risk patients (55%–65% of patients with chest pain) are admitted or observed for OCT.[12,13] However, <10% of these patients are ultimately diagnosed with ACS, the majority of which are high-risk patients who are rapidly diagnosed with ACS in the ED based on elevated initial troponin measurements or ischemic ECG changes. Among moderate-risk patients with elevated risk scores, but without elevated troponin measures or ischemic ECG changes, multiple recent studies have questioned the utility of routine OCT.[24–27] The yield of OCT in this moderate-risk population is low and leads to increased downstream invasive angiography and percutaneous coronary intervention, which has no clear mortality benefit over medical management.[28–30]

Despite low diagnostic yield of routine OCT, it remains difficult for emergency providers to discharge moderate-risk patients without this testing. Patients at moderate risk are thought to have adverse cardiac event rates that exceed 2%, which has been suggested as the threshold for OCT.[31,32] However, recent prospective data examining actual 30-day major adverse cardiac events (MACEs: death, MI, or coronary revascularization) rate among moderate-risk patients is lacking. This analysis examined the MACE rate among non–low-risk patients and evaluated whether rates differed based on key clinical variables, such as ECG changes or initial troponin measures and prior coronary artery disease (CAD; prior MI, stents, coronary artery bypass surgery, or coronary stenosis ≥ 70% on catheterization). These data will explore whether non–low-risk patients can be further risk stratified to identify a larger population of patients that could safely be discharged from the ED without OCT. The objective of this study was to describe the MACE rate in moderate-risk patients and how it differs based on history of CAD. We hypothesize that moderate-risk patients (HEAR score ≥ 4, nonischemic ECG, and negative initial troponin measures) with no prior CAD will have 30-day MACE rates below the 2% testing threshold for OCT.

METHODS

Study design and oversight

A preplanned subgroup analysis of non–low-risk patients in the HEART Pathway Implementation Study was conducted. A waiver of informed consent was used to prospectively accrue participants from November 2013 to January 2016. This study was registered with ClinicalTrials.gov (NCT02056964) and was institutional review board approved. Methods of the HEART Pathway Implementation Study, a prospective pre-post interrupted time series, have been previously published.[12,33]

Study setting and population

This study took place at three hospitals in North Carolina: Wake Forest Baptist Medical Center (WFBMC), with approximately 114,000 ED visits annually; Davie Medical Center (DMC), with 12,000 annual ED visits; and Lexington Medical Center (LMC), with 37,000 annual ED visits. The population examined was adult patients (>21 years of age) who presented to the ED for chest pain or other symptoms suggestive of possible ACS. Patients with evidence of ST-segment elevation myocardial infarction (STEMI) on ECG were excluded. For this analysis we included a subset of patients who were found to be non–low-risk by ED providers using the HEART Pathway. To be considered non–low-risk patients had a History,

ECG, Age, and Risk factors (HEAR) score ≥ 4; a history of prior CAD; an ischemic ECG; or an elevated troponin. Patients who were identified as low risk (HEAR < 4) by the HEART Pathway were excluded from this analysis.

At WFBMC and DMC, participants were accrued into the preimplementation (November 2013 to October 2014) or the postimplementation (February 2015–January 2016) cohorts. A wash-in period (November 2014–January 2015) was used to train providers and beta-test an electronic health record (EHR)-based HEART Pathway decision support tool. LMC accrued patients into the preimplementation (January–July 2015) and postimplementation cohorts (July 2015–January 2016), with a 1-month wash-in period. Patients entered each cohort based on the date of their initial ED visit; any subsequent visits for chest pain were considered recurrent care. To prevent accruing more ED repeat users/high utilizers (who often have more comorbid conditions) into the preimplementation cohort, patients with an ED visit for possible ACS at any site in the year before the study began ($n = 523$) were excluded. Patients transferred within the network or visiting multiple sites were classified based on their original ED visit. For transfers, care at the receiving hospital was considered part of their index encounter.

HEART Pathway risk stratification

The HEART Pathway was fully integrated into EPIC (Clarity-Epic Systems Corp) as an interactive clinical decision support (CDS) tool. For all adult patients with chest pain who had at least one troponin ordered in the postimplementation period, ED providers saw an interruptive pop-up alert for the HEART Pathway tool as a best practice advisory in the EHR. In addition, providers could manually access the HEART Pathway in patients presenting with other symptoms concerning for ACS (i.e., dyspnea, left arm pain, or jaw pain) or prior to placing a troponin order.

The HEART Pathway CDS tool prompted providers to answer a series of questions to prospectively risk stratify patients in real time. Patients with known CAD or acute ischemic changes on ECG (e.g., new T-wave inversions or ST-segment depression in contiguous leads) were immediately classified as non–low risk and no HEAR score assessment was conducted in these patients. Among patients without STEMI, known CAD, or acute ischemic ECG changes, providers answered additional flow sheet questions to determine a HEAR score based on the HEART Pathway trial algorithm (Impathiq Inc.).[32–36] The HEART Pathway risk assessment was automatically

