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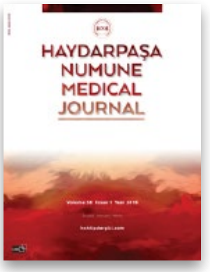

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ORIGINAL ARTICLE

Prediction of In-Hospital Mortality in ST-Segment Elevation Myocardial Infarction: What is the Role of Thrombolysis in Myocardial Infarction Risk Index?

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Abstract

Introduction: Thrombolysis in myocardial infarction (TIMI) risk index has been developed to predict the prognosis in patients with coronary artery disease. In this study, we evaluated the prognostic value of TIMI risk index in patients with ST-segment elevation myocardial infarction (STEMI) when TIMI risk index was calculated in the emergency department (ED) and patients were referred to an interventional center.

Methods: In this retrospective analysis, we evaluated the in-hospital mortality prognostic impact of TIMI risk index on 944 patients with STEMI treated with primary percutaneous coronary intervention. Patients were divided into two groups according to the presence of in-hospital mortality and the baseline features were compared between these groups. Multivariate analysis was implemented to detect independent predictors of in-hospital mortality.

Results: TIMI risk index was an independent predictor (OR: 5.75; 95% confidence interval: 2.09–15.8; p=0.0007) of in-hospital mortality besides Killip stage, chronic kidney disease, and total ischemic time according to the results of the multivariate regression analysis. ROC analysis showed that the best cutoff value of the TIMI risk index to predict in-hospital mortality was 29.3 with 79.1% sensitivity and 80.7% specificity.

Discussion and Conclusion: Our study indicated that TIMI risk index calculated in the ED is an independent prognostic factor for in-hospital mortality in patients with STEMI.

Keywords: Mortality; ST-segment elevation myocardial infarction; thrombolysis in myocardial infarction risk index.

ST-segment elevation myocardial infarction (STEMI) preserves its position as a paramount cause of in-hospital morbidity and mortality despite serious advances in interventional procedures. STEMI has a high incidence ranged from 43 to 144/100.000 per year in Europe[1]. Therefore, higher incidence and in-hospital mortality rates necessitate an accurate management in emergency departments (ED) to reach optimal medical and interventional targets in

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these fragile patients. Management of STEMI starts with the accurate designation of the patients with persistent chest pain, other ischemic symptoms and ST-segment elevation in at least two contiguous leads, and continues with revascularization of the infarct related artery as soon as possible[2]. Risk stratification has an important role to determine in-hospital and long-term outcomes and should be easily applicable in these patients at the time of the emergency admission.

Several algorithms have been postulated with the aim of predicting in-hospital outcomes in patients with STEMI. Thrombolysis in myocardial infarction (TIMI) risk score, Syntax I score, Syntax II score, and GRACE risk score have been reported to be independent predictors on in-hospital outcomes in STEMI[3-6]. While these aforementioned scores have a prognostic value, a score rapidly obtainable in an ED is still needed to assess the prognosis of the patients with STEMI. TIMI risk index, calculated using the equation (heart rate X [age/10]2)/systolic blood pressure, corresponds the feasible risk stratification in patients with STEMI. The TIMI risk index has been tested in more than 150.000 patients with STEMI from the National Registry of Myocardial İnfarction -3 and -4 databases[7]. However, there is lack of evidence in regard to predictive value of TIMI risk index in patients with STEMI when calculated by emergency medicine specialists. Thus, the aim of this study was to assess the prognostic value of TIMI risk index for in-hospital mortality in patients with STEMI, calculated in an ED before referral to the same tertiary center.

Materials and Methods

Sample and Study Design

From January 2014 to January 2017, 944 patients who diagnosed as acute STEMI and underwent primary percutaneous coronary intervention (PPCI), evaluated in two different tertiary central ED, one of which was a referral tertiary center for angiography were enrolled in our retrospective study. Inclusion criteria were (1) men or women, over 18 years old; (2) diagnosis of STEMI at ED admission; and (3) transfer to the catheterization laboratory within 12 h after symptom onset and underwent PPCI. Patients with missing variables and who were not eligible to calculate TIMI risk index were excluded to provide standardization and to test the effect of TIMI risk index on in-hospital mortality. The Local Ethical Committee of Our hospital approved the study protocol.

