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Thrombolysis in Myocardial Infarction Risk Index Predicts 1-Year Mortality in Patients with Heart Failure: An Analysis of the SELFIE-TR Study

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Highlights of the Study

- The Thrombolysis in Myocardial Infarction Risk Index (TIMI-RI) is a predictor of mortality after myocardial infarction.
- We proposed that it may also be used to estimate survival in heart failure.
- High TIMI index was associated with reduced survival and more rehospitalizations.
- Predictive accuracy of TIMI index for mortality was limited but acceptable.
- TIMI index would be most useful for the prediction of mortality during the initial assessment.

Keywords
Heart failure · Mortality · Thrombolysis in Myocardial Infarction Risk Index

Abstract

Objective: Predicting outcomes is an essential part of evaluation of patients with heart failure (HF). While there are multiple individual laboratory and imaging variables as well as risk scores available for this purpose, they are seldom useful during the initial evaluation. In this analysis, we aimed to elucidate the predictive usefulness of Thrombolysis in Myocardial Infarction Risk Index (TIMI-RI), a simple index calculated at the bedside with three commonly available variables, using data from a multicenter HF registry. ***Subjects and Methods:*** A total of 728 patients from 23 centers were included in this analysis. Data on hospitalizations and mortality were collected by direct interviews, phone calls, and electronic databases. TIMI-RI was calculated as heart rate × $(age/10)^2$/systolic pressure. Patients were divided into three equal tertiles to perform analyses. ***Results:*** Rehospitalization for HF was significantly higher in patients within the 3rd tertile, and 33.5% of patients within the 3rd tertile had died within 1-year follow-up as compared to 14.5% of patients within the 1st tertile and 15.6% of patients within the 2nd tertile ($p < 0.001$, log-rank $p < 0.001$ for pairwise comparisons). The association between TIMI-RI and mortality remained significant (OR: 1.74, 95% CI: 1.05–2.86, $p = 0.036$) after adjustment for other variables. A TIMI-RI higher than 33 had a negative predictive value of 84.8% and a positive predictive value of 33.8% for prediction of 1-year mortality. ***Conclusion:*** TIMI-RI is a simple index that predicts 1-year mortality in patients with HF; it could be useful for rapid evaluation and triage of HF patients at the time of initial contact.

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Introduction

Despite multiple advances in the understanding and treatment of heart failure (HF), mortality rates remain high in patients with HF, and risk stratification is an important element for practitioners to determine which patients are more likely to die due to HF [1, 2]. As a single parameter or laboratory measurement seldom has adequate power to predict mortality, several risk scores have been developed to assess prognosis in HF [3–7]. These scores are usually cumbersome, need multiple (sometimes complex and difficult to obtain) parameters for an accurate estimation of prognosis, and are validated for a single clinical setting. As such, they are usually not useful for clinicians during the initial assessment of a patient or for those working in a rural setting, where resources are limited.

Thrombolysis in Myocardial Infarction Risk Index (TIMI-RI) is an easily obtainable index that is calculated using 3 variables, age, heart rate (HR), and systolic blood pressure (SBP), which are universally available for all patients. This index was initially developed to predict mortality and HF following acute myocardial infarction but was later found to be a useful index for predicting short-term mortality in patients with acute HF [8, 9]. Nonetheless, it remains unknown whether TIMI-RI could predict prognosis for a longer timescale or whether it is useful for a broader population of HF patients presenting with differing clinical scenarios.

SELFIE-TR (Snapshot Evaluation of Acute and Chronic Heart Failure Patients in Turkey) registry was a multicenter project that collected data on HF patients admitted to cardiology outpatient clinics or emergency departments, and 1-year survival data were recently published [10, 11]. In the present analysis, our aim was to investigate whether TIMI-RI is related to repeated hospitalizations and all-cause mortality in patients with HF and to ascertain whether TIMI-RI has additional prognostic usefulness over other demographic or clinical data that are available at the initial assessment of a HF patient.

Methods

Details of the SELFIE-TR project have been published previously [10]. In short, patients who were diagnosed or being followed up with HF in 23 centers across Turkey between October and November 2015 were approached for inclusion to the SELFIE-TR registry. Diagnosis of HF was established using a combination of clinical evaluation, echocardiographic and laboratory findings by at least two cardiologists working at each study center. All patients who were 18 years of age or older and accepted enrollment to the study were included; no exclusion criteria were used. A total of 1,054 patients were enrolled, and 1-year survival data were available for 1,022 out of these 1,054 patients. A further 294 patients were excluded as one or more variables needed to calculate TIMI-RI were missing. As such, the present analysis was conducted using data from 728 patients. The study population was divided into three TIMI-RI tertiles for statistical analyses (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000527214 for all online suppl. material). All measurements were done at individual study centers as per SELFIE-TR registry protocols.

