### Abstract:

Objective: The Thrombolysis in Myocardial Infarction (TIMI) score is a validated tool for risk stratification of acute coronary syndrome (ACS). We hypothesized that the TIMI risk score would be able to risk stratify observation unit patients for ACS.

Methods: Study Design: Retrospective cohort study of consecutive adult patients placed in an urban academic hospital emergency department observation unit with an average annual census of 65,000 between 2004 and 2007. Exclusion criteria included elevated initial cardiac biomarkers, ST segment changes on ECG, unstable vital signs, or unstable arrhythmias. A composite of significant coronary artery disease (CAD) indicators including diagnosis of myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, or death within 30 days and 1 year were abstracted via chart review and financial record query. The entire cohort was stratified by TIMI risk scores (0-7) and composite event rates with 95% CI were calculated.

Results: In total 2,228 patients were analyzed. Average age was 54.5 years, 42.0% male. The overall median TIMI risk score was 1. Eighty (3.6%) patients had 30 day and 119 (5.3%) had 1-year coronary artery disease indicators. There was a trend toward increasing rate of composite coronary artery disease indicators at thirty days and one year with increasing TIMI score, ranging from a 1.2% event rate at thirty days and 1.9% at one year for TIMI=0 and 12.5% at thirty days and 21.4% at one year for TIMI ≥4.

Conclusions: In an observation unit cohort, the TIMI risk score is able to risk stratify patients into low, moderate and high-risk groups.
Dear Dr. Steinberg,

Thank you so much for sending along the reviewer’s comments and recommendations for revision of the paper entitled “Thrombolysis in Myocardial Infarction Risk Score in an Observation Unit Setting.” We appreciate their constructive and thoughtful suggestions and have addressed each of them as described below.

Comment #1: My main concern is the actual clinical significance of this paper, even after careful scrutiny of the authors’ Intro and Discussion. As a practicing Emergency Physician, I am not sure how this paper would change my management. Regardless of TIMI risk score, I would still admit this same low-risk (but not zero-risk) group of patients to an OBS unit (or inpatient ward if hospital does not have OBS) for serial biomarker testing followed by cardiac stress testing. This is standard of care, regardless of modified TIMI score.

Response: It is true that all of these patients ended up in an observation unit regardless of TIMI risk score. The observed trends discussed in the paper do not necessarily indicate whether or not there is a distinct group of patients that should be sent home, but that there are distinct groups within the observation unit cohort that could be stratified by TIMI risk score and patient outcome. Before this paper it was unclear whether there was a subset of these patients that were either very high or very low risk for ACS and whether the TIMI score could easily identify such patients. It was also unclear whether the TIMI score could identify those who needed a higher level of care than observation. Using this information to guide clinical practice is beyond the scope of the paper and will require further study.

Comment #2: I re-read the original TIMI risk score paper by Antman et al (JAMA 2000). The TIMI score was derived from two trial databases that enrolled patients with NSTEMI or high-risk unstable angina, since enrollment required ST-deviation, elevated biomarkers, or known CAD. Hence, the derivation cohort is much higher risk than the typical OBS unit patient. Furthermore, the TIMI risk score was developed to compare the efficacy of Enoxaparin vs. UFH across the ACS risk spectrum. Thus, applying TIMI score to help better disposition low risk ACS patients does not seem appropriate, even if there is an "association" between TIMI score and adverse events.

Response: We are applying this score, which was derived in a much higher risk population, to a much lower risk population. This was an attempt at validating risk stratification based on TIMI score in patients at lower risk for ACS. It was previously not known whether or not the TIMI score could risk-stratify low risk patients based on patient outcome. Prior work suggests that the TIMI score could stratify an undifferentiated ED population. The population discussed is a narrowly selected group, namely patients without obvious ACS but whom by physician gestalt could not be safely discharged from the ED.
Comment #3: The authors’ primary endpoint looked at a composite of "adverse clinical events," but I am not convinced that most of the events (except death) were "adverse." Instead, they were "expected," as a small percentage of low-risk ACS patients will indeed rule-in for an MI with serial biomarker testing or have a positive stress test, and this will appropriately lead to PCI or CABG. In Table 3, there were only 3 deaths at 30 days and 13 at 1-year, so the study findings were really driven by these "pseudo-adverse" events.

Response: “Adverse” was perhaps a poor choice of terms. We used the term, which is a relatively standard definition of outcome, as a composite indicator of significant disease. We will use “significant coronary artery disease indicators” instead. The fact there was a predictably low rate of events in our population does not reduce the validity of using TIMI score an indicator of ACS.

