ORIGINAL ARTICLE

TIMI risk score: does it work equally well in both males and females?

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Objective: The TIMI (Thrombolysis In Myocardial Infarction) risk score is a seven item risk stratification tool derived from trials of patients with non-ST segment elevation acute coronary syndromes (ACS) that has been validated in emergency department (ED) patients with potential ACS. We hypothesised that it might have different prognostic abilities in male and female patients.

Methods: This was a prospective cohort study of ED patients with potential ACS. Data included demographics, medical and cardiac history, and components of the TIMI risk score. Investigators followed the hospital course daily. The main outcome was death, acute myocardial infarction (AMI), or revascularisation within 30 days as stratified by TIMI risk score and compared between genders using χ^2 tests.

Results: There were 2022 patients enrolled: 1204 (60%) females and 818 (40%) males. The incidence of 30 day death, AMI, revascularisation (n = 168) according to TIMI score is as follows (female vs male): TIMI 0 (n = 670), 1.6% vs 2.0%, p = 0.2; TIMI 1 (n = 525), 4.6% vs 8.5%, p = 0.02; TIMI 2 (n = 378), 6.3% vs 10.4%, p = 0.05; TIMI 3 (n = 234), 6.5% vs 24.6%, p<0.001; TIMI 4 (n = 157), 22.7% vs 24.4%, p = 0.15; TIMI 5 (n = 52), 35.5% vs 39.1%, p = 0. 2; TIMI 6 or 7 (n = 6), 33.3% vs 66.7%, p = 1.0. The relationship between TIMI score and outcome was highly significant (p<0.001) for each gender; however, males tended to have worse outcomes at lower TIMI risk scores.

Conclusions: The TIMI risk score successfully risk stratifies both males and females with potential ACS at the time of ED presentation; however, males have worse outcomes at lower TIMI scores than females.

In the United States, coronary artery disease is the single largest killer of both men and women, with one death occurring every minute.[1] Several algorithms such as the TIMI (Thrombolysis In Myocardial Infarction) risk score have been developed in order to risk stratify patients with coronary artery disease.[2–4] However, risk stratification of female patients with coronary artery disease remains difficult due to their atypical presentations and variable responses to traditional screening methods.[5–7]

There have been a number of studies which indicate that there are distinct differences with respect to the presentation of acute coronary syndromes (ACS) in men and women.[5 8] There are also differences in the impact of individual risk factors in men and women with ACS,[9 10] as well as differences in the predictive value of standard diagnostic testing between the genders.[7 11] Most of the risk stratification algorithms that physicians have come to rely on are based on presenting symptoms, risk factors, and results of diagnostic testing.[2 12 13] Differences in presentation and risk factors between genders raises the question as to whether risk stratification models can be expected to be equally effective in women as in men.

The TIMI risk score is a seven item tool that does not rely on presentation specific details that was originally derived in patients with non-ST segment ACS to predict 14 day outcomes. It has been validated for use in the emergency department (ED) to predict 30 day likelihood of death, acute myocardial infarction (AMI), or revascularisation in a broad based ED patient population.[14 15]

Since the TIMI risk score does not rely on presentation specific characteristics, it is plausible that it is relatively gender blind and can function equally well in men and women despite the fact that women have more atypical presentations. In the present study, we investigated whether gender had an impact on the ability of the TIMI risk score to predict adverse cardiovascular events within 30 days of the initial presentation.

METHODS

Study design

This was a prospective cohort study to determine the differences in the ability of the TIMI risk score to diagnose initial presenting symptoms and predict cardiac events (death, AMI and revascularisation) within 30 days of presentation in men versus women who present to the ED with potential ACS. The study was conducted after approval by our institutional review board and patients provided informed consent.

