The Role of Cardiac Risk Factor Burden in Diagnosing Acute Coronary Syndromes in the Emergency Department Setting

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Study objective: We seek to determine whether cardiac risk factor burden (defined as the number of conventional cardiac risk factors present) is useful for the diagnosis of acute coronary syndromes in the emergency department (ED) setting.

Methods: This was a post hoc analysis of the Internet Tracking Registry of Acute Coronary Syndromes (i*tr*ACS*) registry, which had 17,713 ED visits for suspected acute coronary syndromes. First visit for US patients who were not cocaine or amphetamine users, who did not leave against medical advice, and for whom ECG and demographic data were complete were included. Acute coronary syndrome was defined by 30-day revascularization, diagnostic-related group codes, or death within 30 days, with positive cardiac biomarkers at index hospitalization. Cardiac risk factors were diabetes, hypertension, smoking, hypercholesterolemia, and family history of coronary artery disease. Cardiac risk factor burden was defined as the number of risk factors present. Because multiple logistic regression analysis revealed that age modified the relationship between cardiac risk factor burden and acute coronary syndromes, a stratified analysis was performed for 3 age categories: younger than 40, 40 to 65, and older than 65 years. Positive likelihood ratios and negative likelihood ratios with their 95% confidence intervals (CIs) were calculated for each total risk factor cutoff.

Results: Of 10,806 eligible patients, 871 (8.1%) had acute coronary syndromes. In patients younger than 40 years, having no risk factors had a negative likelihood ratio of 0.17 (95% CI 0.04 to 0.66), and having 4 or more risk factors had a positive likelihood ratio of 7.39 (95% CI 3.09 to 17.67). In patients between 40 and 65 years of age, having no risk factors had a negative likelihood ratio of 0.53 (95% CI 0.40 to 0.71), and having 4 or more risk factors had a positive likelihood ratio of 2.13 (95% CI 1.66 to 2.73). In patients older than 65 years, having no risk factors had a negative likelihood ratio of 0.96 (95% CI 0.74 to 1.23), and having 4 or more risk factors had a positive likelihood ratio of 1.09 (95% CI 0.64 to 1.62).

Conclusion: Cardiac risk factor burden has limited clinical value in diagnosing acute coronary syndromes in the ED setting, especially in patients older than 40 years. [Ann Emerg Med. 2007; 49:145-152.]

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Editor's Capsule Summary

What is already known on this topic

By definition, cardiac risk factors are associated with an increased likelihood of acute coronary syndrome in the general public.

What question this study addressed

Whether cardiac risk factors as defined for the general population are useful in identifying acute coronary syndrome in patients undergoing emergency department (ED) evaluation for acute coronary syndrome.

What this study adds to our knowledge

In this retrospective analysis of a clinical registry with 10,806 eligible ED patients with suspected acute coronary syndrome, cardiac risk factor burden was moderately predictive of acute coronary syndrome in those younger than 40 years but was not helpful in older patients.

How this might change clinical practice

These data suggest that clinicians should not use cardiac risk factor burden to define the probability of acute coronary syndrome in ED patients who are older than 40 years and are being evaluated for this condition.

INTRODUCTION

Background

Clinicians commonly assume that the more cardiac risk factors a patient has (cardiac risk factor burden), the higher the risk of acute coronary syndromes in those with suspected acute coronary syndromes.[1] In the emergency department (ED) setting, Jayes et al[2] observed that individual risk factors were not useful for diagnosing acute coronary syndromes but did not study the role of cardiac risk factor burden on clinical decisionmaking. As a result, the role of cardiac risk factor burden in the ED setting remains unclear. Recently, the Framingham Heart Study found that patients with 2 or more cardiac risk factors had a substantially higher lifetime risk for cardiovascular disease, but this was a population-based longitudinal study, limiting this study's generalizability to the ED population.[3] Additionally, associations between cardiac risk factors and acute coronary syndromes are not uniform across the entire population. Different cardiac risk factors are associated with acute coronary syndromes in men and women.[2] However, the effect modification of age on the relationship between cardiac risk factor burden and acute coronary syndromes is not well studied.

Goals of This Investigation

Using a contemporary database, we sought to determine whether cardiac risk factor burden was associated with the risk of acute coronary syndromes and to determine its usefulness in the ED setting. In addition, we explored how age and other clinical variables modified the relationship between cardiac risk factor burden and acute coronary syndromes.