Baseline demographic characteristics and related clinical information were obtained from each patient at the time of ED admission. Transthoracic echocardiography was performed using a Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway) to study patients by an expert on cardiovascular imaging. Left ventricular ejection fraction was calculated using Simpson method.[8] A standard 12-lead ECG (Schiller, Cardiovit AT-10 plus) (filter 150Hz, 25 mm/s, 10 mm/mV) was obtained from all patients prior to PPCI.

Angiography was performed using non-ionic [Omnipaque 300 (ioheksol)] contrast dye in all patients. ADP-receptor blockers were given as a loading dose and the type of antiplatelet agent added to acetylsalicylic acid was left to the interventional cardiologist and the drugs administered during and after hospitalization according to the European Society of Cardiology Guidelines[9]. The duration and pressure of balloon inflation, the number of inflations, and the choice of interventional equipment, including balloon and stent, were left to the discretion of the interventional cardiologist performing the procedure.

The study population was divided into quartiles according to calculated log TIMI risk index on ED admission. The study population was also divided into two according to all cause in-hospital mortality through the STEMI hospitalization.

Definitions

In-hospital mortality was defined as death from any cause during hospitalization. Hypertension (HT) was defined as systolic pressure greater than 140 mmHg, or diastolic pressure greater than 90 mm Hg or previously diagnosed HT. Diabetes mellitus (DM) was defined as use of insulin or antidiabetic agents in the patient's medical history or a fasting glucose level greater than 126 mg/dL STEMI was defined according to the European Society of Cardiology Guidelines[10]. TIMI risk index was calculated using the equation (heart rate X [age/10]2)/systolic blood pressure.

Statistical Analysis

Quantitative variables are expressed as mean (± standard deviation) or median (interquartile range) and categorical variables were expressed as perfect (number). The distribution of variables was assessed by histogram plot and Kolmogorov–Smirnov test. After preliminary screening of data, we identified the prior candidate predictors of in-hospital mortality (TIMI risk index, sex, HT, chronic renal failure, etc.) based on clinical evidence, clinical expertise, and literature search. All predictors were assessed at the time of admission. In-hospital observed survival was the primary endpoint. Building of the risk model was conducted according to the transparent reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines. We used multivariable logistic regression models to examine the independent association of each pre-specified variables with the in-hospital survival. Regression models are also presented with results reported as odds ratio (OR) and 95% confidence interval (CI). While presenting baseline characteristics for TIMI risk index, TIMI risk index quartiles were used. Since TIMI risk index had significant right-skewed dispersion, continuous variables were classified following calculation of log TIMI risk index. Numerical variables were inserted to model as flexible smooth parameters with the aid of restricted cubic spine. Relative importance of each predictor in the models was estimated with partial χ^2 value for each predictor divided by the model's total χ^2, which estimates the independent contribution of the predictor to the variance of the outcome. After TIMI risk index was detected as an independent predictor of in-hospital mortality in logistic regression model, the relationship between TIMI risk index and in-hospital mortality was analyzed with ROC curve analysis since the frequency of missing data for all variables <10%, multiple imputation was not performed. All analyses were conducted with R statistical software (version 3.5.0). All tests were two-tailed and $p<0.05$ was considered statistically significant.

Results

Nine hundred and forty-four patients with STEMI enrolled in our study. The average age was 60.1±12.9 years. About 71.5% (675) of the participants were male and 47.7% (451) were smokers. All types of STEMI were included and the most common type of STEMI was İnferior STMI with 38.6%. Patients were divided into quartiles according to the log TIMI risk indices, below 2.66 was grouped as Q1, 2.66–3.02 as Q2, 3.02–3.41 as Q3 and higher than 3.41 as Q4. TIMI risk index of the study population was significantly right-skewed thus log TIMI risk index was used for classification. The histograms of TIMI risk index and log TIMI risk index of the study population presented are as shown in Figure 1. Comparison of demographic and clinical characteristics of patients according to quartiles of calculated log TIMI risk index are shown in Table 1. The patients in Q4 were older, had more frequency of diabetes, chronic renal failure, and HT ($p<0.001$, $p<0.001$, $p<0.001$, and $p<0.001$, respectively). The patients in Q1 had notably higher systolic and diastolic blood pressure and lower heart rate ($p<0.001$, $p<0.001$, and $p<0.001$, respectively).

