Predictors of left ventricular ejection function decline in young patients with ST-segment elevation myocardial infarction

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SUMMARY

OBJECTIVE: A decrease in the left ventricular ejection fraction (≤40%) in the setting of ST-segment elevation myocardial infarction is a significant predictor of mortality in the young ST-segment elevation myocardial infarction population. In this study, we aimed to investigate the predictors of left ventricular ejection fraction reduction and evaluate the long-term mortality rates in young ST-segment elevation myocardial infarction patients with or without decreased left ventricular ejection fraction.

METHODS: We enrolled retrospectively 411 consecutive ST-segment elevation myocardial infarction patients aged 45 years or below who underwent primary percutaneous coronary intervention. Young ST-segment elevation myocardial infarction patients were divided into two groups according to their left ventricular ejection fraction (≤40%, n=72 and >40%, n=339), which were compared with each other.

RESULTS: Statin use, white blood cell count, C-reactive protein, peak creatine kinase-MB, prolonged ischemia time, left anterior descending artery-related infarction, proximally/ostial located lesion, and no-reflow were independently associated with low left ventricular ejection fraction. Additionally, long-term mortality was considerably higher in the left ventricular ejection fraction ≤40% group than those in the left ventricular ejection fraction >40% group (18.1% versus 2.4%; p<0.001).

CONCLUSIONS: In young ST-segment elevation myocardial infarction patients, lesion properties (left anterior descending lesion, proximally located lesion), no-reflow, and prolonged ischemia time appeared to be important determinants for the left ventricular ejection fraction decline, rather than coronary disease severity or demographic and hematological parameters. Statin use may be preventive in the development of left ventricular ejection fraction decline in young ST-segment elevation myocardial infarction patients.

KEYWORDS: STEMI, Mortality, Adult, Percutaneous coronary intervention.

INTRODUCTION

The incidence of ST-segment elevation myocardial infarction (STEMI) is 0.05–0.15% annually, and a significant number of STEMIs (5.5–11.6%) have been found at a young age (≤45 years)1-3. Although in-hospital and long-term mortality rates are better in younger patients with myocardial infarction than in the older population, compared with the general male population, the risk of mortality is 2–4 times higher in men and even higher in women4,5. To date, for different age groups or general STEMI patients, many parameters related to mortality have been introduced, including Killip class, advanced age, delay in treatment, coronary disease severity, renal failure, left ventricular ejection fraction (LVEF), post-percutaneous coronary intervention (PCI), thrombolysis in myocardial infarction (TIMI) flow, and noncompliance with pharmacological recommendations1,3,6. In young patients, LVEF decrease (≤40%) in the course of STEMI is a strong predictor of mortality, consistent with the general STEMI population7. Aside from being a significant predictor of mortality, the reduced LVEF is also associated with reduced functional capacity and quality of life and with increased hospitalization and the economic burden in surviving patients after myocardial infarction7.

In young STEMI patients, the precise predictors of decreased LVEF, which is associated with poor outcomes, have not yet been discovered. In this study, we aimed to

1) investigate the predictors of LVEF reduction and;
2) evaluate the long-term mortality rates in young STEMI patients with LVEF>40% and LVEF≤40% who were treated with primary PCI (pPCI).
METHODS

Study population
This study was performed in accordance with the Principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee. We conducted this study by retrospectively enrolling consecutive 435 patients aged 45 years or below with STEMI who underwent pPCI between January 2012 and January 2017. Of these, 24 were excluded from the study because of previously known myocardial infarction and/or heart failure (n=16) and missing clinical and/or long-term follow-up data from hospital files (n=8). Thus, the final study consisted of 411 patients. Telephone interviews, hospital records, and the death registry database were the sources of long-term follow-up data. STEMI was defined according to the current guidelines1.

Data collection
Patients’ medical history and data on baseline clinical and demographic characteristics were obtained from hospital records and patient files. These records indicated that blood biochemical parameters and a complete blood count had been obtained for all patients upon admission to the hospital. Blood samples were retested every 6 h for creatine kinase-myocardial band (CK-MB) and troponin T until peak levels were detected. LVEF obtained before discharge, which was assessed using a modified version of Simpson’s method, was considered in the study.