MATERIALS AND METHODS

Study Design and Setting

This was a post hoc analysis of Internet Tracking Registry of Acute Coronary Syndromes (i*tr*ACS*), a multicenter registry of 17,713 patients with possible acute coronary syndromes presenting to one of 8 EDs in the United States and 1 in Singapore. This registry was a prospective observational cohort study and was developed because there was an absence of any recent observational studies of well-characterized patient populations presenting to EDs with any suspicion of acute coronary syndromes. The i*tr*ACS* registry contains a representative sample of patients with suspected acute coronary syndromes across the entire spectrum of risk. Enrolling institutions and detailed methods of data collection are detailed elsewhere.[4] The institutional review boards or ethics committees approved patient enrollment without informed consent at 8 of the 9 centers; at one center, verbal informed consent was required from the patients before data collection.

Selection of Participants

The registry contains a convenience sample of patients prospectively enrolled between June 1999 and August 2001. Patients were identified and enrolled in the ED by trained research assistants or the treating physician. Most participating sites used research assistants and enrolled patients only when research assistants were available.

Patients were included in the registry if they were older than 18 years and were suspected of having acute coronary syndromes, primarily indicated by ordering of a 12-lead ECG or cardiac biomarkers and additionally indicated by the treating physician. Patients were excluded from the registry if they were transferred from another institution or if the ECG was obtained for nonacute coronary syndromes evaluations. For this analysis, only index visits enrolled in the United States were included. Repeated visits were excluded to prevent clustering. Because previous reports have found Singapore patients to have different clinical factors associated with acute coronary syndromes, patients from Singapore were excluded.[5] In community-based studies, risk scores using cardiac risk factors and developed in the United States tended to overestimate coronary heart disease in non-US populations.[6-8] Additionally, cultural differences are likely to result significant heterogeneity in risk factor reporting. Patients were also excluded from this analysis if they reported recent use of cocaine or amphetamines, left the ED against medical advice, or had missing 12-lead ECG or demographic data.

Methods of Measurement

Diabetes, hypertension, current smoker, hypercholesterolemia, and family history of premature coronary artery disease in a first-

degree relative were obtained by both patient interview and medical record review. Cardiac risk factor burden was calculated as the sum of these risk factors for each patient. To represent clinical practice, each cardiac risk factor was weighted equally. Because there were few (0.6%) patients with 5 risk factors, patients with 4 and 5 cardiac risk factors were combined to facilitate analysis.

Data Collection and Processing

Each enrolling site used standardized case report forms filled out by the research assistant.[4] Patient demographics, medical history, medications, presenting symptoms, initial cardiac biomarkers, and 12-lead ECG interpretation were collected prospectively. Medical records were used to supplement data collection. The ECG was interpreted by the treating physician; no attempt was made to confirm 12-lead ECG reading by a second reader. ED and hospital course were obtained through either medical record review or daily follow-up of patients admitted to the hospital. Thirty-day outcomes were obtained primarily by telephone interview. Medical record review and death registry were used to follow up patients who could not be contacted by telephone. Follow-up was completed in 95.6% of enrolled patients. Within the registry, the presence of cardiac risk factors was recorded, but the absence was not. Therefore, we considered the risk factor variables to indicate known presence (risk factor positive) compared to no known presence (risk factor negative).

Outcome Measures

The primary outcome variable was acute coronary syndromes. We used a definition previously established by our group,[5] which is a conservative modification of the joint European Society of Cardiology/American College of Cardiology Committee definition of acute myocardial infarction.[9] This definition uses objective evidence for acute coronary syndromes and minimizes false-positive results.[10] Creatinine kinase-MB, troponin I, and troponin T assays were used to support a diagnosis of acute coronary syndromes. Because the 12-lead ECG was not confirmed by a second reader, we did not incorporate 12-lead ECG in our definition of acute coronary syndromes. A positive biomarker result was defined as 2 measures considered positive and at least 1 measure above twice the upper limit of normal or measured only once, with the result at least 3 times the upper limit of normal. Patients were considered to have acute coronary syndromes if they had one of the following:

- Death within 30 days, with a positive cardiac biomarker during the index hospitalization
- Diagnostic-related group code indicating acute myocardial infarction, with or without death and with a positive cardiac biomarker
- Diagnostic-related group code indicating unstable angina, with or without death and with percutaneous coronary intervention or coronary artery bypass graft
- Percutaneous coronary intervention or coronary artery bypass graft during index hospitalization or within 30 days

The diagnostic-related group code for unstable angina was not used as an independent criterion because this diagnosis could be made without any objective clinical evidence. Any diagnostic-related group code of unstable angina had to be accompanied with revascularization, regardless of increased cardiac biomarker levels.