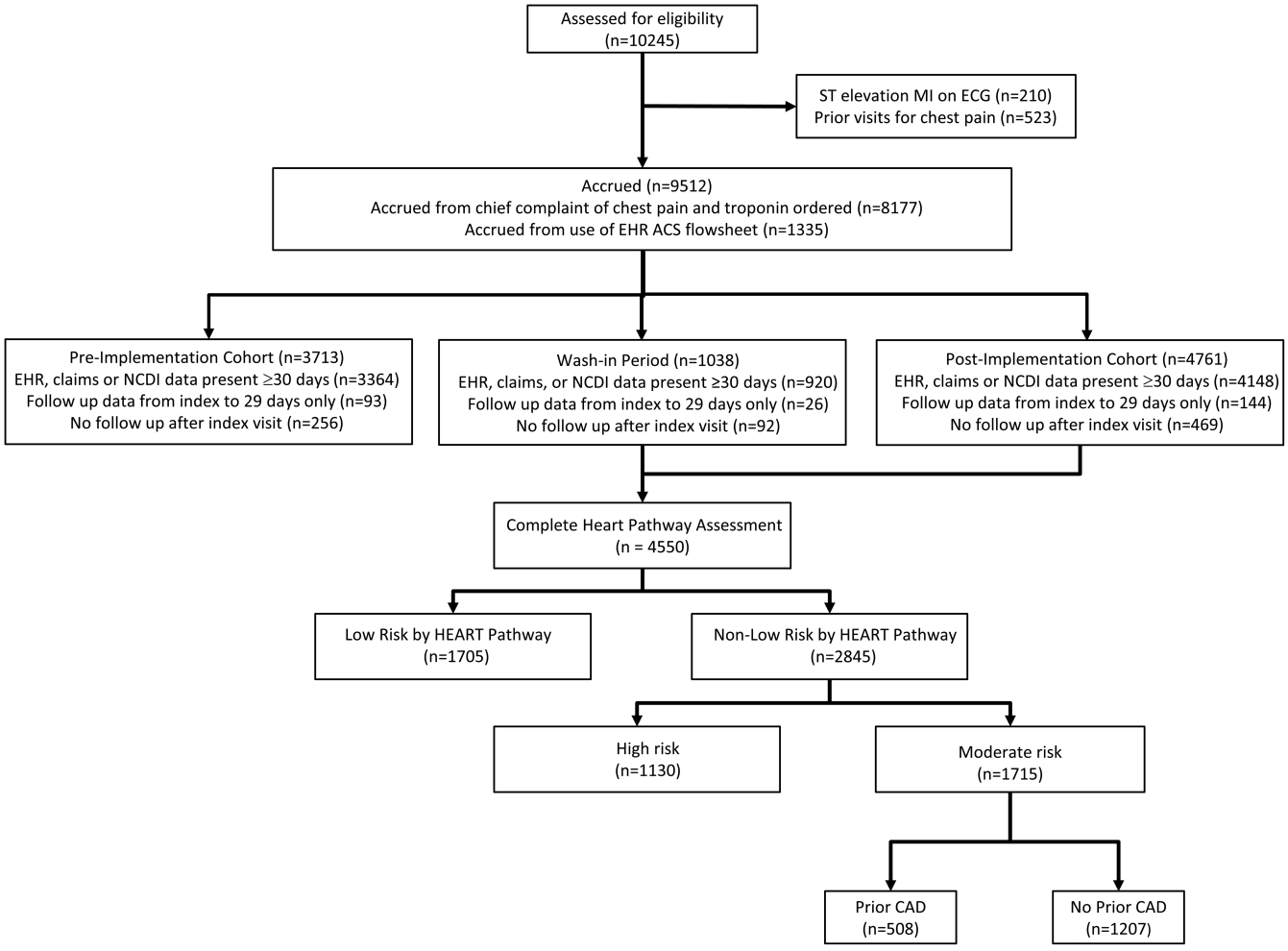

FIGURE 1 The patient flow diagram. ACS, acute coronary syndrome; CAD, coronary artery disease; EHR, electronic health record; MI, myocardial infarction; NCDI, North Carolina Death Index

calculated based on the HEAR score combined with 0- and 3-h troponin measures. Patients with HEAR scores < 4 without elevated troponin measures were classified as low risk and recommended for discharge from the ED without OCT. Patients with a HEAR score of ≥4, an elevated troponin, known CAD, or ischemic ECG changes were classified as non–low risk and designated for further testing and/or admission (Figure 1). Serum troponin was measured using the ADVIA Centaur platform TnI-Ultra assay (Siemens) or the Access AccuTnI+3 assay (Beckman Coulter).

Data collection

As previously described, the health system EHR (Clarity-Epic Systems Corp.) was examined for the index encounter for the patient. Patient demographics, comorbidities, troponin results, HEART Pathway assessments, dispositions, diagnoses, and vital status were obtained using prevalidated structured EHR variables or diagnoses and procedure codes (CPT, ICD9, and ICD10).[34–38] The EHR was the primary outcomes data source. EHR data were supplemented with insurers' claims and state death index data for events occurring outside of network. Claims data were available on patients insured by Blue Cross Blue Shield of North Carolina (the dominant insurer in North Carolina), MedCost, and North Carolina Medicaid. The North Carolina State Center for Health Statistics death index was also used.