The digital angiograms (Dicom-viewer; MedCom GmbH, Darmstadt, Germany) of all patients who were treated with pPCI by experienced interventional cardiologists were analyzed quantitatively in terms of lesion and intervention characteristics. The coronary blood flow patterns before and after pPCI were evaluated based on TIMI flow grade, and epicardial no-reflow was defined as a TIMI flow grade <3 in the target vessel lesion. The thrombus burden was assessed according to the TIMI thrombus grading scale, as defined previously8. The patients’ SYnergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery (SYNTAX) score was calculated using the online SYNTAX score calculator (www.syntaxscore.org) to indicate the severity of coronary artery disease.

Statistical analysis
SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to analyze the normality of the data. Continuous variables with normal distribution were expressed as mean±standard deviation and were compared using the independent t-test. Non-normal data were expressed as median (0.25–0.75 percentiles) values and compared using the Mann-Whitney U test. Fisher’s exact test or χ2 test was used to compare the categorical variables which were expressed as percentages. Multivariate logistic regression analyses were performed to identify the independent predictors of reduced LVEF, using the variables that showed a marginal association in the univariate analysis. Power analysis was performed with G*Power version 3.1.9.4 and the power values obtained in the post-hoc power analysis of the parameters found as predictors in the logistic regression analysis were between 0.684 and 0.988. The Kaplan-Meier survival curve analysis was used to demonstrate the event-free survival curves of the patients with LVEF ≤40% or >40%, and the log-rank test was used for comparison. A p-value of <0.05 indicated statistical significance.

RESULTS
The study population consisted of 411 young STEMI patients (mean age: 40±4 years; 8.5% female) who underwent pPCI. The average LVEF of the patients was 47.28±8.76. The patients were divided into two groups according to their LVEF values: the high (>40%) LVEF group (n=339, mean LVEF: 50.30±6.13) and the reduced (≤40%) LVEF group (n=72, mean LVEF: 33.07±3.92). The baseline characteristics of all the patients and those of the low and high LVEF groups are shown in Table 1. In patients in the low LVEF group, diabetes mellitus and dyslipidemia were more common. Patients in the low LVEF group had a higher prevalence of Killip class >1 (on admission), higher heart rate, and higher values of white blood cells (WBC), neutrophils, neutrophil-to-lymphocyte ratio (NLR), blood glucose, peak CK-MB, and C-reactive protein (CRP) than those in the high LVEF group. Furthermore, patients in the low LVEF group had lower levels of hemoglobin and estimated glomerular filtration rate than those in the high LVEF group. In comparing the properties of angiography and ischemia, patients in the low LVEF group had a higher prevalence of Killip class >1 (on admission), higher heart rate, and higher values of white blood cells (WBC), neutrophils, neutrophil-to-lymphocyte ratio (NLR), blood glucose, peak CK-MB, and C-reactive protein (CRP) than those in the high LVEF group. Furthermore, patients in the low LVEF group had lower levels of hemoglobin and estimated glomerular filtration rate than those in the high LVEF group. In comparing the properties of angiography and ischemia, patients in the low LVEF group had a longer total ischemia time and a higher SYNTAX score than those in the high LVEF group. Infarct-related artery (IRA) of the left anterior descending (LAD), proximal/ostial localization of the culprit lesion, no-reflow phenomenon, and high-grade thrombus burden were more frequent in the low LVEF group. The rate of long-term mortality was found to be considerably higher in the low LVEF group than in the high LVEF group (Table 1).
Table 1. Characteristics of all patients and patient groups with low and high Left ventricular ejection fraction.