Comment #4: The trends in Figure 1 look impressive on first pass, but on closer inspection it is clear that wide confidence intervals for TIMI 4 or 5 should exist. Table 4 demonstrates only 48 patients with TIMI =4, and only 8 with TIMI=5. Thus, with the authors’ study cohort restricted to low risk patients in an OBS unit, this study really only has sufficient power to look at events related to TIMI scores of 0, 1, or 2.

Response: This is true - we had wanted to be as transparent possible when presenting the data. We will group TIMI 4 and 5 into >4.

Thank you very much for your time and consideration. If there is any other information we may provide or if you have any further feedback, please let us know.

Sincerely,

Jean Chavez
Duke University School of Medicine
M.D. Candidate, Class of 2015
Title: Thrombolysis in Myocardial Infarction Risk Score in an Observation Unit Setting

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Running Title: TIMI in Observation Units
Thrombolysis in Myocardial Infarction Risk Score in an Observation Unit Setting

ABSTRACT

Objective: The Thrombolysis in Myocardial Infarction (TIMI) score is a validated tool for risk stratification of acute coronary syndrome (ACS). We hypothesized that the TIMI risk score would be able to risk stratify observation unit patients for ACS.

Methods: Study Design: Retrospective cohort study of consecutive adult patients placed in an urban academic hospital emergency department observation unit with an average annual census of 65,000 between 2004 and 2007. Exclusion criteria included elevated initial cardiac biomarkers, ST segment changes on ECG, unstable vital signs, or unstable arrhythmias. A composite of significant coronary artery disease (CAD) indicators including diagnosis of myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, or death within 30 days and 1 year were abstracted via chart review and financial record query. The entire cohort was stratified by TIMI risk scores (0-7) and composite event rates with 95% CI were calculated.

Results: In total 2,228 patients were analyzed. Average age was 54.5 years, 42.0% male. The overall median TIMI risk score was 1. Eighty (3.6%) patients had 30 day and 119 (5.3%) had 1-year coronary artery disease indicators. There was a trend toward increasing rate of composite coronary artery disease indicators at thirty days and one year with increasing TIMI score, ranging from a 1.2% event rate at thirty days and 1.9% at one year for TIMI=0 and 12.5% at thirty days and 21.4% at one year for TIMI ≥4.

Conclusions: In an observation unit cohort, the TIMI risk score is able to risk stratify patients into low, moderate and high-risk groups.

Key words: Acute coronary syndrome, observation units, risk stratification
INTRODUCTION

Chest pain is one of the most common presenting chief complaints in the emergency department (ED), accounting for approximately 6 million patients every year[1]. Many of these patients are admitted for further testing and evaluation in order to rule out an acute coronary syndrome (ACS) due to the nonspecificity of history and exam for diagnosis[2, 3]. However, considering the fact that only 1 in 4 admitted patients will have a discharge diagnosis of ACS[1], the need for viable alternatives to admission is evident.

One potential solution is the Thrombolysis In Myocardial Infarction (TIMI) score[4], an easily calculable tool originally meant to address the challenge of risk stratification in patients exhibiting symptoms of unstable angina/non ST-segment elevation myocardial infarction (UA/NSTEMI)[5]. Since the score’s introduction in 2000, there have been multiple independent validations of the TIMI score for general patients presenting to an ED with chest pain or symptoms suspicious for MI with respect to 30 day and 1-year outcomes[6-15]. Comprised of seven binary variables that evaluate patient history, ECG changes, clinical presentation, cardiac enzymes, aspirin use, and age, the TIMI score is readily utilized in clinical practice. However, it is not known whether this score retains its discriminative function when applied to a population that is already deemed low risk by physician gestalt, such as that found within a typical observation unit. One initial study suggests that TIMI does correlate with adverse events, however this study was limited by a small number of outcomes[16].

Patients placed in observation units for chest pain represent the most challenging disposition decisions, since they do not clearly require inpatient admission but are not considered safe for discharge directly from the ED. The goal of our investigation was to determine whether the TIMI score has utility as a risk stratification tool for ACS in a population of patients placed in an observation unit based on physician gestalt. Specifically, we sought to determine whether there was a correlation between higher rates of composite coronary artery disease indicators (myocardial infarction, revascularization procedure, or death) within 30 days or 1 year with
higher TIMI scores. We secondarily sought to determine the rates of abnormal cardiac stress testing with progressively higher TIMI scores.