Outcomes

The primary outcome was 30-day MACE, defined as the composite of all-cause death, MI, or coronary revascularization. Individual components of the MACE composite at the index visit and over

TABLE 1 Cohort demographics

Patient characteristics	High risk, n = 1,130 (%)	Moderate risk, n = 1,715 (%)	Moderate risk with CAD, n = 508 (%)	Moderate risk without CAD, n = 1,207 (%)
Age (years), mean (±SD)	60.9 (±15.0)	61.4 (±12.3)	64.1 (±12.2)	60.2 (±12.2)
Sex				
Women	500 (44.2)	950 (55.4)	202 (39.8)	748 (62.0)
Race				
White	732 (64.8)	1,219 (71.1)	403 (79.3)	816 (67.6)
Black	363 (32.1)	428 (25.0)	92 (18.1)	336 (27.8)
Other	35 (3.1)	68 (4.0)	13 (2.6)	55 (4.6)
Ethnicity				
Hispanic or Latino	34 (3.0)	53 (3.1)	7 (1.4)	46 (3.8)
Site				
WFBMC	929 (82.2)	1,390 (81.0)	427 (84.1)	963 (79.8)
DMC	78 (6.9)	149 (8.7)	34 (6.7)	115 (9.5)
LMC	123 (10.9)	176 (10.3)	47 (9.3)	129 (10.7)
Insurance status				
Private	259 (22.9)	412 (24.0)	98 (19.3)	314 (26.0)
Medicaid	145 (12.8)	183 (10.7)	54 (10.6)	129 (10.7)
Medicare	520 (46.0)	797 (46.5)	276 (54.3)	521 (43.2)
Other insurance	72 (6.4)	133 (7.8)	34 (6.7)	99 (8.2)
Self-pay/uninsured	134 (11.9)	190 (11.1)	46 (9.1)	144 (11.9)
Risk factors				
Hypertension	917 (81.2)	1,373 (80.1)	455 (89.6)	918 (76.1)
Smoking	757 (67.0)	1,066 (62.2)	368 (72.4)	698 (57.8)
BMI > 30 kg/m^2	510 (45.6)	886 (53.0)	229 (45.8)	657 (56.1)
Hyperlipidemia	655 (58.0)	1,031 (60.1)	338 (76.4)	643 (53.3)
Known CAD	252 (36.1)	508 (29.6)	508 (100)	0 (0)
Diabetes	465 (41.2)	630 (36.7)	211 (41.5)	419 (34.7)
Cerebrovascular disease	210 (18.6)	276 (16.1)	110 (21.7)	166 (13.8)
PVD	262 (23.2)	266 (15.5)	127 (25.0)	139 (11.5)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; DMC, Davie Medical Center; LMC, Lexington Medical Center; PVD, peripheral vascular disease; WFBMC, Wake Forest Baptist Medical Center.

30 days were secondary outcomes. Additional secondary outcomes included 30-day hospitalization, OCT, and early discharge (patients discharged from the ED without OCT) rates. Acute MI and coronary revascularization were determined using diagnosis and procedure codes validated by prior cardiovascular trials.[34–38] Coronary revascularization rate, a secondary endpoint, was defined as coronary artery bypass grafting, stent placement, or other percutaneous coronary intervention.

Data analysis

Statistical design for the overall study was described previously.[13,33] Patients identified as non–low risk by the HEART Pathway were further classified into two groups on the basis of initial troponin measures and ECG: "high-risk" patients had an elevated 0- or 3-h troponin measure or an ischemic ECG while "moderate-risk" patients had two negative troponin measures and a nonischemic ECG. Moderate-risk patients were further subdivided by the presence or absence of CAD (moderate risk with known CAD and moderate risk without prior CAD). Sensitivities, specificities, negative and positive predictive values (NPV and PPV), and negative and positive likelihood ratios (−LR and + LR) for 30-day MACE were calculated for moderate risk compared to high risk, moderate risk with CAD compared to high risk, and moderate risk without CAD compared to the composite of moderate risk with CAD and high risk. Exact binomial 95% confidence intervals (CIs) were calculated for sensitivity, specificity, NPV, and PPV. For −LRs and + LRs, 95% CIs were calculated using the approach described in Simel et al.[39] Safety outcome proportions were compared between groups using chi-square tests, and 95% CIs were computed for the difference in proportions. To adjust for potential confounders, multiple logistic regression was used to model the outcomes by patient cohort, using sex, race, and age as covariates. These variables were selected based on clinical experience and previous disparities work using data from the HEART Pathway Implementation Study. If the number of events precluded full adjustment, age was prioritized for inclusion, followed by sex and then race. Model assumptions were evaluated using residual plots

TABLE 2 Safety outcome frequencies of non–low-risk patients grouped by troponin levels, ECG, and CAD