Primary Data Analysis

To determine whether cardiac risk factor burden was associated with acute coronary syndromes and which clinical variables modified this relationship, multivariable logistic regression was performed. The covariates in the initial model were cardiac risk factor burden, age category, sex, race, and history of coronary artery disease. In addition, 2 factor interactions between cardiac risk factor burden and age category, history of coronary artery disease, sex, and race were incorporated into the multivariable model. Age was categorized as younger than 40 years, 40 to 65 years, and older than 65 years according to previous work.[11-13] Interactions with $P>.05$ were removed one by one until a parsimonious model was achieved. Likelihood ratio tests (assessing the difference between –2 log likelihood) were conducted for each model to see whether there was significant change when each interaction term was removed. Because age category×cardiac risk factor burden was the only significant interaction to remain in the model (Table E1, http://www.annemergmed.com), multivariable logistic regression analyses stratified by age category were performed. These stratified models were adjusted for sex, coronary artery disease history, and race. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Hosmer-Lemeshow test was performed to assess goodness of fit, and regression diagnostics were performed to test for collinearity among the explanatory variables. Any regression model with a condition index greater than 30 was considered to have severe collinearity.

To assess for clinical utility, the area under the receiver operating characteristic curve, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were calculated. The receiver operating characteristic curves were constructed from the sensitivity and specificity obtained when using 1, 2, 3, or 4 or more risk factors as cutoffs; 95% CIs were calculated for sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio.[14] All statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC) and Excel 2003 (Microsoft Inc., Seattle, WA).

RESULTS

All inclusion and exclusion criteria were met by 10,806 patients (Figure 1), of whom 871 (8.1%) met criteria for acute coronary syndromes. Overall demographics, cardiac risk factors, and cardiac risk factor burden stratified by the presence of acute coronary syndromes are listed in Table 1. Patients with acute coronary syndromes were more likely to be older, men, and white and have a higher proportion of cardiac risk factors, with

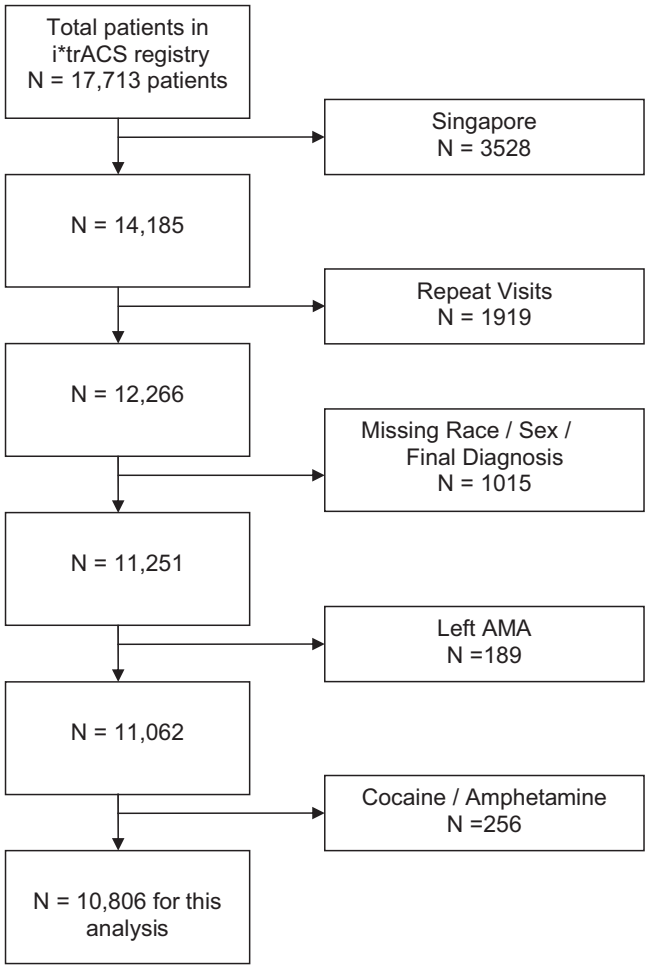

Figure 1. Inclusion and exclusion criteria. The number of patients within each exclusion criterion is different from that of previous reports because the order in which the exclusion criteria were applied was different.[5] *AMA,* Against medical advice.