Definitions and Goals

A patient was considered to have HF if the patient had typical symptoms with or without signs of HF at presentation and if the patient had evidence of structural and/or functional heart disease at presentation. For patients with a left ventricular ejection fraction (EF) <50%, no additional evidence for heart disease was sought. For those with an EF ≥50%, at least one additional imaging or laboratory finding consistent with HF (such as left ventricular hypertrophy, evidence for increased left ventricular filling pressure on echocardiography, or an elevated natriuretic peptide concentration) was required for inclusion. As resources were limited at some study centers, natriuretic peptides were not used as an entry criterion but were used to support the diagnosis if such resources are available. Acute HF was defined as admission to the emergency department with symptoms compatible with HF or hospitalization for at least 1 day due to HF, with administration of parenteral drugs during hospitalization. All other cases were accepted as chronic HF. Mortality was defined as all-cause mortality within 1 year of follow-up.

The primary goal of this study was to compare survival across TIMI-RI tertiles. Secondary goals of the study were to ascertain whether TIMI-RI offered additional prognostic information on top of clinical data available at presentation, to analyze the optimal cutoff value for TIMI-RI to predict mortality, and to study whether the main findings were also valid for two subgroups: patients with an EF <40% or ≥40% and patients who presented with acute or chronic HF.

Collection of Clinical, Laboratory, and Imaging Data

Past medical history was obtained, and physical examination was done by participating investigators. Blood was withdrawn for laboratory investigations at the time of enrollment. Due to differences in the availability of resources at each center, some biochemical tests were not done in some patients. A two-dimensional echocardiographic examination was done by experienced cardiologists within 24 h of enrollment.

Calculation of TIMI-RI

TIMI-RI was calculated using three variables according to the following equation [8]: Eq1. TIMI-RI = $[HR \times (age/10)^2]/SBP$, where HR is the heart rate and SBP is the systolic blood pressure. Both HR and SBP were measured after at least 5 min of rest in a quiet environment. HR was measured using a 12-channel ECG. Ten cycles were averaged for those with any irregular rhythm, and this average was used to calculate HR. SBP was measured while the patient was resting on an armchair, and a calibrated aneroid sphygmomanometer was used to take measurements. Two measurements were taken from each arm 1 min apart, and an average of these two measurements was used. The arm with the higher SBP

Table 1. Demographic, clinical, laboratory, and imaging characteristics for TIMI-RI tertiles