Safety outcomes	High risk, *n* = 1130 (%)	Moderate risk, *n* = 1715 (%)	Moderate risk with CAD, *n* = 508 (%)	Moderate risk without CAD, *n* = 1,207 (%)
Index visit				
Death	12 (1.1)	1 (0.1)	1 (0.2)	0 (0)
MI	357 (31.6)	15 (0.9)	12 (2.4)	3 (0.2)
Revascularization	145 (12.8)	29 (1.7)	19 (3.7)	10 (0.8)
Death + MI	364 (32.2)	16 (0.9)	13 (2.6)	3 (0.2)
MACE	373 (33.0)	40 (2.3)	29 (5.7)	11 (0.9)
30-day follow-up period				
Death	17 (1.5)	6 (0.3)	2 (0.4)	4 (0.3)
MI	29 (2.6)	1 (0.1)	1 (0.2)	0 (0)
Revascularization	33 (2.9)	8 (0.5)	6 (1.2)	2 (0.2)
Death + MI	44 (3.9)	7 (0.4)	3 (0.6)	4 (0.3)
MACE	66 (5.8)	14 (0.8)	8 (1.6)	6 (0.5)
30-day (index + follow-up)				
Death	29 (2.6)	7 (0.4)	3 (0.6)	4 (0.3)
MI	364 (32.2)	16 (0.9)	13 (2.6)	3 (0.2)
Revascularization	175 (15.5)	37 (2.2)	25 (4.9)	12 (1.0)
Death + MI	382 (33.8)	23 (1.3)	16 (3.1)	7 (0.6)
MACE	397 (35.1)	53 (3.1)	36 (7.1)	17 (1.4)
Utilization outcomes				
Index				
Hospitalization	1.036 (91.7)	1.385 (80.8)	430 (84.6)	955 (79.1)
Objective cardiac testing	455 (40.3)	889 (51.8)	211 (41.5)	678 (56.2)
Early discharge	71 (6.3)	305 (17.8)	74 (14.6)	231 (19.1)
30 day (index + follow-up)				
Hospitalization	1,050 (92.9)	1,400 (81.6)	432 (85.0)	968 (80.2)
Objective cardiac testing	511 (45.2)	942 (54.9)	232 (45.6)	710 (58.8)

Abbreviations: CAD, coronary artery disease; MACE, major adverse cardiac event; MI, myocardial infarction.

and model fit was evaluated using Brier scores, area under the curve, and Hosmer-Lemeshow goodness-of-fit tests. Unadjusted and adjusted odds ratios (aOR) and corresponding 95% CIs were computed.

RESULTS

During the study period, 4,550 patients had a complete HEART Pathway assessment. Among these, 62.5% (2,845/4,550) were non–low risk, with 24.8% (1,130/4,550) high risk (with a positive troponin or an ischemic ECG) and 37.7% (1,715/4,550) moderate risk (with a nonischemic ECG and negative serial troponin measures). As shown in Table 1, 55.4% of moderate-risk patients were female (950/1,715) and 25.0% (428/1715) were Black, compared to 44.2% (500/1,130) female and 32.1% (363/1,130) Black in the high-risk group. The mean (±SD) age was 61.4 (±12.3) years for moderate-risk patients and 60.9 (±15.0) years for high-risk patients. Among moderate-risk patients, known CAD was present in 29.6% (508/1,715), leaving 70.4% (1207/1715) without CAD. The patient flow diagram for this analysis is presented in Figure 1.

The incidence of MACE at 30 days (Table 2) in high-risk patients was 35.1% (397/1,130) compared to 3.1% (53/1715) among moderate-risk patients ($p < 0.0001$). However, moderate-risk patents with CAD had an incidence of 30-day MACE of 7.1% (36/508) compared to 1.4% (17/1207) for moderate risk without CAD ($p < 0.0001$). The NPV and −LR for 30-day MACE for moderate risk without CAD patients compared to the composite of moderate risk with CAD and high risk were 98.6% (95% CI = 97.9 to 99.3) and 0.08 (95% CI = 0.05 to 0.12), respectively. Test characteristics for moderate risk, moderate risk with CAD, and moderate risk without CAD are summarized in Tables 3.

Among moderate-risk patients with no known history of CAD there were four deaths, three MIs, and 10 revascularizations without MI at 30 days. Among the four deaths, two clearly were from noncardiovascular causes. Three patients experienced MI. However, upon further chart review, two of these had improperly calculated HEART Pathway assessments owing to their serial troponins being drawn too early. Had they been appropriately collected, the HEART Pathway would likely have ruled-in these patients for acute MI. Finally, among the 10 patients who experienced revascularization without MI, one patient's HEART Pathway assessment was incorrect as his history of CAD (previous MI) was overlooked by the scoring provider. Table S1 describes MACE events among moderate-risk patients with and without known CAD in detail.

Among all patients in this analysis, 30-day MACE was least likely to occur in the moderate risk without CAD group (aOR = 0.04, 95% CI = 0.03 to 0.07). Among all moderate-risk patients, 30-day MACE was more likely in those with a history of CAD compared to those without CAD (aOR = 4.19, 95% CI = 2.30 to 7.90). The presence of an elevated troponin or an ischemic ECG was strongly associated with 30-day MACE (aOR = 18.05, 95% CI = 13.43 to 24.72).

TABLE 3 Test characteristics for MACE from index visit through 30 days

	30-day MACE		
Patient category	**Yes (*n*)**	**No (*n*)**	**Total**
High risk —Elevated troponin *or* —Ischemic ECG	397	733	1130
Moderate risk —Negative troponins *and* —Nonischemic ECG	53	1662	1715
With CAD	36	472	508
Without CAD	17	1190	1207
Total	450	2395	2845

Patient category	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**+LR**	**−LR**
Moderate risk[a]	88.2 (85.2–91.2)	69.4 (67.6–71.2)	3.5 (3.2–3.8)	96.9 (96.1–97.7)	2.88 (2.69–3.09)	0.17 (0.13–0.22)
Moderate risk with CAD[a]	91.7 (89.1–94.3)	39.2 (35.4–41.9)	35.1 (32.4–37.9)	92.9 (90.7–95.1)	1.51 (1.43–1.59)	0.21 (0.15–0.29)
Moderate risk without CAD[b]	96.2 (94.5–98)	49.7 (47.7–51.7)	26.4 (24.3–28.6)	98.6 (97.9–99.3)	1.91 (1.83–2.0)	0.08 (0.05–0.12)

Note: Data are reported as % (95% CI).

Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram; LR, likelihood ratio; MACE, major adverse cardiovascular event; NPV, negative predictive value; PPV, positive predictive value.

[a]Comparison group: high risk.

[b]Comparison group: high risk + moderate risk with CAD.

TABLE 4 Safety outcome comparisons between non–low-risk groups

Outcomes	High risk vs. moderate risk	High risk vs. moderate risk with CAD	Moderate risk with CAD vs. moderate risk without CAD	Moderate risk without CAD vs. high risk + moderate risk with CAD
Index visit				
Death	18.40[a] (3.62–335.41)	5.44[a] (1.07–99.28)	NA	NA
MI	55.44 (33.97–97.98)	23.15 (13.04–44.13)	9.71[a] (3.07–42.75)	0.01 (0–0.02)
Revascularization	8.70 (5.86–13.37)	4.70 (2.93–7.96)	4.34[b] (2.03–9.84)	0.09 (0.04–0.15)
Death + MI	53.51 (33.22–92.82)	22.07 (13.01–40.99)	10.54[a] (3.38–46.12)	0.009 (0–0.02)
MACE	21.78 (15.67–31.07)	10.00 (6.81–15.25)	5.13 (2.53–11.09)	0.03 (0.02–0.05)
30-day follow-up period				
Death	3.71[b] (1.52–10.41)	3.86[a] (1.10–24.43)	NA	0.37[b] (0.11–1.01)
MI	44.85[b] (9.91–799.81)	13.44[c] (2.85–240.20)	NA	NA
Revascularization	5.92 (2.85–13.90)	2.98 (1.32–7.99)	NA	0.09 (0.01–0.28)
Death + MI	9.39 (4.47–22.97)	7.91 (2.86–32.83)	NA	0.14 (0.0–0.34)
MACE	7.13 (4.09–13.34)	4.58 (2.30–10.46)	3.20[a] (1.11–9.77)	0.13 (0.05–0.28)
30-day (index + follow-up)				
Death	5.45[c] (2.48–13.69)	4.85[c] (1.70–20.40)	NA	0.23[c] (0.07–0.60)
MI	53.29 (33.08–92.44)	21.98 (12.95–40.82)	10.54[a] (3.38–46.12)	0.01 (0–0.02)
Revascularization	8.46 (5.92–12.40)	4.47 (2.93–7.10)	3.76 (1.85–8.03)	0.08 (0.04–0.14)
Death + MI	40.13 (26.63–63.54)	19.64 (12.08–34.31)	4.74[b] (2.00–12.47)	0.02 (0.01–0.04)
MACE	18.05 (13.43–24.72)	8.98 (6.29–13.18)	4.19 (2.30–7.90)	0.04 (0.03–0.07)

Note: Data are reported as adjusted[d] OR (95% CI). Hosmer-Lemeshow goodness-of-fit test *p*-value >0.05 for all models. All Brier scores were ≤0.10 for high versus moderate risk, ≤0.17 for high risk versus moderate risk with CAD, ≤0.02 for moderate with CAD versus moderate without CAD, and ≤0.12 for moderate without CAD versus all else. All models had area under the curve (AUC) > 0.70 except for the 30-day MACE model (not inclusive of index events) between the moderate risk with CAD versus moderate rish without CAD groups (AUC = 0.64). NA, regression model not calculated due to small sample size.

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; MACE, major adverse cardiac event.

[a]Unadjusted due to small sample size.

[b]Only adjusted for age due to small sample size.

[c]Only adjusted for age and sex due to small sample size.

[d]Adjusted for age, sex, and race.

The association between an elevated troponin or an ischemic ECG with 30-day MACE was still significant even if we were to rule out the moderate-risk–no-CAD group (aOR = 8.98, 95% CI = 6.29 to 13.18). Adjusted safety outcome comparisons among non–low-risk groups are summarized in Table 4. Unadjusted comparisons are included in Table S2. Table S3 presents absolute percentage differences in safety outcomes between non–low-risk groups.

DISCUSSION

This secondary analysis demonstrates that among non–low-risk patients, those at moderate risk with a HEAR score of ≥4, nonischemic ECG, and negative serial troponin measures have low 30-day MACE rates. However, MACE rates among moderate-risk patients with a history of prior CAD were significantly higher. Thus, the key finding

of this analysis is that moderate risk patients without a history of CAD have a very low 30-day MACE rate with a −LR of 0.08. This −LR meets the 0.10 threshold typically cited for clinical utility of a rule-out test. These findings suggest that additional testing in these patients, such as stress testing, may be unnecessary.