In-hospital mortality rate was 10.6% in patients with STEMI in the study. Comparison of demographic and clinical characteristics of patients, according to incidence of in-hospital mortality, is shown in Table 2. In-hospital mortality group was significantly older, had had higher more frequency of DM, HT and chronic kidney disease ($p<0.001$, $p<0.001$, $p=0.014$, and $p<0.001$, respectively). Diastolic and systolic blood pressures were lower and heart rate was higher in in-hospital (+) group when compared to survivors ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). In adjusted analysis, OR was significantly increased for in-hospital mortality in patients with higher TIMI risk index (OR=17, 95% CI 10–30, $p<0.0001$). According to the results of the multivariate regression analysis, TIMI risk index was an independent predictor (OR: 5.75; 95% CI: 2.09–15.8; $p=0.0007$) of in-hospital

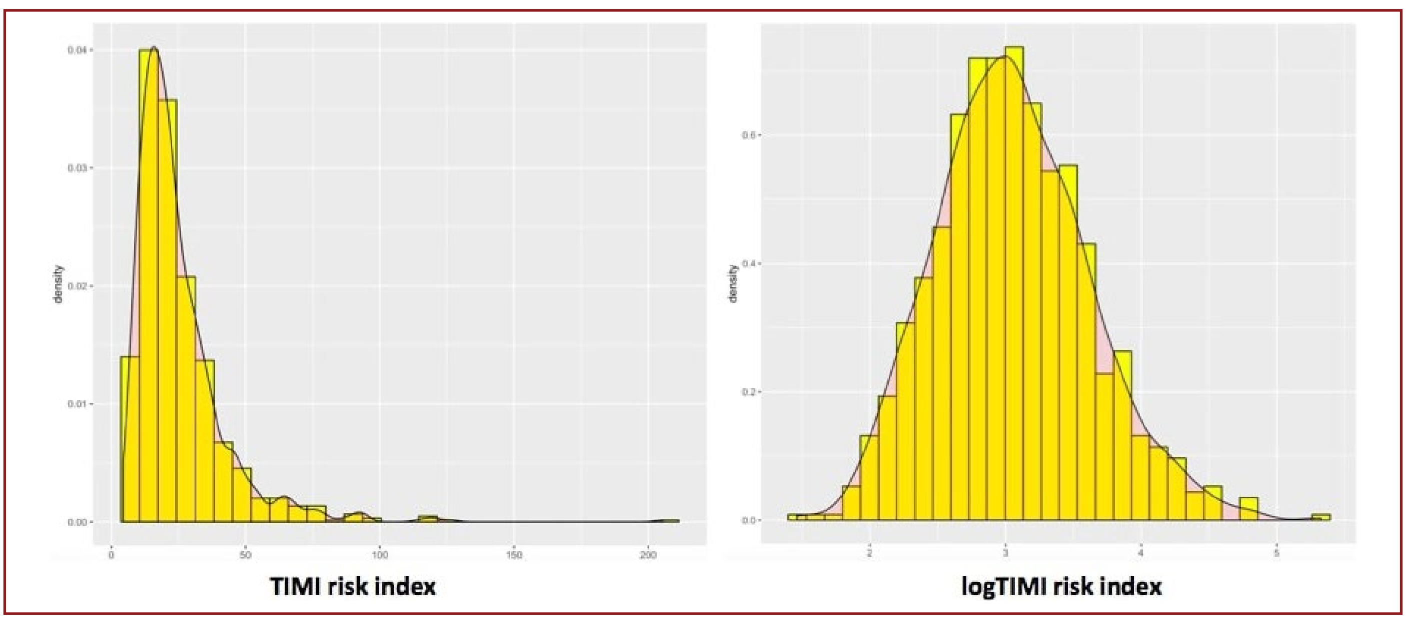

Figure 1. The histograms of thrombolysis in myocardial infarction (TIMI) risk index and log TIMI risk index of the study population.