Characteristic	1st tertile (*n* = 242)	2nd tertile (*n* = 244)	3rd tertile (*n* = 242)	*p* value
Demographic and clinical variables				
Age, years	50±10	64±7***	76±8***	<0.001
Gender, female, *n* (%)	54 (22.3)	79 (32.4)	91 (37.6)	0.014
Weight, kg (*n* = 679)	79.4±15.4	77.9±13.9	74.4±14.1***	<0.001
Height, cm (*n* = 674)	167.0±8.7	167.3±8.2	165.5±7.5	0.052
BMI, kg/m^2 (*n* = 670)	28.6±5.3	27.9±4.5	27.1±4.9**	0.008
Presentation, *n* (%)				
Acute HF	39 (16.1)	79 (32.4)	139 (57.4)	<0.001
Chronic HF	203 (83.9)	165 (67.6)	103 (42.6)	
Diabetes	64 (26.4)	94 (38.5)	68 (28.1)	0.008
Previous/active hypertension	95 (39.3)	149 (61.6)	127 (52.5)	<0.001
Atrial fibrillation (*n* = 667)	58 (27.4)	55 (22.5)	74 (30.6)	0.27
Active smoking	43 (17.8)	25 (10.2)	16 (6.6)	<0.001
Previous MI	117 (48.3)	129 (52.9)	127 (52.5)	0.54
Previous revascularization, *n* (%)				
PCI	93 (38.4)	108 (44.2)	93 (38.4)	0.32
CABG	49 (20.2)	73 (29.5)	53 (21.9)	0.04
Intracardiac devices, *n* (%)				
VVI pacemaker	25 (10.3)	10 (4.1)	6 (2.5)	<0.001
DDD pacemaker	12 (5.0)	12 (4.9)	10 (4.1)	0.89
ICD	74 (30.6)	47 (19.3)	29 (12.0)	<0.001
Cardiac resynchronization	17 (7.0)	21 (8.6)	7 (2.8)	0.03
Functional classification (*n* = 686), *n* (%)				
NYHA 1–2	170 (77.3)	85 (63.0)	106 (43.8)	
NYHA 3–4	50 (22.7)	145 (39.7)	130 (53.7)	<0.001
Medications, *n* (%)				
ACE inhibitor	180 (74.4)	159 (65.2)	158 (65.3)	0.04
Angiotensin receptor blocker	83 (34.3)	90 (36.9)	86 (35.5)	0.83
Beta-blocker	225 (93.0)	220 (90.1)	219 (90.5)	0.49
Mineralocorticoid receptor antagonist	172 (71.1)	150 (61.5)	145 (59.9)	0.02
Ivabradine (*n* = 545)	34 (18.9)	32 (17.1)	23 (12.9)	0.29
Digoxin (*n* = 722)	31 (12.8)	26 (10.7)	29 (12.2)	0.77
Diuretics (*n* = 722)	99 (40.9)	118 (48.8)	109 (45.8)	0.22
Laboratory and imaging variables				
Hemoglobin, g/dL (*n* = 672)	13.77±1.79	12.90±2.02***	12.42±1.98***	<0.001
Blood urea nitrogen, mg/dL (*n* = 407)	26.82±15.80	32.92±18.00*	37.19±20.64***	<0.001
Creatinine, mg/dL (*n* = 661)	1.11±0.65	1.23±0.65	1.30±0.57**	0.006
Sodium, mEq/L (*n* = 457)	137.59±3.73	136.93±4.66	137.52±4.58	0.21
Potassium, mEq/L (*n* = 663)	4.50±0.51	4.48±0.67	4.49±0.79	0.91
NT-proBNP, pg/mL (*n* = 192)	1,012.0 (2,697.0)	1,282.0 (2,518.0)	2,425.0 (4,286.0)	0.24
Alanine aminotransferase, U/L (*n* = 620)	21.0 (17.3)	19.0 (15.0)*	19.1 (18.8)	0.04
Total bilirubin, mg/dL (*n* = 406)	1.01±0.95	1.11±0.93	1.18±0.85	0.30
Albumin, mg/dL (*n* = 381)	4.03±0.54	3.94±0.64	3.61±0.69***	<0.001
LV end-diastolic diameter, mm (*n* = 588)	61.33±9.96	57.79±9.90***	56.98±8.94***	<0.001
LV EF, % (*n* = 611)	30.55±10.05	32.82±10.64	33.66±11.03**	0.01
Systolic pulmonary artery pressure, mm Hg (*n* = 483)	39.92±15.66	42.65±14.54	45.61±13.65**	0.002

BMI, body mass index; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, intracardiac cardioverter-defibrillator; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; NT-proBNP, N-terminal pro B-type natriuretic peptide; LV, left ventricle. * $p < 0.05$ compared to 1st tertile. ** $p < 0.01$ compared to 1st tertile. *** $p < 0.001$ compared to 1st tertile.

Table 2. Outcome variables for TIMI-RI tertiles

Characteristic	1st tertile (n = 242)	2nd tertile (n = 244)	3rd tertile (n = 242)	p value
At least one hospitalization, n (%)				
Acute HF (n = 249)	30 (81.1)	57 (73.1)	96 (71.6)	0.51
Chronic HF (n = 454)	82 (42.1)	87 (54.4)	66 (66.6)	<0.001
Number of hospitalizations during follow-up (n = 703)	0 (1)	1 (2)	1 (2)***	<0.001
All-cause 1-year mortality, n (%)	35 (14.5)	38 (15.6)	81 (33.5)	<0.001

*** $p < 0.001$ compared to 1st tertile.

measurement was recorded as the final measurement. All measurements were done according to the relevant international guidelines.

Follow-Up

Patients were followed up by direct outpatient visits or by phone interviews. Mortality data were obtained by phone calls to patients' relatives in case a patient could not be contacted, by using institutional or national electronic medical databases or by using the electronic database provided by the General Directorate of Population and Citizenship Affairs.