| Characteristic                                      | All patients | LVEF >40 (n=339) | LVEF ≤40 (n=72) | p-value |
|-----------------------------------------------------|--------------|-------------------|-----------------|---------|
| Age (years)                                         | 40 ±4        | 40 ±4             | 41 ±4           | 0.403   |
| Female gender n (%)                                 | 35.0 (8.50)  | 33.0 (9.70)       | 2.0 (2.80)      | 0.055   |
| Diabetes mellitus n (%)                             | 57.0 (13.90) | 40.0 (11.80)      | 17.0 (23.60)    | 0.009   |
| Hypertension n (%)                                  | 67.0 (16.30) | 51.0 (15.00)      | 16.0 (22.20)    | 0.135   |
| Dyslipidemia n (%)                                  | 213.0 (51.80)| 118.0 (34.80)     | 40.0 (55.60)    | 0.001   |
| Family history of CAD n (%)                         | 132.0 (32.10)| 113.0 (33.30)     | 19.0 (26.40)    | 0.252   |
| Smoking n (%)                                       | 319.0 (77.60)| 264.0 (77.90)     | 55.0 (76.40)    | 0.784   |
| Medications                                         |              |                   |                 |         |
| Acetylsalicylic acid n (%)                          | 4.0 (1.00)   | 2.0 (0.60)        | 2.0 (2.80)      | 0.086   |
| β-Blocker n (%)                                     | 28.0 (6.80)  | 22.0 (6.50)       | 6.0 (8.30)      | 0.573   |
| ACEI/ARB n (%)                                      | 35.0 (8.50)  | 28.0 (8.30)       | 7.0 (9.70)      | 0.687   |
| Statin n (%)                                        | 83.0 (20.20) | 78.0 (23.00)      | 5.0 (6.90)      | 0.002   |
| Insulin n (%)                                       | 7.0 (1.70)   | 5.0 (1.50)        | 2.0 (2.80)      | 0.438   |
| Killip class >1 on admission n (%)                  | 60.0 (14.60) | 35.0 (10.30)      | 25.0 (34.70)    | <0.001  |
| Arrest on admission n (%)                           | 13.0 (3.20)  | 11.0 (3.20)       | 2.0 (2.80)      | 0.837   |
| Systolic blood pressure (mm Hg)                     | 124 ±24      | 125 ±21           | 118 ±35         | 0.196   |
| Heart rate (bpm)                                    | 78 ±15       | 76 ±13            | 88 ±17          | <0.001  |
| Hemoglobin (g/dL)                                   | 14.5 ±1.7    | 14.6 ±1.4         | 13.9 ±2.4       | <0.001  |
| White blood cell count (×10⁹/L)                     | 13.61 ±3.85  | 12.85 ±3.13       | 17.14 ±4.83     | <0.001  |
| Platelet count (×10⁹/L)                             | 271 ±74      | 271 ±73           | 270 ±79         | 0.797   |
| Neutrophil count (×10⁹/L)                           | 10.37 ±3.87  | 9.59 ±3.21        | 14.05 ±4.58     | <0.001  |
| Lymphocyte count (×10⁹/L)                           | 2.00 (1.50-3.00) | 2.10 (1.50-3.00) | 1.65 (1.40-2.60) | 0.074   |
| Neutrophil-to-lymphocyte ratio                      | 4.87 (2.79-7.92) | 4.38 (2.60-7.06) | 7.19 (4.63-12.26) | <0.001  |
| Blood glucose on admission (mg/dL)                  | 118 (102-144)| 115 (101-142)     | 127 (109-179)   | 0.003   |
| C-reactive protein (mg/dL)                          | 8.76 (4.52-16.50) | 7.74 (4.32-13.20) | 24.50 (15.40-45.00) | <0.001  |
| Serum albumin (g/dL)                                | 3.95 ±0.49   | 3.93 ±0.46        | 4.05 ±0.60      | 0.109   |
| Estimated glomerular filtration rate (mL/min)       | 102.01 ±20.44 | 103.20 ±20.09     | 96.38 ±21.27    | 0.049   |
| Peak creatine kinase MB (ng/mL)                     | 171 (99-308) | 143 (87-235)      | 478 (373-678)   | <0.001  |
| LVEF (%)                                             | 47.28 ±8.76  | 50.30 ±6.13       | 33.07 ±3.92     | <0.001  |
| Total ischemia time (min)                           | 166 (110-254)| 145 (95-217)      | 270 (172-430)   | <0.001  |
| LAD as the infarct-related artery n (%)             | 254 (61.80)  | 184 (54.30)       | 70 (97.20)      | <0.001  |
| Proximal/ostial lesion for IRA n (%)                | 236 (57.40)  | 175 (51.60)       | 61 (84.70)      | <0.001  |
| High-grade thrombus burden n (%)                    | 259 (63.00)  | 193 (56.90)       | 66 (91.70)      | <0.001  |
| No-reflow n (%)                                     | 35 (8.50)    | 14 (4.10)         | 21 (29.20)      | <0.001  |
| Left main coronary artery n (%)                     | 5 (1.20)     | 5 (1.50)          | 0 (0.00)        | -       |
| Three vessels disease n (%)                         | 25 (6.10)    | 18 (5.30)         | 7 (9.70)        | 0.155   |
| Presence of chronic total occlusion n (%)           | 28 (6.80)    | 22 (6.50)         | 6 (8.30)        | 0.573   |
| Basal syntax score                                  | 16.41 ±4.04  | 15.89 ±4.10       | 18.85 ±2.68     | <0.001  |
| Long-term mortality n (%)                           | 21 (5.1)     | 8 (2.4)           | 13 (18.1)       | <0.001  |
| Follow-up time (month)                              | 38 ±13       | 39 ±11            | 31 ±19          |         |

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blocker; LVEF: left ventricular ejection fraction; LAD: left anterior descending; IRA: infarct-related artery. Bold indicates significant p-value.
Multivariate regression analysis was performed to determine the independent predictors of reduced LVEF, using the parameters found to be associated with reduced LVEF in the univariate analysis. Statin use, WBC, CRP, peak CK-MB, total ischemia time, LAD as the IRA, proximal/ostial lesion for IRA, and no-reflow were found to be independently associated with low LVEF (Table 2).