Table 1. Comparison of demographic and clinical characteristics of patients according to quartiles of calculated log TIMI risk index. Continuous variables are presented as mean±SD. Nominal variables presented as frequency (%)

	Q1 (n=236)	Q2 (n=236)	Q3 (n=236)	Q4 (n=236)	p
Age, year	46.9±7.6	56.3±6.6	63.6±8.2	73.7±10.0	<0.001
Gender, male	194 (82)	189 (80)	168 (71)	124 (52)	<0.001
Smoking	162 (68)	137 (58)	100 (42)	52 (22.4)	<0.001
Diabetes mellitus	39 (16)	51 (21)	62 (26)	93 (39)	<0.001
Hypertension	73 (31)	73 (31)	119 (50)	137 (58)	<0.001
Heredity	95 (40)	68 (28)	47 (20)	22 (9)	<0.001
Killip class ≥2	6 (2)	14 (5)	21 (8)	63 (26)	<0.001
Cerebrovascular disease	5 (2)	9 (3)	8 (3)	22 (9)	0.006
Previous myocardial infarction	44 (18)	42 (17)	47 (19)	51 (21)	0.689
Atrial fibrillation	0 (0)	0 (0)	3 (1)	11 (4)	<0.001
Chronic kidney disease	2 (1)	4 (2)	11 (4)	25 (11)	<0.001
Revascularization	172 (72)	175 (74)	170 (72)	169 (72)	0.986
Total ischemic time, minute	150 (80–270)	180 (90–360)	240 (135–540)	270 (155–900)	<0.001
Pain-to-door time, minute	60 (30–150)	60 (30–150)	90 (30–360)	150 (60–720)	<0.001
Door-to-balloon time, minute	73 (30–143)	60 (30–140)	90 (30–180)	100 (30–180)	0.016
Systolic blood pressure, mm Hg	146±28	140±29	134±28	119±31	<0.001
Diastolic blood pressure, mm Hg	84±17	79±15	75±15	68±16	<0.001
Heart rate, beats per minute	73±16	77±17	83±19	98±23	<0.001

Table 2. Comparison of demographic and clinical characteristics of patients according to incidence of in-hospital mortality. Continuous variables are presented as mean±SD. Nominal variables presented as frequency (%)

	In-hospital mortality (–) (n=843)	In-hospital mortality (+) (n=101)	p
Age, year	58.8±12.1	69.7±14.7	<0.001
Gender, male	683 (81)	63 (62)	<0.001
Smoking	648 (76)	39 (38)	<0.001
Diabetes mellitus	221 (26)	42 (41)	<0.001
Hypertension	384 (45)	58 (57)	0.014
Heredity	254 (30)	6 (5)	<0.001
Killip class ≥2	47 (6)	67 (7)	<0.001
Cerebrovascular disease	37 (4)	12 (11)	<0.001
Previous myocardial infarction	169 (20)	33 (32)	0.002
Atrial fibrillation	14 (2)	2 (2)	0.712
Chronic kidney disease	27 (3)	21 (20)	<0.001
Revascularization	684 (81)	77 (76)	0.037
Total ischemic time, minute	180 (105–420)	570 (240–3240)	<0.001
Pain-to-door time, minute	60 (30–180)	180 (60–1440)	<0.001
Door-to-balloon time, minute	90 (30–163)	100 (40–240)	0.199
Systolic blood pressure, mm Hg	137±28	106±36	<0.001
Diastolic blood pressure, mm Hg	78±16	62±18	<0.001
Heart rate, beats per minute	81±19	96±27	<0.001
Ejection fraction	47±10	32±11	<0.001
TIMI risk index	19.3 (13.8–22.4)	44.7 (31.2–62.5)	<0.001
Log TIMI risk index	2.9±0.5	3.7±0.5	<0.001

mortality besides Killip stage (OR: 3.07; 95% CI: 2.04–4.65; p<0.0001), chronic kidney disease (OR: 4.28; 95% CI: 1.25–14.7; p=0.020), and total ischemic time (OR: 1.002; 95% CI: 1.000–1.004; p=0.024) (Table 3). The relation of log odds of in-hospital mortality with TIMI risk index was presented as shown in Figure 2. Furthermore, the importance of each

Table 3. Multivariate logistic regression analyses independent relationship between analyses between in-hospital mortality and demographic and clinical characteristics of patients

	Adjusted OR, 95% CI	p
TIMI risk index	5.75 (2.09–15.8)	0.0007
Gender, female	0.91 (0.25–3.30)	0.892
Diabetes mellitus	0.91 (0.29–2.83)	0.875
Total ischemic time	1.002 (1.000–1.004)	0.024
Hypertension	0.89 (0.28–2.78)	0.843
Previous myocardial infarction	1.20 (0.14–9.99)	0.865
Revascularization	0.89 (0.32–2.50)	0.830
Chronic kidney disease	4.28 (1.25–14.7)	0.020
Smoking	1.01 (0.48–2.13)	0.972
Killip class	3.07 (2.04–4.65)	<0.0001

CI: Confidence interval.