Table 1. Patient demographics, cardiac risk factors, and cardiac risk factor burden for all patients and for patients with and without acute coronary syndromes.*

Variable	All Patients, N=10,806	ACS+, N=871	ACS–, N=9,935
Age, y (IQR)	52 (42,77)	63 (52,72)	52 (41,65)
Men	4,833 (44.7)	538 (61.8)	4,295 (43.2)
White	5,221 (48.3)	577 (66.3)	4,664 (46.7)
Previous CAD	2,024 (18.7)	302 (34.8)	1,722 (17.3)
Diabetes	2,118 (19.6)	254 (29.2)	1,864 (18.8)
Hypertension	5,183 (52.0)	487 (55.8)	4,696 (47.3)
Current smoker	3,128 (29.0)	258 (29.6)	2,870 (29.0)
Hypercholesterolemia	2,244 (20.8)	286 (32.8)	1,958 (19.7)
Family history	4,009 (37.1)	369 (42.4)	3,640 (36.6)
Risk factors, No.			
0	2,133 (19.7)	104 (11.9)	2,029 (20.4)
1	3,476 (32.1)	237 (27.2)	3,239 (32.6)
2	3,017 (27.9)	272 (31.2)	2,745 (27.6)
3	1,617 (14.9)	173 (19.9)	1,444 (14.5)
4 or 5	563 (5.2)	85 (9.8)	478 (4.8)

ACS, Acute coronary syndromes; *CAD,* coronary artery disease.
*Age is expressed in median and interquartile range (IQR). All other variables are expressed as No. (%).

Table 2. Patient demographics, cardiac risk factors, and cardiac risk factor burden for each age category.*

Variable	<40 y, N=2,057	40–65 y, N=5,919	>65 y, N=2,830
Age, y (IQR)	34 (29,37)	51 (45,57)	75 (70,80)
Men	953 (46.3)	2,750 (46.5)	1,130 (39.9)
White	812 (39.5)	2,801 (47.3)	1,608 (56.8)
Previous CAD	61 (3.0)	994 (16.8)	969 (34.2)
Diabetes	162 (7.9)	1,216 (20.5)	740 (26.2)
Hypertension	448 (21.8)	2,957 (50.0)	1,778 (62.8)
Current smoker	761 (37.0)	2,028 (34.3)	339 (12.0)
Hypercholesterolemia	147 (7.2)	1,322 (22.3)	775 (27.4)
Family history	749 (36.4)	2,421 (40.9)	839 (29.7)
Risk factors, No.			
0	660 (32.1)	995 (16.8)	478 (16.9)
1	770 (37.4)	1,784 (30.1)	922 (32.6)
2	433 (21.1)	1,722 (29.1)	862 (30.5)
3	151 (7.3)	1,010 (17.1)	456 (16.1)
4 or 5	43 (2.1)	408 (6.9)	112 (4.0)

*Age is expressed in median and interquartile range (IQR). All other variables are expressed as No. (%).

the exception of current smoking, than patients without acute coronary syndromes. Table 2 lists patient demographics, cardiac risk factors, and cardiac risk factor burden stratified by age category. Compared with the patients younger than 40 years, older age groups had higher proportions of cardiac risk factors, except for current smoking and family history; 1.8%, 8.2%, and 12.4% of patients younger than 40, between 40 and 65, and older than 65 years had acute coronary syndromes, respectively.