Multiple studies, including prior HEART Pathway trials, have examined the evaluation and treatment of low-risk chest pain patients. The HEART Pathway is able to safely identify low-risk patients for early discharge without OCT.[14,15,20] Other tools such as EDACS and T-MACS also identify low-risk patients with acute chest pain for early discharge.[12,13,17–19] However, few studies have addressed whether additional patients who are classified as non–low-risk by a risk score or pathway can be identified for safe, early discharge from the ED without OCT.

Safely evaluating and dispositioning moderate-risk chest pain patients challenges emergency providers every shift. Traditionally, most of these patients are admitted to the hospital or to an observation unit for OCT.[24–27] However, recent studies have called into question routine OCT evaluations and hospitalizations for patients without ischemic ECGs or elevated troponin measures.[24,38–43] Routine in-hospital chest pain evaluations for moderate-risk patients have a low diagnostic yield and are associated with iatrogenic risks from false-positive testing, radiation exposure, and anxiety without evidence for improved clinical outcomes.[24,40–45] This study highlights the low frequency of MACE in patients without an ischemic ECG, elevated troponin, or known CAD and calls into question the need for routine OCT in these patients prior to discharge.

This study may expand the early discharge boundaries of the HEART Pathway by suggesting that most moderate-risk patients can safely be evaluated and dispositioned without OCT. The 30-day MACE rate for moderate risk patients with no known CAD was 1.4% (17/1,207). This is below the 2% pretest probability threshold, which has been suggested for determining whether OCT is indicated.[31,32] On the other hand, missing MACE in 1.4% of patients is above what most physicians find acceptable.[28–30] However, closer inspection of the 17 MACE events among moderate-risk patients without known CAD demonstrated that at least two of the four deaths were clearly due to noncardiac causes and two of the three missed MIs were due to serial troponin protocol violations. In addition, one missed revascularization event was due to an inaccurate HEART Pathway assessment by the treating provider. Furthermore, 10 of the 12 revascularization events were among patients without acute MI. Revascularization events among patients without evidence of MI are of questionable significance as revascularization has not been shown to improve outcomes in these patients compared to medical management.[45–50] Finally, it is likely that with high-sensitivity assays, the MACE rate among non–low-risk patients with negative troponin measures would be even smaller.

Another key finding in this analysis is the importance of known CAD in predicting 30-day MACE even among patients with initial negative troponin measures and nonischemic ECGs. The 7.1% 30-day MACE rate among moderate-risk patients with a history of CAD was much higher than those without known CAD. This finding suggests that ED providers need to be cautious in the evaluation of patients with prior CAD, even in the absence of ischemic ECG findings or elevated troponin measures. Our findings agree with prior studies that have demonstrated that prior CAD confers a higher downstream risk of MACE.[46–51] Furthermore, our findings may be important in light of newer high-sensitivity troponin-based pathways, such as the European Society of Cardiology 0/1-h algorithm, which do not differentiate between patients with and without prior CAD.[52]

LIMITATIONS

This secondary analysis, which includes a subgroup of patients from the HEART Pathway Implementation Study, has several limitations. Although this was a multisite study, our findings may not be generalizable to all ED settings. Additionally, the EHR and insurance claims data were used to determine events, possible decreasing detection. Finally, this study did not use high-sensitivity troponin assays.

CONCLUSION

This study indicates that moderate-risk patients (History, ECG, Age, and Risk factors score ≥ 4; nonischemic electrocardiogram; and negative serial troponin measures) with no prior coronary artery disease have a low 30-day major adverse cardiac events rate. However, patients with a history of coronary artery disease are at higher risk for adverse events, even in the absence of elevated troponins or acute ischemic electrocardiogram changes. These data suggest that routine objective cardiac testing may not be indicated in moderate-risk patients without a history of coronary artery disease. Prospective research evaluating the safety and efficacy of avoiding hospitalization and objective cardiac testing among moderate-risk patients without prior coronary artery disease is needed.