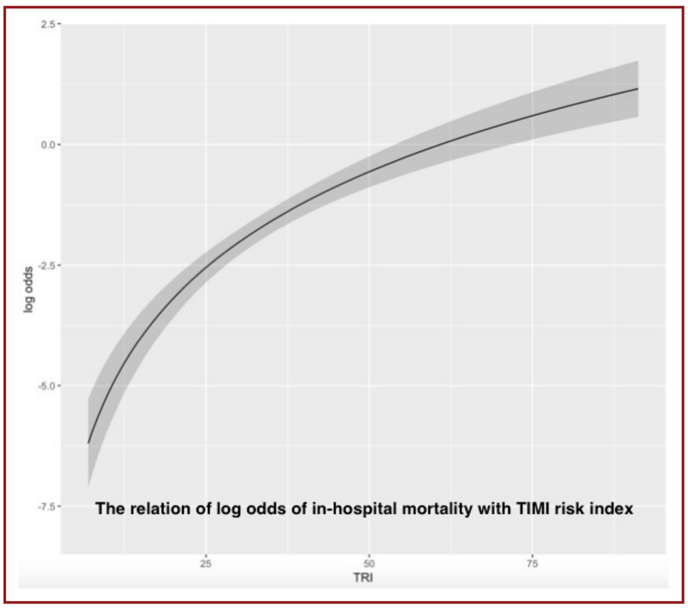

Figure 2. The relation of log odds of in-hospital mortality with thrombolysis in myocardial infarction risk index.

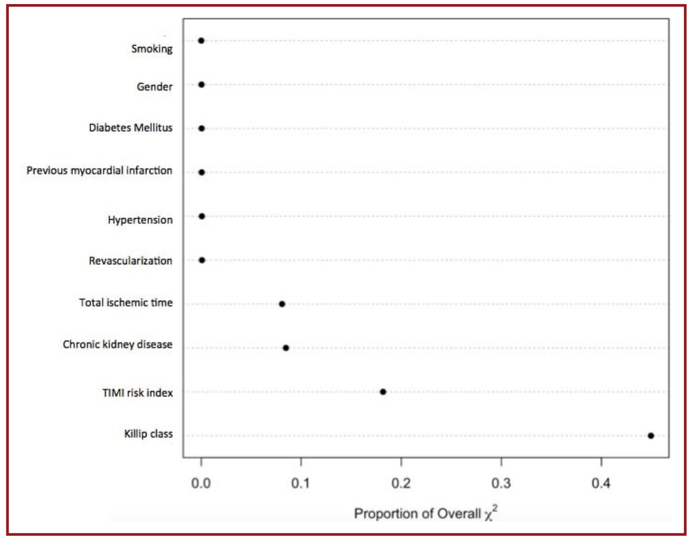

Figure 3. The importance of each predictor in our model.

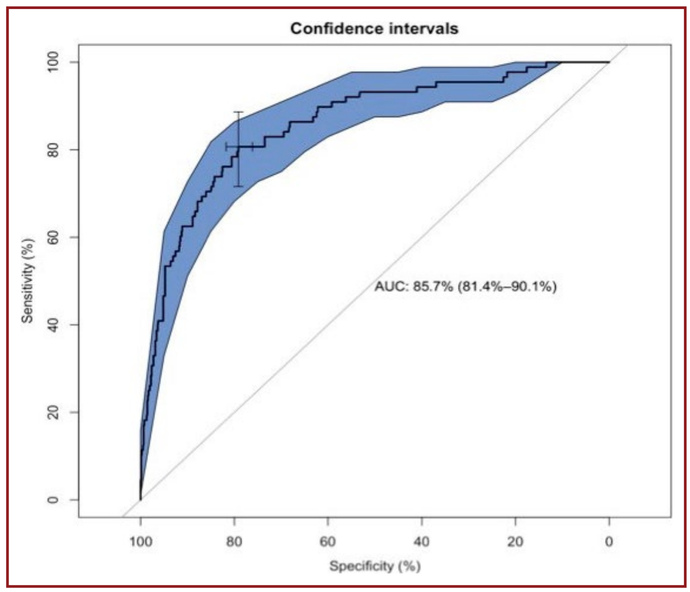

Figure 4. Cutoff value of the thrombolysis in myocardial infarction risk index to predict in-hospital mortality.

predictor in our model was calculated as the proportion of explainable outcome variation contributed by each predictor is presented in Figure 3 (variable importance). ROC analysis showed that the best cutoff value of the TIMI risk index to predict in-hospital mortality was 29.3 with 79.1% sensitivity and 80.7% specificity (AUC: 0.85; 95% CI: 0.81–0.90; p<0.001), as shown in Figure 4.