Adjusted ORs (95% CI) stratified by age category are listed in Table 3. The association between male sex and acute coronary syndromes remained strong across all age strata. In patients younger than 40 years, increasing numbers of cardiac risk factors markedly increased the odds of acute coronary syndromes. A patient with 4 or more risk factors was 22.5 (95% CI 3.9 to 131.4) times more likely to have acute coronary syndromes than a patient with no risk factors. In patients older than 65 years, the ORs remained close to unity, regardless of the number of risk factors present. For all stratified models, the Hosmer-Lemeshow tests were not statistically significant (minimum P=.705), indicating good fit. The condition index was less than 5.2 for all models, indicating that there was little collinearity between the explanatory variables.

To determine the clinical utility of cardiac risk factor burden in diagnosing acute coronary syndromes, receiver operating characteristic curves were constructed for all patients (Figure 2) and for each age category (Figure 3). Area under the receiver operating characteristic curves and likelihood ratios for each cutoff are listed in Table 4 for all patients and stratified by age. The area under the receiver operating characteristic curve for

Table 3. Multivariable logistic models for cardiac risk factor burden stratified by age and adjusted for sex, history of coronary artery disease, and race: total number of risk factors.*

Variables	<40 y	40–65 y	>65 y
Male	2.55 (1.18–5.49)	2.03 (1.66–2.47)	2.00 (1.59–2.52)
Previous CAD	8.69 (3.79–19.90)	1.62 (1.30–2.02)	1.27 (1.00–1.61)
White	1.80 (0.87–3.70)	1.91 (1.56–2.33)	1.65 (1.29–2.11)
Risk factors, No.			
0	1.00	1.00	1.00
1	2.57 (0.53–12.51)	1.49 (1.05–2.13)	1.02 (0.73–1.45)
2	9.19 (2.07–40.74)	1.79 (1.26–2.54)	1.22 (0.86–1.72)
3	7.86 (1.51–40.92)	2.60 (1.80–3.74)	1.02 (0.67–1.54)
4 or 5	22.53 (3.86–131.36)	3.67 (2.42–5.55)	1.22 (0.65–2.27)

*Adjusted ORs with their 95% CI for each risk factor and their association with acute coronary syndromes stratified by age category. Zero risk factors is the reference category.

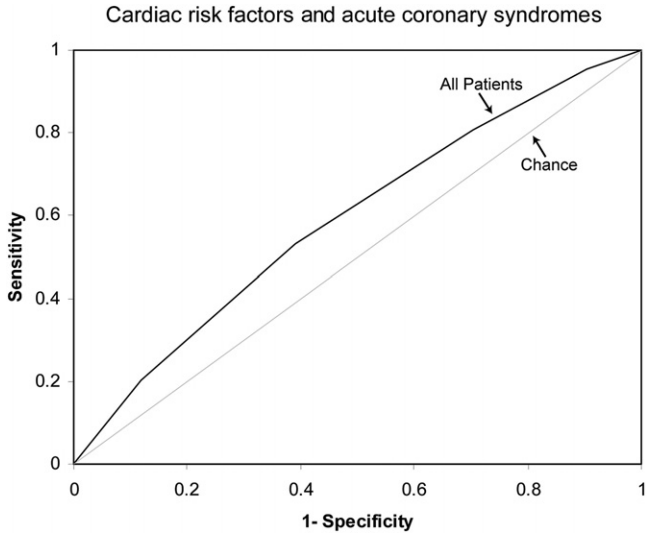

Figure 2. Receiver operating characteristic curve for cardiac risk factor burden and acute coronary syndromes. Area under the curve=0.591.

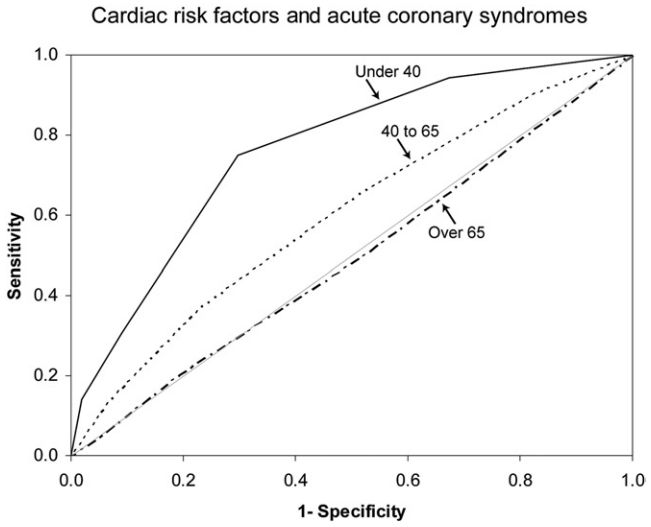

Figure 3. Receiver operating characteristic curve for cardiac risk factor burden and acute coronary syndromes stratified by age. Areas under the curve were 0.763, 0.602, and 0.518 for patients younger than 40, 40 to 65, and older than 65 years, respectively.