**METHODS**

**Study Design**

This was a retrospective observational cohort study of patients older than 18 years of age who were evaluated for acute coronary syndrome in an ED-based observation unit at an urban academic tertiary care hospital ED with an average annual census of 65,000 visits from 2004 to 2007.

**Study Setting and Population**

Patients who presented to the emergency department with potential symptoms of ACS were eligible for this study. Patients were included if, after emergency department evaluation, the treating attending physician determined that they need further risk stratification for ACS and were stable for the observation unit but did not have acute ST segment changes on ECG, positive initial cardiac biomarkers, unstable vital signs, or unstable dysrhythmias. In this observation unit, patients with suspected ACS received serial cardiac markers (Roche Elecsys Troponin T), ECGs, and cardiac stress testing according to a defined protocol. The choice of stress test modality was guided by protocol, but the treating emergency physician made any final decisions regarding stress testing in consultation with a board-certified cardiologist. All stress tests were performed by board-certified cardiologists according to standard guidelines.

**Study Protocol**

Since all the data for this study were drawn from an existing database created for quality assurance purposes, this study received exemption from human subjects research review by our Institutional Review Board (IRB). Patients were identified by clinical records documenting consecutive patients who were cared for in our emergency department-based observation unit. We obtained data via retrospective data abstraction from electronic medical records. A total of 6 research staff abstracted data, all of whom were blinded to this hypothesis. All abstractors were
trained in a one-hour didactic session in which the data abstraction spreadsheet, data variable definitions, and electronic patient record format were reviewed. The abstractors also completed a practice set of ten records that had been previously reviewed by the senior investigator, and they thereafter used a standardized abstraction form. Abstractors used the treating emergency physician’s notes as the source of all data and any TIMI risk factor not recorded was assumed to be absent. The senior investigator periodically met with abstractors to assess for problems or questions. Ten percent of the patient records were independently abstracted by a second reviewer and outcomes were compared for inter-rater reliability. All patients’ electronic medical charts were reviewed for at least 1 year after their index visit. We also checked our institutional financial billing records via a web-based portal for any International Classification of Disease-9 codes for acute myocardial infarction, coronary angioplasty, coronary stent placement, coronary artery bypass surgery, and death.

Measures

Our primary outcome was a composite of acute myocardial infarction (either ICD-9 code or a subsequent troponin elevation >0.1 ng/mL), coronary angioplasty, coronary stent placement, coronary artery bypass surgery, and death within 30 days and 1 year. Our secondary outcome was a positive cardiac stress test: either wall motion abnormalities during stress echo or reversible perfusion defect on nuclear imaging or cardiac magnetic resonance imaging.

Data Analysis

Simple proportions and means were calculated for baseline characteristics. The entire cohort was stratified by TIMI risk scores (0-7) and binomial proportions with 95% confidence intervals for the rate of significant coronary artery disease indicators and positive stress tests were calculated using SAS Enterprise Guide 4.2 (Cary, NC).

RESULTS
In total, 2,231 patients at low risk for potential ACS were placed in the ED observation unit during the study period. A total of three patients had missing record information and were excluded from analysis because TIMI score could not be calculated. For the remaining patients, 42% were male and the overall mean age was 54.5. The overall demographics are shown in Table 1 and distribution of TIMI risk score components is shown in Table 2. The overall median TIMI risk score was 1. The most common TIMI risk components was age >65 years. Of note, patients with either elevated troponins or ECG ST segment changes were systematically excluded from the observation unit and thus our study. However, 17 patients were placed in observation despite elevated troponin values, presumably because these were known to be chronically elevated. These patients were initially included in the overall analysis then removed for comparison. The primary outcome was defined as composite significant coronary artery disease indicators at thirty days and one year, which included acute myocardial infarction, coronary angioplasty, coronary stent placement, coronary artery bypass surgery, and death. For the total sample, 80 (3.6%) patients had thirty-day and 119 (5.3%) had one-year coronary artery disease indicators. Sixteen patients had initially normal troponin values that subsequently elevated (Table 3).

Figure 1 and Table 4 shows the distribution of composite coronary artery disease indicators by TIMI score. There was a trend toward increasing rate of composite coronary artery disease indicators at thirty days and one year with increasing TIMI score, ranging from a 1.2% event rate at thirty days and 1.9% at one year at TIMI=0 and 12.5% at thirty days and 21.4% at one year for TIMI ≥4.