CONFLICT OF INTEREST

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REFERENCES

1. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the emergency department?: a clinical survey. *Int J Cardiol*. 2013;166(3):752-754. doi:10.1016/j.ijcard.2012.09.171
2. Dezman ZD, Mattu A, Body R. Utility of the history and physical examination in the detection of acute coronary syndromes in emergency department patients. *West J Emerg Med*. 2017;18(4):752-760. doi:10.5811/westjem.2017.3.32666
3. Hess EP, Brison RJ, Perry JJ, et al. Development of a clinical prediction rule for 30-day cardiac events in emergency department patients with chest pain and possible acute coronary syndrome. *Ann Emerg Med*. 2012;59(2):115-25.e1. doi:10.1016/j.annemergmed.2011.07.026
4. Mokhtari A, Dryver E, Söderholm M, Ekelund U. Diagnostic values of chest pain history, ECG, troponin and clinical gestalt in patients with chest pain and potential acute coronary syndrome assessed in the emergency department. *Springerplus*. 2015;4:219. doi:10.1186/s40064-015-0992-9
5. Carlton EW, Than M, Cullen L, Khattab A, Greaves K. "Chest pain typicality" in suspected acute coronary syndromes and the impact of clinical experience. *Am J Med*. 2015;128(10):1109-1116.e2. doi:10.1016/j.amjmed.2015.04.012
6. Body R, Cook G, Burrows G, Carley S, Lewis PS. Can emergency physicians "rule in" and "rule out" acute myocardial infarction with clinical judgement? *Emerg Med J*. 2014;31(11):872-876. doi:10.1136/emermed-2014-203832
7. Oliver G, Reynard C, Morris N, Body R. Can emergency physician gestalt "rule in" or "rule out" acute coronary syndrome: validation in a multicenter prospective diagnostic cohort study. *Acad Emerg Med*. 2020;27(1):24-30. doi:10.1111/acem.13836
8. Kline JA, Stubblefield WB. Clinician gestalt estimate of pretest probability for acute coronary syndrome and pulmonary embolism in patients with chest pain and dyspnea. *Ann Emerg Med*. 2014;63(3):275-280. doi:10.1016/j.annemergmed.2013.08.023
9. Lee TH, Rouan GW, Weisberg MC, et al. Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. *Am J Cardiol*. 1987;60(4):219-224. doi:10.1016/0002-9149(87)90217-7
10. Trzeciak S, Rivers EP. Emergency department overcrowding in the United States: an emerging threat to patient safety and public health. *Emerg Med J*. 2003;20(5):402-405. doi:10.1136/emj.20.5.402
11. Pines JM, Pollack CV Jr, Diercks DB, Chang AM, Shofer FS, Hollander JE. The association between emergency department crowding and adverse cardiovascular outcomes in patients with chest pain. *Acad Emerg Med*. 2009;16(7):617-625. doi:10.1111/j.1553-2712.2009.00456.x
12. Mahler SA, Riley RF, Hiestand BC, et al. The HEART pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. *Circ Cardiovasc Qual Outcomes*. 2015;8(2):195-203. doi:10.1161/CIRCOUTCOMES.114.001384
13. Mahler SA, Lenoir KM, Wells BJ, et al. Safely identifying emergency department patients with acute chest pain for early discharge. *Circulation*. 2018;138(22):2456-2468. doi:10.1161/circulationaha.118.036528
14. Than M, Flaws D, Sanders S, et al. Development and validation of the emergency department assessment of chest pain score and 2 h accelerated diagnostic protocol. *Emerg Med Australas*. 2014;26(1):34-44. doi:10.1111/1742-6723.12164
15. Body R, Carlton E, Sperrin M, et al. Troponin-only Manchester acute coronary syndromes (T-MACS) decision aid: single biomarker re-derivation and external validation in three cohorts. *Emerg Med J*. 2017;34(6):349-356. doi:10.1136/emermed-2016-205983
16. Musey PI Jr, Bellolio F, Upadhye S, et al. Guidelines for reasonable and appropriate care in the emergency department (GRACE): recurrent, low-risk chest pain in the emergency department. *Acad Emerg Med*. 2021;28(7):718-744. doi:10.1111/acem.14296
17. Roberts R, Kleiman NS. Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a "new diagnostic mind-set". *Circulation*. 1994;89(2):872-881. doi:10.1161/01.cir.89.2.872
18. Heller GV, Stowers SA, Hendel RC, et al. Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. *J Am Coll Cardiol*. 1998;31(5):1011-1017. doi:10.1016/s0735-1097(98)00057-6
19. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med*. 2012;366(15):1393-1403. doi:10.1056/NEJMoa1201163
20. Body R, Carley S, McDowell G, et al. The Manchester Acute Coronary Syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. *Heart*. 2014;100(18):1462-1468. doi:10.1136/heartjnl-2014-305564
21. Alghamdi A, Reynard C, Morris N, et al. Diagnostic accuracy of the troponin-only Manchester acute coronary syndromes (T-MACS) decision aid with a point-of-care cardiac troponin assay. *Emerg Med J*. 2020;37(4):223-228. doi:10.1136/emermed-2019-208882
22. Six AJ, Cullen L, Backus BE, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol*. 2013;12(3):121-126. doi:10.1097/HPC.0b013e31828b327e
23. Stopyra JP, Riley RF, Hiestand BC, et al. The HEART pathway randomized controlled trial one-year outcomes. *Acad Emerg Med*. 2019;26(1):41-50. doi:10.1111/acem.13504
24. Sandhu AT, Heidenreich PA, Bhattacharya J, Bundorf MK. Cardiovascular testing and clinical outcomes in emergency department patients with chest pain. *JAMA Intern Med*. 2017;177(8):1175-1182. doi:10.1001/jamainternmed.2017.2432
25. Meyer MC, Mooney RP, Sekera AK. A critical pathway for patients with acute chest pain and low risk for short-term adverse cardiac events: role of outpatient stress testing. *Ann Emerg Med*. 2006;47(5):427-435. doi:10.1016/j.annemergmed.2005.10.010
26. Scheuermeyer FX, Innes G, Grafstein E, et al. Safety and efficiency of a chest pain diagnostic algorithm with selective outpatient stress testing for emergency department patients with potential ischemic chest pain. *Ann Emerg Med*. 2012;59(4):256-264.e3. doi:10.1016/j.annemergmed.2011.10.016
27. Manini AF, McAfee AT, Noble VE, Bohan JS. Prognostic value of the Duke treadmill score for emergency department patients with chest pain. *J Emerg Med*. 2010;39(2):135-143. doi:10.1016/j.jemermed.2007.12.034
28. Spertus JA, Jones PG, Maron DJ, et al. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med*. 2020;382(15):1408-1419. doi:10.1056/NEJMoa1916370
29. Chaitman BR, Alexander KP, Cyr DD, et al. Myocardial infarction in the ISCHEMIA trial. *Circulation*. 2021;143(8):790-804. doi:10.1161/CIRCULATIONAHA.120.047987
30. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382(15):1395-1407. doi:10.1056/NEJMoa1915922