patients younger than 40 years was 0.763, indicating fair diagnostic performance. In this subgroup, having no risk factors moderately decreased the probability of acute coronary syndromes (negative likelihood ratio 0.17; 95% CI 0.04 to 0.66), and having 4 or more risk factors moderately increased the probability of acute coronary syndromes (positive likelihood ratio 7.39; 95% CI 3.09 to 17.67). The area under the receiver operating characteristic curves for the entire cohort and other age groups showed limited diagnostic utility, and the likelihood ratios for each cutoff minimally changed the probability of acute coronary syndromes.

LIMITATIONS

This analysis was a post hoc analysis of a registry study, and the limitations of registry studies are well documented.[15] Referral bias may have occurred; patients who were young and without cardiac risk factors may not have received an ECG or cardiac biomarkers and, as a result, may have not been enrolled in the study. However, it is routine practice to perform a screening 12-lead ECG in patients complaining of chest pain, regardless of age or cardiac risk factors present; having only an ECG would have met inclusion criteria into the registry. Because this was a convenience sample, selection bias may have occurred. Because patients at some sites were typically enrolled during the day when the research assistant was available, patients who presented to the ED in the early morning may have been missed. Potentially, these patients were sicker, and exclusion of these patients may have biased our findings.

The largest limitation is primarily related to the method of risk factor assessment. Risk factors were determined by patient interview and the medical record. It is possible that patients with undiagnosed or unknown risk factors were missed. As a result, the relationship between cardiac risk factor burden and acute coronary syndromes may have been attenuated. However,

Table 4. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and area under the receiver operating characteristic curve for each cardiac risk factor burden cutoff for all patients and stratified by age.

Risk Factors, No.	Sensitivity	Specificity	+LR	–LR
All patients*				
0	100.0	0.0	—	—
1	95.2 (94.8–95.6)	9.8 (7.8–11.7)	1.05 (1.03–1.08)	0.49 (0.40–0.61)
2	80.7 (79.9–81.4)	29.6 (26.6–32.7)	1.15 (1.10–1.20)	0.65 (0.59–0.73)
3	53.0 (52.0–54.0)	60.9 (57.6–64.1)	1.35 (1.24–1.47)	0.77 (0.73–0.82)
4 or 5	20.4 (19.6–21.2)	88.1 (85.9–90.2)	1.71 (1.42–2.06)	0.90 (0.88–0.93)
<40 y†				
0	100.0	0.0	—	—
1	94.4 (87.0–100.0)	32.6 (30.5–34.6)	1.40 (1.29–1.52)	0.17 (0.04–0.66)
2	75.0 (60.9–89.1)	70.3 (68.3–72.3)	2.53 (2.07–3.09)	0.36 (0.20–0.63)
3	30.6 (15.5–45.6)	90.9 (89.7–92.2)	3.37 (2.02–5.63)	0.76 (0.61–0.95)
4 or 5	13.9 (2.6–25.2)	98.1 (97.5–98.7)	7.39 (3.09–17.67)	0.88 (0.77–1.00)
40–65 y‡				
0	100.0	0.0	—	—
1	90.7 (88.1–93.3)	17.5% (16.5–18.5)	1.10 (1.07–1.13)	0.53 (0.40–0.71)
2	65.9 (61.7–70.1)	48.1% (46.8–49.4)	1.27 (1.19–1.36)	0.71 (0.62–0.80)
3	37.0 (32.7–41.3)	77.2% (76.1–78.3)	1.62 (1.43–1.84)	0.82 (0.76–0.88)
4 or 5	13.4 (10.4–16.5)	93.7% (93.0–94.3)	2.13 (1.66–2.73)	0.92 (0.89–0.96)
>65 y§				
0	0.0	100.0	—	—
1	83.8 (79.9–87.6)	17.0 (15.5–18.5)	1.01 (0.96–1.06)	0.96 (0.74–1.23)
2	52.4 (47.2–57.6)	49.7 (47.8–51.7)	1.04 (0.94–1.15)	0.96 (0.85–1.08)
3	19.4 (15.2–23.5)	79.8 (78.3–81.4)	0.96 (0.77–1.19)	1.01 (0.96–1.07)
4 or 5	4.3 (2.2–6.4)	96.1 (95.3–96.9)	1.09 (0.64–1.62)	1.00 (0.97–1.02)