The secondary outcome was a positive cardiac stress test in the observation unit. A positive cardiac stress test was defined as wall motion abnormalities during stress echo or reversible perfusion defect on nuclear imaging or cardiac MRI. In total, 134 (6.8%) of patients had a positive stress test. With increasing TIMI score, there was a general trend of increasing rate of positive stress test ranging from 4.5% for TIMI =0 to 13.9% for TIMI ≥4 (Table 4). The TIMI score distribution for patients with chronically elevated troponins was as follows: 2 patients with
TIMI = 0, 9 patients with TIMI = 1, 5 patients with TIMI = 2, and 1 patient each with TIMI = 3 and 4. When patients with chronically elevated troponins were removed from analysis, the 30 day and 1-year event rates for TIMI = 1 and 2 were changed to 3.5%, 4.7% and 5.2%, 7.0%, respectively.

**DISCUSSION**

This study demonstrated that the TIMI risk score is able to risk stratify patients who are placed in an observation unit for potential ACS based on physician gestalt. There was a trend toward an increasing rate of composite coronary artery disease indicators at 30 days and one year, as well as positive stress testing, with increasing TIMI risk score. One other study has evaluated the use of TIMI for risk stratification of patients placed in an observation unit for ACS and demonstrated that the scoring method can be used to distinguish risk groups for adverse coronary events among this patient population but this study featured only 18 patients with adverse outcomes [16]. To date, this is the largest study to examine the TIMI risk score in an observation unit with nearly 80 patients with adverse outcomes. In revealing a trend of increasing composite indicators for coronary artery disease with increasing TIMI scores, our study affirms that TIMI can be used as a tool to measure patient risk of significant coronary artery disease indicators for those placed on an observation unit for ACS by physician gestalt.

The use of observation units within the ED for patients presenting with ACS is cost effective and reduces inpatient admissions and resource utilization [17, 18]. For this reason, it is desirable to place patients in these observation units over higher cost alternatives as long as patient safety and quality of care is maintained. In our study, while the highest rate of composite indicators for coronary artery disease was seen in the intermediate and high-risk groups, their relatively low rate of short-term coronary artery disease indicators suggests that these patients can be safely evaluated in an observation unit. Given that patients in higher risk TIMI groups can be safely evaluated in observation units, one may expect that patients of low risk TIMI groups may not
require even observation. In our study, however, even the lowest risk group still had a significant rate of coronary artery disease indicators at 30 days and 1 year and thus placement in an observational unit is still desirable.

The ease with which the TIMI score can be calculated makes the scoring method ideally suited for ACS evaluation in emergency departments and observation units. The patients in this study had already been deemed by physician gestalt as being low enough risk to not require inpatient hospitalization. This suggests that TIMI adds value above gestalt at the low end of the risk spectrum. Furthermore, removing 2 of the listed factors (ST segment deviation on ECG and elevated troponin values) did not change the results markedly, suggesting that the TIMI score could be simplified even further to just 5 criteria. This simplified TIMI rule mirrors clinical practice in that patients with these 2 eliminated factors are already triaged to inpatient management routinely[19, 20]. Examining the resource utilization impact of a simplified TIMI rule as an exclusion criteria for observation units may also contribute to improvement in the cost and quality of patient care.

LIMITATIONS

All data in this study was obtained by retrospective abstraction from electronic medical records. The accuracy and breadth of data was therefore dependent on the precision of the medical record. While our abstractors were thoroughly trained and blinded to the hypothesis, potential sources of bias and confounding variables cannot be overlooked.

The results of this study are further limited by the fact that all patient data was obtained from those seen at a single institution, namely an urban academic tertiary care hospital ED with an average annual census of 65,000 from 2004 to 2007. Thus, our results may not be applicable to patient populations seen at other institutions.

A final limitation is that patient data loss due to follow-up is uncertain. An significant indicator for coronary artery disease not recorded was assumed to be absent. It cannot be said with
certainty that the absence of indicators for coronary disease was due to the event not occurring or patients not following-up the event within the medical system in a way that led to documentation within their electronic medical records. However, we used a prolonged follow-up period, and extensive financial record database query to ascertain any significant indicators of coronary artery disease. Lack of follow up would not necessarily bias our results unless it occurred unevenly across TIMI risk score groups or led to disproportionate missing of adverse events.

CONCLUSION
The data collected and subsequent analysis indicates that the TIMI score can be used as an ACS risk stratification tool for a patient population placed in an ED observation unit based on physician gestalt. For patients placed in the observation unit, higher TIMI score was associated with an increasing rate of 30-day and 1-year composite coronary artery disease indicators. In addition, we observed a trend where higher TIMI score correlated with a greater incidence of positive stress testing. However, those that fell within the low-risk stratification group based on TIMI score still experienced significant coronary artery disease indicators, suggesting that using a patient’s TIMI score may add value to treatment decisions made based on physician gestalt.