Statistical Analyses

Continuous variables were given as mean ± SD or median and interquartile range, depending on the distribution of the variable in question. Categorical parameters are presented as percentages. Either one-way ANOVA or Kruskal-Wallis tests were used for comparisons between tertiles depending on the distribution of variables. A Welch correction was used if the variables did not show homoscedasticity. Again, depending on the distribution of variables, post hoc analyses were done with either Tukey's HSD, Games-Howell, or Dwass-Stein-Critchlow-Fligner tests. For categorical variables, χ^2 test was used. Kaplan-Meier curves were constructed to analyze 1-year survival, and log-rank test was used to compare mortality across TIMI-RI tertiles. A logistic regression model was constructed using demographic, clinical, and examination data to understand whether TIMI-RI provides a significant contribution to the prediction of 1-year mortality at the initial assessment. Components of TIMI-RI were not included to the regression analyses to avoid confounding, and variables with >1% missing data were excluded to avoid data loss. As the second step, remaining variables were eliminated starting with the variables with the lowest likelihood ratio. The Akaike information criterion was used to test whether there was any loss of information caused by the elimination process. Receiver operator characteristic curves were drawn for TIMI-RI and individual components of TIMI-RI. Areas under receiver operator characteristic curves were compared using DeLong's test, and the value with the highest Youden's index was given as the cutoff point for TIMI-RI. The c-statistic for TIMI-RI was bootstrapped 5,000 times to internally validate the result.

All statistical analyses were done with Jamovi version 1.2 (The Jamovi Project, Sydney, NSW, Australia), which is an open-source graphical user interface for R software, version 3.6 (R Foundation for Statistical Computing, Vienna, Austria). A p value <0.05 was accepted as statistically significant.

Results

The mean age of the study population was 63.3 ± 13.4 years, and 213 patients (29.3%) of the study population were female. 371 patients (51.0%) had either active or a past diagnosis of hypertension, 226 (31.0%) had diabetes, 373 (51.2%) had a previous diagnosis of acute myocardial infarction, and 208 (28.6%) had coronary artery disease without a previous history of acute myocardial infarction. 257 patients (35.3%) had acute HF at presentation. EF was available for 611 patients, and the mean EF for these patients was 32.4 ± 10.7%. Of these 611 patients, 45 (7.4%) had an EF ≥50%, 110 (18.0%) had an EF between 40%, and 50% and the remaining 456 (74.6%) had an EF <40%. Data for hospitalizations were available for 711 patients. Out of 711 patients, 418 (59.5%) patients had at least one hospitalization during follow-up, and the median number of hospitalizations was 1 (2). 154 patients (21.2%) died during the 1-year follow-up, and 205 (28.2%) patients died during the entire follow-up period. The distribution of TIMI-RI in the study population is given in online supplementary Figure 2.

Data on the demographic, clinical, imaging, and laboratory variables for TIMI tertiles are provided in Table 1. Patients within the 3rd tertile were older, more likely to have acute HF at presentation, and more likely to have a worse functional capacity at presentation as compared to those within the 1st tertile, though EF was significantly higher in the 3rd tertile as compared to the 1st tertile. Table 2 summarizes outcomes for patients within TIMI tertiles. Patients who had chronic HF at admission and a high TIMI-RI were more likely to be hospitalized during the follow-up period, and the total number of hospitalizations was also significantly higher in those within the 3rd tertile. Finally, all-cause mortality within 1 year was higher in patients within the 3rd tertile.