AUC, Area under the receiver operating characteristic curve; *−LR,* negative likelihood ratio; *+LR,* positive likelihood ratio.
*AUC=0.591.
†AUC=0.763.
‡AUC=0.602.
§AUC=0.518.

we believe that this study possesses generalizability to the ED population because our methodology mimics conventional ED practice in which confirmation of cardiac risk factors is challenging.

In our analysis, cardiac risk factors were treated as dichotomous variables, which is not physiologically accurate, because certain diseases (eg, hypertension, hypercholesterolemia) have a spectrum of severity. Patients with severe hypertension or hypercholesterolemia may have increased acute coronary syndromes risk compared to those with mild disease. In addition, it is unknown how long our patients had these cardiac risk factors. Patients with positive risk factors for a longer period may have higher risk for acute coronary syndromes. We also did not account for past smoking history. In addition, cardiac risk factors were equally weighted when cardiac risk factor burden was calculated; the purpose of the study was not to develop a clinical prediction rule for acute coronary syndromes but to assess the clinical utility of a common clinical practice in which clinicians tend to weight cardiac risk factors equally.

In the i*tr*ACS* database, the presence of cardiac risk factors, and not their absence, was documented. Three thousand eight hundred fifty-eight patients had missing information for all risk factors. We assumed these to represent the absence of all cardiac risk factors, although it is possible some records in those with acute coronary syndromes risk factors were truly missing. If we had chosen to eliminate patients according to missing cardiac risk factor information, we would have biased our sample toward the older age groups. To assess possible error arising from including these patients, we evaluated the rate of acute coronary syndromes among those with and without risk factor information. Patients with missing history were the youngest and had the lowest acute coronary syndromes rates (Table E2; available online at http://www.annemergmed.com). The data suggest it is acceptable to consider the missing data as negative, given the low rate of acute coronary syndromes and young age in this group.

Verification bias may have occurred because not all patients received cardiac catheterization. Young patients with no risk factors may have been less likely to receive cardiac catheterization, and patients with unstable angina may have been missed. We have also previously reported that blacks are less likely to receive noninvasive testing and cardiac catheterization, which may explain why being white was independently associated with acute coronary syndromes.[16]

In addition, we defined a positive biomarker as either (1) 2 measures considered positive and at least 1 measure above twice the upper limit of normal or (2) measured only once, with the result at least 3 times the upper limit of normal. Patients with

diagnostic-related group codes of acute myocardial infarction had to have a positive biomarker. It is possible that patients had 2 sets of increased cardiac biomarker levels but none that were above twice the upper limit of normal. As a result, the incidence of acute coronary syndromes may have been underestimated, and the diagnostic performance may have been overestimated.

Some of the 95% CIs were wide because of the small sample size of certain subgroups. Because this was a post hoc analysis of an existing database, we were limited by the available data. Additional studies with larger samples will need to be performed to gain better precision of these estimates.

DISCUSSION

Population-based studies have shown that individual risk factors are associated with cardiovascular disease,[17-20] but they are often excluded from clinical decision rules because of their limited clinical utility.[21-25] Jayes et al[2] found that the addition of cardiac risk factors minimally increased the area under the receiver operating characteristic curve of the Acute Cardiac Ischemia Time Insensitive Prediction Instrument. However, the relationship between cardiac risk factor burden and acute coronary syndromes in the ED setting has not been well characterized.