During an average follow-up of 38±13 months, 21 (5.1%) deaths from all causes were reported. The rate of long-term mortality was significantly higher among patients in the low LVEF group than among those in the high LVEF group (n=13, 18.1% versus n=8, 2.4%; p<0.001). The Kaplan-Meier survival curve of long-term mortality is shown in Figure 1.

**DISCUSSION**

In this study, we evaluated the predictors of reduced LVEF in patients with STEMI aged ≤45 years. The demographic features were not determined as predictors of decreased LVEF development, whereas statin use from the pharmacological history was found to be protective in the occurrence of decreased LVEF. While WBC and CRP were independent predictors of reduced LVEF, NLR, as an inflammatory parameter, was not a predictor of reduced LVEF. The most considerable findings of this study were that lesion localization, procedure characteristics (i.e., IRA, proximal/ostial lesion, and no-reflow), and prolonged ischemia time were the main causes of reduced LVEF.

**Table 2. Univariate and multivariate logistic regression analysis of characteristics for prediction of reduced LVEF (LVEF≤40).**

| Variable                          | Univariate analysis of reduced LVEF | Multivariate analysis of reduced LVEF |
|----------------------------------|-------------------------------------|--------------------------------------|
|                                  | Odds ratio | 95%CI     | p-value | Odds ratio | 95%CI     | p-value |
| Female gender                    | 0.265      | 0.062–1.130 | 0.073 | –         | –         | –       |
| Diabetes mellitus                | 2.310      | 1.223–4.365 | 0.010 | –         | –         | –       |
| Dyslipidemia                     | 1.157      | 1.034–1.434 | 0.040 | –         | –         | –       |
| Statin use                       | 0.250      | 0.097–0.641 | 0.004 | 0.011     | 0.001–0.117 | <0.001 |
| Hemoglobin (g/dL)                | 0.773      | 0.668–0.895 | <0.001 | –         | –         | –       |
| White blood cell count (×10⁹/L)  | 1.338      | 1.236–1.449 | <0.001 | 1.947     | 1.156–3.278 | 0.012 |
| Neutrophil count (×10⁹/L)        | 1.360      | 1.252–1.477 | <0.001 | –         | –         | –       |
| Lymphocyte count (×10⁹/L)        | 0.880      | 0.709–1.091 | 0.244 | –         | –         | –       |
| Neutrophil-to-lymphocyte ratio   | 1.163      | 1.098–1.233 | <0.001 | –         | –         | –       |
| Basal blood glucose level (mg/dL)| 1.003      | 1.000–1.006 | 0.340 | –         | –         | –       |
| C-reactive protein (mg/dL)       | 1.120      | 1.088–1.153 | <0.001 | 1.123     | 1.054–1.197 | <0.001 |
| Peak creatine kinase MB (ng/mL)  | 1.012      | 1.009–1.015 | <0.001 | 1.018     | 1.011–1.025 | <0.001 |
| Total ischemia time (min)        | 1.008      | 1.006–1.010 | <0.001 | 1.018     | 1.010–1.027 | <0.001 |
| LAD as IRA                       | 29.484     | 7.114–122.187 | <0.001 | 218.725   | 13.049–3666.318 | <0.001 |
| Proximal/ostial lesion for IRA   | 5.197      | 2.642–10.222 | <0.001 | 1.033     | 1.005–1.245 | <0.001 |
| No-reflow                        | 8.321      | 3.511–19.722 | <0.001 | 15.311    | 2.271–103.252 | 0.005 |
| High-grade thrombus burden (Grade 4/5) | 9.559 | 4.570–19.192 | <0.001 | –         | –         | –       |
| Syntax score                     | 1.200      | 1.120–1.286 | <0.001 | –         | –         | –       |

LVEF: left ventricular ejection fraction; CI: confidence interval; LAD: left anterior descending; IRA: infarct-related artery. Bold indicates significant p-value.
The fact that LVEF is closely related to death and poor quality of life and that data about reduced LVEF predictors in young STEMI patients are lacking has prompted us to investigate the predictors of LVEF decline in young STEMI patients. In our study, the demographic characteristics of the patients, including diabetes and hyperlipidemia, were not predictors of reduced LVEF. The reason that diabetes is not related to LVEF may be that many years are required to develop microvascular dysfunction and diabetic cardiomyopathy. In parallel with previous randomized studies showing that statin use could reduce the risk of developing heart failure, in our study, the use of statin was a predictor of preventing the development of heart failure in young STEMI patients.