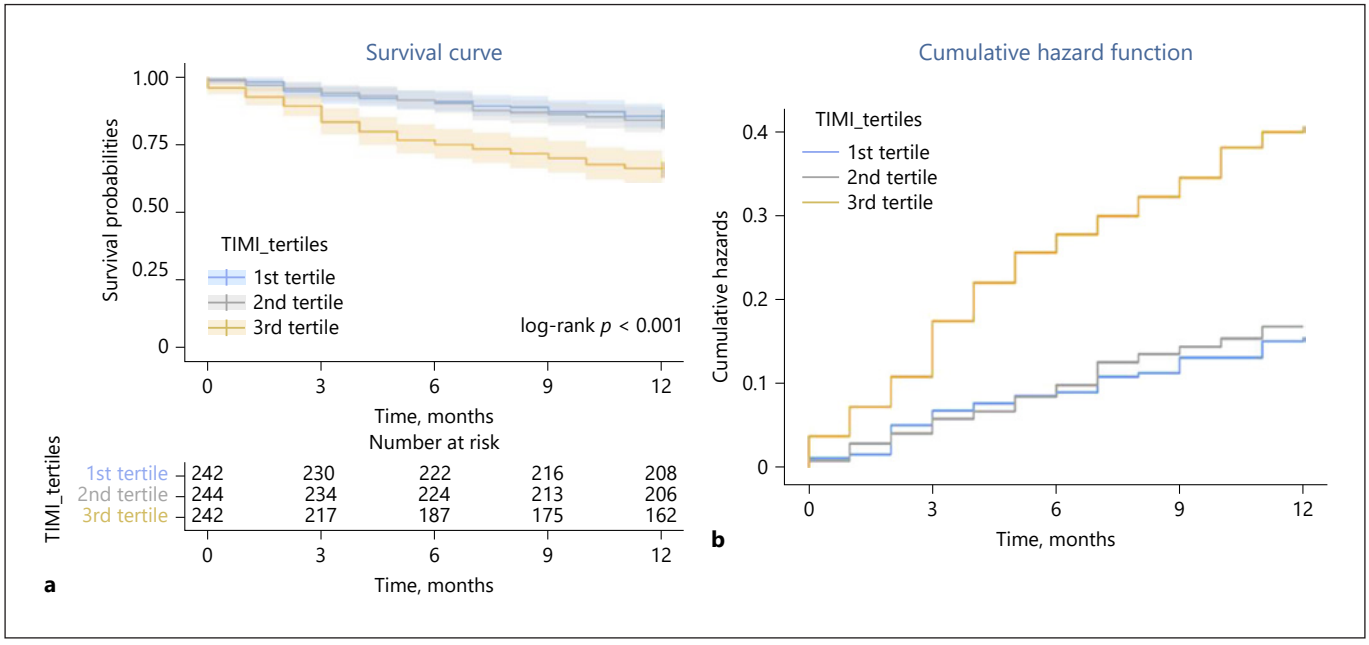

Fig. 1. Kaplan-Meier curves (**a**) and cumulative hazard curves (**b**) for 1-year survival for TIMI-RI tertiles. Colored zones around lines in Kaplan-Meier curves show 95% confidence interval, and the bottom table summarizes numbers at risk.

Kaplan-Meier curves for 1-year mortality and cumulative hazard functions for TIMI tertiles are presented in Figure 1. Patients within the 3rd tertile had significantly lower survival compared to patients within the 1st and 2nd tertiles (Bonferroni-corrected log-rank $p < 0.001$ for both pairwise comparisons).

Results for logistic regression analyses are shown in online supplementary Table 1. An initial model was constructed using all variables that had a statistically significant association with 1-year mortality. This initial model consisted of 8 variables (previous myocardial infarction, presence of dyspnea at admission, symptoms of congestion, paroxysmal nocturnal dyspnea, jugular venous distention at admission, any degree of pretibial edema at admission, presentation with acute HF, and being in the 3rd TIMI-RI tertile). After eliminating variables with a likelihood ratio $p > 0.05$, the final model consisted of 4 variables (symptoms of congestion, paroxysmal nocturnal dyspnea, presentation with acute HF, and being in the 3rd TIMI-RI tertile). The Akaike information criterion was 667 for the initial model and 666 for the final model, indicating no significant loss of information occurred by the elimination process.

Receiver operator curves for age, SBP, HR, and TIMI-RI for the prediction of 1-year mortality were given in "Figure 2." The c-statistic was highest for TIMI-RI (0.634 ± 0.026), which was statistically significant as compared to age (0.602 ± 0.026, $p = 0.02$) and HR (0.569 ± 0.025, $p = 0.02$). While the c-statistic for TIMI-RI was also higher than SBP (0.581 ± 0.026), the difference was not statistically significant ($p = 0.11$). The optimal cutoff value for TIMI-RI was 33, and for this cutoff value, it had a sensitivity of 51.3%, a specificity of 73%, a positive predictive value of 33.8%, and a negative predictive value of 84.8%. Same results were obtained after bootstrapping the dataset 5,000 times.

Subgroup Analyses

For patients admitted with acute HF, there were no differences between tertiles in terms of survival (log-rank $p = 0.144$), while in those with chronic HF, survival was significantly lower in patients within the 3rd tertile as compared to patients within the 1st and 2nd tertiles (log-rank $p = 0.002$, Bonferroni-corrected log-rank $p < 0.01$ for both pairwise comparisons) (online suppl. Fig. 3).