31. Kline JA, Johnson CL, Pollack CV Jr, et al. Pretest probability assessment derived from attribute matching. *BMC Med Inform Decis Mak*. 2005;5:26. doi:10.1186/1472-6947-5-26
32. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Suspected Non–ST-Elevation Acute Coronary Syndromes, Tomaszewski CA, Nestler D, Shah KH, Sudhir A, Brown MD. Clinical policy: critical issues in the evaluation and management of emergency department patients with Suspected non-ST-elevation acute coronary syndromes. *Ann Emerg Med*. 2018;72(5):e65-e106. doi:10.1016/j.annemergmed.2018.07.045
33. Mahler SA, Burke GL, Duncan PW, et al. HEART pathway accelerated diagnostic protocol implementation: prospective pre-post interrupted time series design and Methods. *JMIR Res Protoc*. 2016;5(1):e10. doi:10.2196/resprot.4802
34. Culler SD, Kugelmass AD, Brown PP, Reynolds MR, Simon AW. Trends in coronary revascularization procedures among Medicare beneficiaries between 2008 and 2012. *Circulation*. 2015;131(4):362-370; discussion 370. doi:10.1161/CIRCULATIONAHA.114.012485
35. Riley RF, Don CW, Powell W, Maynard C, Dean LS. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circ Cardiovasc Qual Outcomes*. 2011;4(2):193-197. doi:10.1161/CIRCOUTCOMES.110.958744
36. So L, Evans D, Quan H. ICD-10 coding algorithms for defining comorbidities of acute myocardial infarction. *BMC Health Serv Res*. 2006;6:161. doi:10.1186/1472-6963-6-161
37. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak*. 2015;15:31. doi:10.1186/s12911-015-0155-5
38. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83
39. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. *J Clin Epidemiol*. 1991;44(8):763-770. doi:10.1016/0895-4356(91)90128-v
40. Ashburn NP, Smith ZP, Hunter KJ, et al. The disutility of stress testing in low-risk HEART pathway patients. *Am J Emerg Med Published Online August*. 2021;45:227-232. doi:10.1016/j.ajem.2020.08.032
41. Reinhardt SW, Lin CJ, Novak E, Brown DL. Noninvasive cardiac testing vs clinical evaluation alone in acute chest pain: a secondary analysis of the ROMICAT-II randomized clinical trial. *JAMA Intern Med*. 2018;178(2):212-219. doi:10.1001/jamainternmed.2017.7360
42. Foy AJ, Liu G, Davidson WR Jr, Sciamanna C, Leslie DL. Comparative effectiveness of diagnostic testing strategies in emergency department patients with chest pain: an analysis of downstream testing, interventions, and outcomes. *JAMA Intern Med*. 2015;175(3):428-436. doi:10.1001/jamainternmed.2014.7657
43. Redberg RF. Stress testing in the emergency department: not which test but whether any test should be done. *JAMA Intern Med*. 2015;175(3):436. doi:10.1001/jamainternmed.2014.7698
44. Einstein AJ, Knuuti J. Cardiac imaging: does radiation matter? *Eur Heart J*. 2012;33(5):573-578. doi:10.1093/eurheartj/ehr281
45. Journy N, Dreuil S, Rage E, et al. Projected future cancer risks in children treated with fluoroscopy-guided cardiac catheterization procedures. *Circ Cardiovasc Interv*. 2018;11(11):e006765. doi:10.1161/CIRCINTERVENTIONS.118.006765
46. Pizzi C, Xhyheri B, Costa GM, et al. Nonobstructive versus obstructive coronary artery disease in acute coronary syndrome: a meta-analysis. *J Am Heart Assoc*. 2016;5(12):e004185. doi:10.1161/JAHA.116.004185
47. Hollander JE, Chang AM, Shofer FS, et al. One-year outcomes following coronary computerized tomographic angiography for evaluation of emergency department patients with potential acute coronary syndrome. *Acad Emerg Med*. 2009;16(8):693-698. doi:10.1111/j.1553-2712.2009.00459.x
48. Budoff MJ, Mayrhofer T, Ferencik M, et al. Prognostic value of coronary artery calcium in the PROMISE study (prospective multicenter imaging study for evaluation of chest pain). *Circulation*. 2017;136(21):1993-2005. doi:10.1161/CIRCULATIONAHA.117.030578
49. Koshy AN, Ha FJ, Gow PJ, et al. Computed tomographic coronary angiography in risk stratification prior to non-cardiac surgery: a systematic review and meta-analysis. *Heart*. 2019;105(17):1335-1342. doi:10.1136/heartjnl-2018-314649
50. Hadamitzky M, Freissmuth B, Meyer T, et al. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. *JACC Cardiovasc Imaging*. 2009;2(4):404-411. doi:10.1016/j.jcmg.2008.11.015
51. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50(12):1161-1170. doi:10.1016/j.jacc.2007.03.067
52. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the Management of Acute Coronary Syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315. doi:10.1093/eurheartj/ehv320

SUPPORTING INFORMATION

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