Study setting and population

Patients were enrolled between 1 July 2003 and 31 July 2005 at an urban tertiary care hospital ED with an annual census of approximately 51 000. Patients >30 years of age who presented to the ED with a chief complaint of chest pain and received an ECG for evaluation of potential ACS were included. Patients were excluded if they were <30 years of age, did not have chest pain, or did not receive an ECG. Patients who self-reported or tested positive for recent cocaine use were also excluded, since the TIMI risk score does not work well in cocaine users and cocaine use is more common in men.[16 17]

Study protocol

Trained research assistants screened and enrolled patients in the ED 16 h a day, 7 days per week using a standardised protocol.[18] Patient information was obtained via a standardised

Abbreviations: ACS, acute coronary syndromes; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; ED, emergency department; TIMI, Thrombolysis In Myocardial Infarction

data collection form at the time of presentation to the ED. Data included demographics, medications, initial vital signs, physical examination, characteristics of chest pain and associated symptoms, cardiac risk factors, prior cardiac testing, ECG interpretation, calculated TIMI risk score, and final ED diagnosis. All core criteria in the standardised reporting guidelines were collected.[19] Admitted patients were followed daily during their hospital stay and any complications or interventions were recorded. Patient follow-up was obtained via telephone 30 days after presentation. Patients or their proxies were questioned about the occurrence of death, MI and revascularisation. We used patient or proxy report as the 30 day outcome. There was no independent verification.

Table 1 Baseline characteristics of study population

Patient characteristics	Female n (%)	Male n (%)
Mean (SD) age (years)	54 (14.5)	53 (13.5)
Race		
African American	897 (75)	447 (55)
Caucasian	273 (23)	338 (41)
Asian	22 (2)	19 (2)
Hispanic	7 (0.6)	9 (1)
Chest pain onset (min)	240	192
Chest pain duration (min)	120	90
Cardiac risk factors		
Hypertension	666 (55)	470 (58)
Diabetes	256 (21)	172 (21)
Elevated cholesterol	301 (25)	174 (21)
Family history of CAD	195 (16)	112 (14)
Tobacco use	412 (34)	357 (44)
Past medical history		
Coronary artery disease	215 (18)	210 (26)
Congestive heart failure	144 (12)	106 (13)
Angina	166 (14)	154 (19)
Myocardial infarction	146 (12)	141 (17)
Undiagnosed chest pain	145 (12)	73 (9)
Prior CABG	42 (4)	65 (8)
Prior stress testing	331 (28)	264 (32)
Abnormal findings	43 (13)	62 (24)
Prior cardiac catheterisation	219 (18)	207 (25)
Abnormal findings	93 (43)	110 (53)
TIMI risk factors		
Age ⩾65	279 (23)	155 (19)
Known coronary stenosis	180 (15)	202 (25)
Cardiac risk factors ⩾3	288 (24)	250 (31)
ASA use in prior 7 days	366 (30)	313 (38)
Anginal events ⩾2 over past 24 h	396 (33)	256 (31)
ST segment deviation	45 (4)	64 (8)
Elevated cardiac markers	55 (5)	56 (7)
Initial ECG impression		
Normal	643 (53)	373 (46)
Non-specific	345 (29)	204 (25)
Early repolarisation	9 (0.8)	22 (3)
Abnormal, not diagnostic	93 (8)	84 (10)
Ischaemia, known to be old	63 (5)	57 (7)
Ischaemia not known to be old	43 (4)	49 (6)
Suggestive of myocardial infarction	8 (0.7)	27 (3)
Other ECG findings		
ST segment elevation	44 (4)	70 (9)
Q waves	62 (5)	63 (8)
Left bundle branch block	35 (3)	21 (3)
Right bundle branch block	32 (3)	44 (5)
Initial ED diagnosis		
AMI	23 (2)	30 (4)
Angina	263 (22)	237 (29)
Atypical chest pain	446 (37)	283 (35)
Non-ischaemic chest pain	467 (39)	267 (33)

AMI, acute myocardial infarction; ASA, acetylsalicylic acid (aspirin); CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; ECG, electrocardiogram; ED, emergency department.
All values are reported as absolute number and percent frequency occurrence unless otherwise noted.

Definitions

Myocardial infarction at index presentation was defined using the European Society of Cardiology criteria of serially elevated cardiac troponin I >2 ng/ml or creatine kinase (CK)-MB >10 ng/ml.[20] Revascularisation was defined as percutaneous coronary intervention and/or coronary artery bypass graft surgery (CABG). Death was defined as all cause mortality. Patients diagnosed with myocardial infarction during the index visit were included as an adverse outcome; thus the TIMI score was being assessed to both diagnose AMI during initial visit as well as during the 30 day follow up period.