One-year mortality was significantly higher for those within the 3rd tertile as compared to both 1st and 2nd tertiles for patients with an EF <40% (log-rank $p < 0.001$, Bonferroni-corrected log-rank $p < 0.001$ for the comparison between 1st and 3rd tertile; Bonferroni-corrected

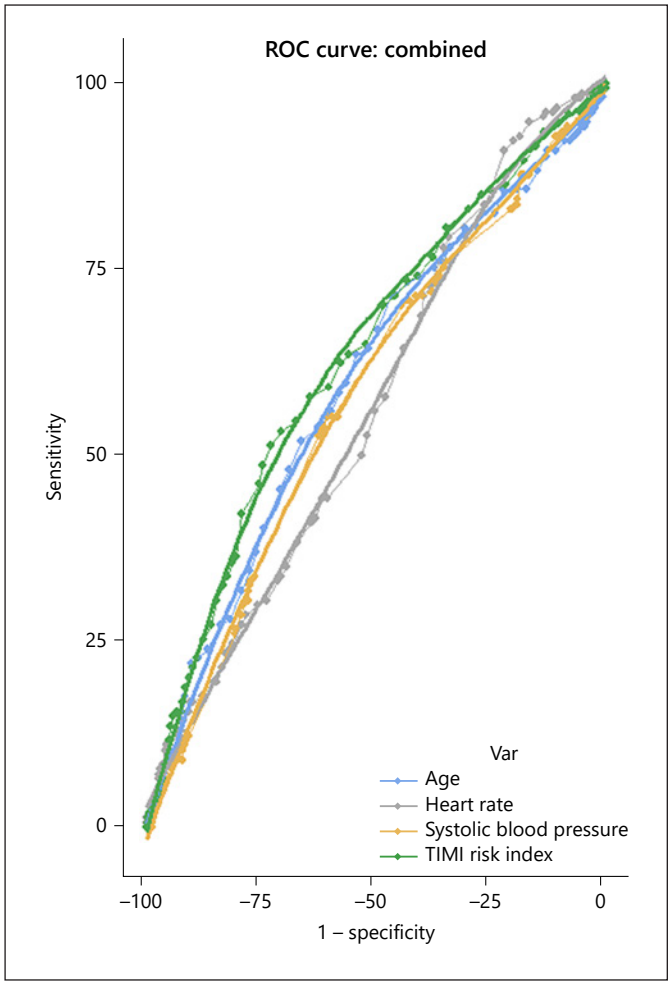

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Fig. 2. Receiver operator characteristic curves for age, SBP, HR, and TIMI risk score for the prediction of 1-year all-cause mortality in HF patients.

log-rank $p = 0.003$ for the comparison between 1st and 3rd tertile). For patients with an EF ≥40%, there was a significant difference between TIMI tertiles in terms of 1-year mortality, though the difference was less pronounced (log-rank $p = 0.035$). In pairwise comparisons, survival was significantly lower in patients within the 3rd tertile as compared to those in the 2nd tertile (Bonferroni-corrected log-rank $p = 0.0018$), but the comparison between the 1st and 3rd tertiles was not significant (Bonferroni-corrected log-rank $p = 0.097$) (online suppl. Fig. 4).

Discussion

HF is an ever-growing problem with a high mortality rate despite recent advances in treatment, and estimating prognosis is important in all patients for clinical decision-making. Findings from the present analysis suggest that hospitalization is more frequent, and survival is significantly lower, in patients with a higher TIMI-RI, and TIMI-RI is useful to assess prognosis at the initial encounter even after adjustment for other clinical and demographic variables. However, the prognostic accuracy of TIMI-RI is modest at best, and it is unclear whether TIMI-RI has incremental prognostic usefulness over other laboratory or imaging variables, such as B-type natriuretic peptide (BNP) or imaging-based predictors of survival.