Discussion

Data considering the association of the TIMI risk index calculated by emergency medicine specialists and in-hospital mortality in STEMI was limited. Our in-hospital follow-up study evaluating TIMI risk index in patients with STEMI revealed TIMI risk index as an independent prognostic factor for prediction of in-hospital mortality. Moreover, total ischemic time, chronic kidney disease, and Killip class were also demonstrated to be additional independent predictors of in-hospital mortality in patients with STEMI.

TIMI risk index includes three vital parameters have been already tested for prognostic purposes individually. Even though age has not been demonstrated as an independent predictor of in-hospital mortality in several studies, it also appears as a contributing factor for risk scores such as TIMI risk score and GRACE score[11,12]. Similarly, in our study, age was not demonstrated to be an independent in-hospital mortality predictor. On the other hand, when included in the calculation of TIMI risk index, age contributed the higher sensitivity and specificity of TIMI risk index to predict in-hospital mortality. Considering systolic blood pressure, it has been reported to be an independent predictor of in-hospital mortality in different cohort of patients with STEMI[13,14]. As a matter of fact, cardiogenic shock, which is characterized with a fatal myocardial contractile deterioration causing failure to provide sufficient cardiac output, includes decreased systolic blood pressure and during the course of STEMI, cardiogenic shock is classified as Killip-4 presentation with the worst outcomes[15]. Accordingly in--hospital mortality in STEMI has been strictly associated with the increased admission heart rate, especially in heart rate ≥90 beat per minute[16]. TIMI risk index has been correlated with in-hospital mortality with the significant effect of these prognostic components in a previous study[7]. In our study, following the calculation of TIMI risk index in the ED and referral of patients to a tertiary center, TIMI risk index with its unsophisticated structure was proved to be a powerful independent predictor of in-hospital mortality.

Door-to-balloon time is an important benchmark to improve the in-hospital outcomes in patients with STEMI. Door-to-balloon time less than ≤90 min has been linked improved short-term outcomes in patients with STEMI[17]. In our study, there was no difference in regard to door-to-balloon time between the patients when grouped according to the in-hospital mortality. Since there was a standard procedure applied to patients with STEMI in our ED during the referral process, it was impossible to see the effect of door-to-balloon time in multivariable analysis. All of the patients were referred to the same hospital from our ED thus limiting the confounding effect of door-to-balloon time.

As a result of multiple contributing factors, our data suggest TIMI risk index to be a simple, feasible, and clinically applicable tool for rapid risk stratification in patients with STEMI. The strength of TIMI risk index originates from its components can be calculated in all ED without increasing the workload.

Study Limitations

The current study has several limitations. First of all, the fact that the study was retrospective and not multi-centered is an important limitation. However, it was performed in two high-volume EDs and all consecutive patients meeting the criteria were included, thereby limiting selection bias. Second, there is a lack of data in regard to the amount of laboratory parameters of the patients. Third, data were limited to compare in-hospital major adverse cardiac events.

Conclusion

There is lack of evidence in regard to predictive value of TIMI risk index in patients with STEMI when calculated by emergency medicine specialists; however, our study indicated that TIMI risk index is an independent prognostic factor for in-hospital mortality of patients with STEMI treated with primary PCI. In metropolises such as Istanbul, multiple STEMI patients may apply to pre-hospital transfer and emergency services at the same time. The TIMI risk index can be used to determine the priority for referral to these cases. This makes the TIMI risk index useful for both emergency medical professionals and paramedics in the field.

Ethics Committee Approval: Haydarpasa Numune Health Application and Research Center Ethics Committee (Approval No: HNEAH-KAEK 2019/160, Approval Date: 02.12.2019).

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Conflict of Interest: None declared.

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