Data analysis

Data were entered into a Microsoft Access 97 database (Microsoft, Redmond, Washington, USA) and were imported into SAS 9.1 (SAS Institute, Cary, North Carolina, USA) for statistical analysis. Continuous data are presented as either means with standard deviations or medians, based upon the distribution of the data. Categorical data are presented as the percent frequency occurrence. The relationship between the TIMI risk score and the triple composite outcome was analysed using χ^2 testing and the Cochran-Armitage trend test. Comparisons between genders at each level of TIMI risk were made using Fisher exact tests.

RESULTS

There were a total of 2190 patients who met the inclusion criteria and were enrolled in the study. Of these, 121 were excluded because of recent cocaine use. An additional 47 (2.2%) patients were excluded due to incomplete follow-up. Of the remaining 2022 patients, 818 (40.5%) were males and 1204 (59.5%) were females. The mean (SD) age of the study population was 54 (14.5) years for females and 53 (13.5) years for males. Patient demographics and presenting characteristics are shown in table 1.

Of the 2022 patients, 577 were discharged home (28.5%); 1098 were admitted to the telemetry floor (54.3%); 147 were admitted to the intensive care unit (7.3%); 118 were admitted to non-telemetry floors (5.8%); 26 went directly to the cardiac catheterisation unit (1.3%).

During the index presentation, the incidence of adverse events was similar between male and female patients (table 2). The TIMI risk score was strongly related to 30 day adverse events in both male and female patients (tables 3 and 4); however the TIMI risk score was associated with a higher likelihood of adverse events in males versus females within the low to intermediate risk groups.

DISCUSSION

Risk stratification of patients with chest pain is an integral part in the management of potential ACS. Maitland *et al*[21]

Table 2 Individual outcomes stratified by gender

	Female (n = 1204)	Male (n = 818)	p Value
In hospital			
Death	11 (0.9%)	3 (0.4%)	0.18
AMI	49 (4.1%)	56 (6.9%)	0.008
Revascularisation	25 (2.1%)	56 (6.9%)	<0.0001
Triple composite	67 (5.6%)	81 (9.9%)	0.0003
30 day			
Death	13 (1.1%)	7 (0.9%)	0.66
AMI	0 (0)	4 (0.5%)	0.026
Revascularisation	5 (0.4%)	12 (1.5%)	0.013
Triple composite	18 (1.5%)	22 (2.7%)	0.07

AMI, acute myocardial infarction.

Table 3 TIMI risk score and triple composite outcome stratified by gender

TIMI score	Female* (n = 1204)	Male* (n = 818)	p Value
0 (n = 670)	7/423 (1.6%)	5/247 (2.0%)	0.2
1 (n = 525)	15/326 (4.6%)	17/199 (8.5%)	0.02
2 (n = 378)	14/224 (6.3%)	16/154 (10.4%)	0.05
3 (n = 234)	8/124 (6.5%)	27/110 (24.6%)	0.001
4 (n = 157)	17/75 (22.7%)	20/82 (24.4%)	0.15
5 or 6 (n = 58)	11/32 (34.4%)	11/26 (42.3%)	0.2

*p<0.001 test for trend signifying higher TIMI scores predict higher likelihood of adverse events.

Table 4 TIMI risk score and composite outcome (acute myocardial infarction or death) stratified by gender

TIMI score	Female* (n = 1204)	Male* (n = 818)	p Value
0 (n = 670)	6/423 (1.4%)	4/247 (1.6%)	1.0
1 (n = 525)	13/326 (4.0%)	11/199 (5.5%)	0.5
2 (n = 378)	12/224 (5.4%)	15/154 (9.7%)	0.1
3 (n = 234)	4/124 (3.2%)	17/110 (15.5%)	0.001
4 (n = 157)	13/75 (17.3%)	11/82 (13.4%)	0.5
5 (n = 52)	7/29 (24.1%)	6/23 (26.1.3%)	1. 0
6–7 (n = 6)	0/3 (0%)	2/3 (66.7%)	0.4

*p<0.001 test for trend signifying higher TIMI scores predict higher likelihood of adverse events.

demonstrated that without the use of risk stratification tools, a significant number of patients are admitted to inappropriate units within the hospital: high-risk patients were mistriaged to floor beds and low-risk patients mistriaged to intensive care units. The use of risk stratification tools allows us to optimise patient care and improves cost-effectiveness.