Ischemic injury induces an inflammatory response, the intensity of which is an important predictor of ventricular remodeling. The CRP levels in STEMI patients have been shown to be closely associated with infarct size, reduced LVEF, and left ventricular volumes, aside from mortality. Similarly, NLR, as a recently identified inflammatory parameter, has been found to be a predictor of LVEF decline and mortality for unselected STEMI patients. In our study, CRP was an independent predictor of reduced LVEF in young STEMI patients, which is consistent with the general STEMI cohort, but NLR was not.

Studies investigating the relationship between the infarct location/size and prognosis have shown that patients with a large infarct size (mostly confirmed by a high peak enzyme level) had a poor in-hospital and long-term prognosis and a reduced LVEF. Similarly, no-reflow has been found to be a strong determinant of infarct size and LVEF decrease. In our study, proximally located and LAD-related STEMI and no-reflow were found to be predictors of reduced LVEF in young STEMI patients, consistently with the aforementioned studies. Moreover, CK-MB was higher in patients with lower LVEF and is a predictor of LVEF decline.

Delay in reperfusion therapy has been shown to be associated with both mortality and LVEF reduction. In patients with delayed reperfusion, the LVEF decline is mostly attributed to increased infarct size. In the present study, prolonged total ischemia time was found to be an independent predictor of reduced LVEF in young STEMI patients, similar to the general STEMI population.

Previous studies evaluating mortality rates of young STEMI patients reported a mortality rate of 3–4%. We also found the long-term mortality rate for 38±13 months of patients with STEMI aged ≤45 years in the present study was 5.1%. LVEF was reduced to an average of 47.28%, and the rate of patients with reduced LVEF (≤40%) was 17.5% in the present study. This rate was consistent with the study investigating reduced LVEF following STEMI in a general STEMI cohort. In the present study, the rate of long-term mortality was considerably higher in the low LVEF group than in the high LVEF group (18.1% versus 2.4%) in young STEMI patients. This finding was consistent with a recent study in young STEMI women, which reported that every 5% increase in LVEF at discharge reduced the mortality rate by 60%.

The possible clinical implication of our study is that revealing the factors associated with LVEF decline more precisely in young STEMI patients may substantially not only contribute to the development of new strategies in STEMI treatment and a reduction of the LVEF decline and its associated mortality rates for this specific patient group but also allow us to identify patients who are at higher risk of developing a reduced LVEF and, therefore, require closer clinical follow-up.

This study has some limitations. Although we determined the adequacy of our sample size by comparing it with similar studies in the literature and performing power analysis, our results should be validated in larger clinical trials. Although cardiac magnetic resonance imaging (CMRI) is the gold standard for assessing left ventricular function, CMRI could not be performed owing to the retrospective nature of the study and the high cost and limited availability of CMRI. LVEF measured before discharge was used in our study and no repeated measurements during the follow-up period were taken into account, as they were beyond the scope of the study. This study had a retrospective design and was based on a registry analysis. As the patients included in the study were young and had experienced their first myocardial infarction, the current reduced LVEF was attributed to their recent STEMI. That is, although there were no data, the presence of heart failure extending before STEMI could not be excluded.

CONCLUSIONS

In young STEMI patients, lesion localization (LAD lesion, proximally located lesion), no-reflow, and prolonged ischemia time seem to be important determinants of the LVEF decline, rather than coronary disease severity or demographic and hemato pathological parameters. Moreover, statins should be used in dyslipidemic young patients to avoid procedural transactions that could cause no-reflow.

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This study protocol was approved by the Ethics Committee of the Kafkas University Medical Faculty. This study was conducted under the principles of the Declaration of Helsinki.
Written informed consent was waived owing to the retrospective nature of the study.

**AUTHORS’ CONTRIBUTIONS**  
**IY:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing.  
**IR:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.  
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