Removing two elements of the original TIMI score, ST segment deviation on ECG and elevated troponin values did not preclude risk-stratifying these patients into low, intermediate and high-risk groups. This suggests that TIMI score, when used to risk stratify patients placed within the observation unit, may be further simplified to five elements, namely known coronary artery stenosis, aspirin use in past 7 days, >2 episodes of severe anginal symptoms, age > 65 years and 3 or more CAD risk factors.

REFERENCES


<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Age (Mean, years)</td>
<td>54.5 years</td>
</tr>
<tr>
<td>Male</td>
<td>42.0%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>47.1%</td>
</tr>
<tr>
<td>Black</td>
<td>47.5%</td>
</tr>
<tr>
<td>Other</td>
<td>5.4%</td>
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</table>
Table 2. TIMI risk score components

<table>
<thead>
<tr>
<th>TIMI* Component</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known Coronary Artery Disease (CAD)</td>
<td>462 (20.7%)</td>
</tr>
<tr>
<td>Aspirin use in past 7 days</td>
<td>426 (19.0%)</td>
</tr>
<tr>
<td>&gt;2 episodes of severe anginal symptoms</td>
<td>180 (8.0%)</td>
</tr>
<tr>
<td>Elevated troponin</td>
<td>17 (0.8%)</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>546 (24.5%)</td>
</tr>
<tr>
<td>3 or More CAD Risk Factors</td>
<td>530 (23.8%)</td>
</tr>
</tbody>
</table>

* TIMI = Thrombolysis in Myocardial Infarction Score; CAD= Coronary Artery Disease
Table 3. Total Significant Indicators for Coronary Artery Disease at 30 days and 1 year (n=2,228)

<table>
<thead>
<tr>
<th>Events</th>
<th>30 days n (%)</th>
<th>1 year n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>25 (1.1%)</td>
<td>54 (2.4%)</td>
</tr>
<tr>
<td>PCI</td>
<td>51 (2.2%)</td>
<td>66 (3.0%)</td>
</tr>
<tr>
<td>CABG</td>
<td>11 (0.5%)</td>
<td>19 (0.9%)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (0.1%)</td>
<td>13 (0.5%)</td>
</tr>
<tr>
<td>Total*</td>
<td>80 (3.6%)</td>
<td>119 (5.3%)</td>
</tr>
</tbody>
</table>

*Totals do not add up in columns because some patients had more than one event. MI- Acute myocardial infarction, PCI- percutaneous coronary intervention (angioplasty or stent), CABG- Coronary Artery Bypass Graft surgery.
Table 4. Thirty-day and 1-year Rates of Significant Indicators of Coronary Artery Disease by TIMI Risk Scores

<table>
<thead>
<tr>
<th>TIMI Score</th>
<th>n</th>
<th>30 day Rate of CAD Indicators</th>
<th>1 year Rate of CAD Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>910</td>
<td>11 (1.2%)</td>
<td>17 (1.9%)</td>
</tr>
<tr>
<td>1</td>
<td>668</td>
<td>25 (3.7%)</td>
<td>35 (5.2%)</td>
</tr>
<tr>
<td>2</td>
<td>407</td>
<td>21 (5.1%)</td>
<td>31 (7.6%)</td>
</tr>
<tr>
<td>3</td>
<td>187</td>
<td>16 (8.6%)</td>
<td>24 (12.8%)</td>
</tr>
<tr>
<td>≥4</td>
<td>56</td>
<td>7 (12.5%)</td>
<td>12 (21.4%)</td>
</tr>
</tbody>
</table>

* TIMI = Thrombolysis in Myocardial Infarction Score
Table 5. Stress Test Results by TIMI score

<table>
<thead>
<tr>
<th>TIMI Score*</th>
<th>n</th>
<th>Positive Stress Test Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>727</td>
<td>37 (4.5%)</td>
</tr>
<tr>
<td>1</td>
<td>537</td>
<td>38 (6.4%)</td>
</tr>
<tr>
<td>2</td>
<td>309</td>
<td>33 (9.8%)</td>
</tr>
<tr>
<td>3</td>
<td>128</td>
<td>24 (15.0%)</td>
</tr>
<tr>
<td>≥4</td>
<td>36</td>
<td>5 (13.9%)</td>
</tr>
</tbody>
</table>

* TIMI = Thrombolysis in Myocardial Infarction Score
Figure 1. Thirty-day and 1-year Rates of Significant Coronary Artery Disease Indicators (%) by TIMI Risk Scores