The TIMI risk score was shown to predict adverse cardiac events within 14 days of the initial presentation in patients already identified as having ACS.[2 22–25] It also has been shown to both diagnose AMI at presentation and predict 30 day or longer outcomes in a broad based ED patient population with potential ACS.[14 15 26] In this study, we examined the ability of the TIMI risk score to risk stratify both men and women, and found that although it worked for both genders, men were at generally higher risk at lower TIMI scores. The TIMI risk score can effectively categorise patients who most benefit from hospital admission and early aggressive treatment.[2 27] This may be especially useful with female patients, who often present with atypical symptoms and non-diagnostic ECGs, making diagnosis more difficult. This may be because the TIMI risk score is not as reliant on presentation characteristics as other risk stratification tools. It relies on objective assessment of age >65 years, prior diagnoses (known coronary disease; the presence of three or more traditional cardiac risk factors; prescribed aspirin (indicating vascular disease)), and objective measures of ischaemia (elevated markers, ST segment changes) for six of the seven items. Only ''severe angina'', which is most commonly interpreted as two or more symptomatic episodes, has a subjective component. The fact that it is comprised of items that are objective may explain its ability to be an accurate risk stratification tool, even in the setting of atypical presentations, which are more common in women.

In light of continuously emerging information pointing to the gender differences of individual risk factors, presentation, and outcomes in ACS, risk stratification for women has been re-evaluated. However, the only risk stratification model specifically designed for women was proposed by Douglas and Ginsburg in 1996.[28] Since then studies have shown that even though women and men presenting with ACS differ, their outcomes are still ultimately dependent on the severity of the illness and not gender.[29] While our study has shown that the TIMI risk score is a good predictive tool in both men and women, we did see a difference with low to intermediate risk patients. Men tended to have worse outcomes than women in the low to intermediate risk groups. A study by Chiriboga *et al*[30] demonstrated that men were much more likely to receive revascularisation procedures than women during hospitalisation for AMI. Our data are similar, as they suggest that men were more likely to receive revascularisation. To eliminate the possibility that the relationship between gender and TIMI risk could be impacted by workup bias (with men receiving more tests and therefore more revascularisation procedures), we performed a secondary analysis that evaluated the composite outcome of death and AMI alone (table 4). The result was consistent with our primary analysis—men still had more adverse events in low to intermediate groups. The slightly increased rate of AMI at 30 days in men is difficult to explain, particularly in view of their increased rate of revascularisation.

Study limitations

There were several limitations to this study. Patients with a self reported history of cocaine use were excluded from the study. However, we cannot be sure that those who were included did not actually use cocaine as urine drug testing was not routinely performed. In order to reduce the risk of this selection bias, we utilised trained research assistants who were present in the ED 16 h per day, 7 days a week. They screened all patients who presented to the ED with chest pain for possible eligibility. We did not examine patients with possible anginal equivalents, such as shortness of breath, which might be more common in women. However, patients with atypical presentations often have a lower ''rule in'' rate and would have biased the study toward further exaggeration of any difference between genders.

Misclassification bias was also reduced by establishing clear definitions of our outcomes (death, AMI, revascularisation). We relied on daily in-hospital tracking of study patients to obtain pertinent information as opposed to medical chart review. We could be prone to some misclassification of our 30 day outcomes since we relied on patient or proxy self report; however, revascularisation and death are straightforward, and AMI after hospital discharge only occurred in four patients. Finally, our study was conducted in an urban, inner-city academic hospital with a predominantly African American patient population; therefore, our results may or may not be applicable to different hospital settings and patient populations.

Conclusions

The TIMI risk score is a good risk stratification tool in both men and women who present to the ED with potential ACS. For low to intermediate risk patients, however, men were more likely than women to have 30 day adverse events.

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