We found that as the number of cardiac risk factors increased, the odds of acute coronary syndromes incrementally increased. Recently, the Framingham Heart Study found that participants with 2 or more cardiac risk factors had a much higher risk of death compared with patients with zero or 1 factor.[3] However, this study consisted of asymptomatic patients living in the community and cannot be generalized to the ED environment. Pollack et al[26] studied the Thrombolysis in Myocardial Infarction risk score in an ED population and observed that patients with 3 or more risk factors had an OR of 1.9 (95% CI 1.5 to 2.5) for 30-day death, acute myocardial infarction, or revascularization. However, other categories of cardiac risk factor burden were not reported.[27]

We found that the relationship between cardiac risk factor burden and acute coronary syndromes was significantly modified by age. For patients older than 65 years, cardiac risk factor burden was less useful for the prediction of acute coronary syndromes. These findings reflect that older age is a powerful risk for acute coronary syndromes in and of itself.

For patients younger than 40 years, we observed that as the number of total cardiac risk factors increased, the odds of acute coronary syndromes dramatically increased. Acute coronary syndromes in patients younger than 40 years is not rare; it is estimated that 4% of all acute myocardial infarctions are in this younger group.[28] Despite this, the role of cardiac risk factors in patients younger than 40 years has not been well studied. As did we, Walker et al[11] found that only 0.3% of young patients with no cardiac risk factors and a normal ECG result had acute coronary syndromes. Marsan et al[12] found that patients younger than 40 years and without any cardiac risk factors, with no adverse cardiac history, and with normal ECG results had a 30-day adverse cardiovascular event rate of 1.0%. Because of the low risk for acute coronary syndromes in young patients with no risk factors, the presence of any risk factor dramatically increases the odds for acute coronary syndromes.

Although we found a statistical association between the cardiac risk factor burden and the presence of acute coronary syndromes, the usefulness of this measure in the clinical setting appears to be limited. The receiver operating characteristic curves indicated that the total number of risk factors had poor diagnostic performance, except in patients younger than 40 years, in which the absence of risk factors moderately decreased the probability of acute coronary syndromes and the presence of 4 or more risk factors moderately increased the probability of acute coronary syndromes. In patients 40 years and older, the likelihood ratios for each cardiac risk factor burden cutoff were insufficient to be used in the clinical setting. In these patient groups, the absence of cardiac risk factors was not sufficient to rule out acute coronary syndromes. Thus, although ORs are helpful in describing statistically significant and independent associations, they do not necessarily reflect clinical relevance.

In conclusion, we found that in ED patients with suspected acute coronary syndromes, the greater the number of cardiac risk factors identified, the greater the odds of acute coronary syndromes being present. However, this association was observed predominantly in patients younger than 40 years and was not observed in those 65 years or older. Cardiac risk factor burden has limited clinical value, especially in patients 40 years and older.

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Author contributions: The post hoc analysis was conceived mainly by JHH, CJL, ABS, and SL; however, the rest of the authors had significant input on the direction of this analysis. The statistical analysis was performed primarily by JHH and CJL. The i*tr*ACS* project was conceived and designed by JWH, JEH, WFP, CVP, and WBG. JWH, JEH, WFP, CVP, and WBG were responsible for obtaining funding and for data collection and quality control. JHH drafted the article, and all the authors contributed substantially to its revision. JHH takes responsibility for the paper as a whole.

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Table E1. Initial logistic regression model with main and 2-factor interactions effects, using type 3 analysis of effects.*

Variables	*df*	χ^2	*P* Value
Main			
Agecat, y (<40, 40–65, >65)	2	85.18	<.001
Men	1	68.75	<.001
White	1	63.68	<.001
Previous CAD	1	13.89	.001
Cardiac RF burden	4	48.1	<.001
Interaction			
Agecat×cardiac RF burden	8	37.96	<.001
White×cardiac RF burden	4	5.09	.278
Male×cardiac RF burden	4	6.64	.156
Previous CAD×cardiac RF burden	4	7.41	.116

Agecat, Age category (<40, 40–65, >65 years old); *CAD,* coronary artery disease; *RF,* risk factor.
*After each nonsignificant (*P*>.05) interaction was systematically removed, only the age category×cardiac risk factor burden interaction was significant.

Table E2. Mean (SD) age and percentage with acute coronary syndromes in patients, with 3,858 patients with missing history and negative and positive history of diabetes.

Variable	Missing History	Negative Diabetes History	Positive Diabetes History
Mean age, y (SD)	45.81 (15.05)	58.27 (15.20)	59.23 (13.97)
Acute coronary syndromes	4.4%	9.2%	11.9%