TIMI-RI integrates several clinical variables that are useful to predict prognosis in a wide variety of cardiovascular disorders and gives a single output to be evaluated, thus facilitating interpretation of important clinical and prognostic data. This index was initially defined to predict outcomes in patients with acute myocardial infarction, and it was successful in predicting mortality and development of HF during in-hospital stay or in the long-term follow-up [8, 12]. Although age, HR, and SBP are well-studied predictors of mortality and adverse cardiovascular outcomes in patients with HF, data for the usefulness of TIMI-RI in the setting of HF are limited to a retrospective analysis of 293 patients with acute HF [9, 13–15]. In this latter study, the authors found that patients who died within 120 days of admission had a higher TIMI-RI, but this analysis was restricted by its retrospective and single-center design [9]. Present data bolster these earlier findings by demonstrating that TIMI-RI is useful for prognosis in patients with HF and had shown incremental usefulness over other demographic, clinical, or examination data when used in conjunction with them. Importantly, TIMI-RI was found to have a more robust predictive accuracy than its individual components, suggesting that an initial assessment of TIMI-RI can be preferred over age, HR, or SBP as standalone prognostic variables.

TIMI-RI has several advantages over existing risk scores. First, this is a simple index with a few variables that are universally available in all HF patients, and thus, it can be calculated at the bedside to have a rapid impression for outcomes. Second, as the present study is an all-comers study, it can be suggested that TIMI-RI can be used regardless of the clinical scenario encountered, though subgroup analyses suggest that it could be more useful in pa-

tients with chronic HF with reduced EF. Finally, as this index does not include more advanced parameters such as cardiopulmonary exercise test or BNP, it can be used in clinics where such resources are rather limited and by clinicians who have a limited experience with prognostication of HF. However, the usefulness of TIMI-RI should not be exaggerated as it has only a modest predictive accuracy and its prognostic usefulness would probably be insignificant when other robust prognostic factors, such as BNP or imaging assessment of left ventricular function, are included in the assessment. As such, it should be considered as a tool for initial assessment at bedside rather than a comprehensive assessment tool. In this context, risk models such as the Seattle Heart Failure Model not only provide an assessment for prognosis but are also useful for selecting patients for cardiac resynchronization treatment or left ventricular assist device implantation [16, 17]. It is not clear whether TIMI-RI has a similar usefulness, though it might be particularly suited to provide an initial insight to determine patients who would benefit from further escalation of care.

A possible method to improve the predictive accuracy of TIMI-RI would be introducing slight modifications to the core equation without making it too cumbersome to calculate at the bedside. To improve accuracy without reducing the practicality of TIMI-RI, new variables that will be introduced to the equation should be easily measurable at the initial contact and should be objective, similar to the variables readily used for calculating TIMI-RI. It was previously suggested that using blood urea nitrogen improves prognostic accuracy of TIMI-RI, though this modification would prevent calculating TIMI-RI at the time of initial assessment until laboratory results are available [9]. A similar modification could be including BMI to the calculation as this is a routinely measured variable consistently found to be a predictor of mortality [18]. While this approach could not be tested using the present dataset due to missing data, it is an interesting aspect for research in future studies.

The present study has several limitations. Data on some important prognostic variables, such as body mass index or New York Heart Association functional class, were missing for a substantial number of cases, and these variables were not introduced to the regression analysis. Also, it is not clear whether TIMI-RI is a risk marker independent of laboratory and imaging data with proven prognostic implications. While the data were obtained from a multicenter registry, the design of this study was retrospective, so there could be confounders that were not accounted for. Finally, these results should be validated before considering TIMI-RI as a useful marker of prognosis in patients with HF.

Conclusions

TIMI-RI is a simple and easily calculable parameter that could be used to predict 1-year mortality for patients with HF. The modest predictive accuracy of TIMI-RI is balanced by its ease of calculation, making it a useful tool for assessing prognosis at the time of initial evaluation. Whether TIMI-RI could be a useful tool beyond initial assessment or whether it could be used for clinical decision-making needs to be studied further.

Statement of Ethics

This study protocol was reviewed and approved by the Cumhuriyet University Clinical Research Ethics Committee (Approval Number 288-AU/003). All patients in the SELFIE-TR registry gave informed consent before enrollment.

Conflicts of Interest Statement

The authors declare that no conflicts of interest exist for the present work.

Funding Sources

None.

Author Contributions

Rengin Çetin Güvenç: study conception and design, data acquisition, and drafting; Tolga Sinan Güvenç: study conception and design, data analysis and interpretation, drafting, and final review; Dilek Ural: data acquisition and interpretation and final review; Yüksel Çavuşoğlu: data acquisition and analysis and final review; and Mehmet Birhan Yılmaz: study conception and design, data interpretation, drafting, and final review.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

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