



Long-term prognostic significance of terminal QRS distortion on patients with stemi and its correlation with the GRACE scoring system

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Introduction

The standard 12-lead electrocardiogram (ECG) continues to serve as the most widely used tool in the diagnosis and risk stratification of patients with acute ST-segment elevation myocardial infarction (STEMI) and several new ECG parameters have been shown to be useful in determining patients at higher risk [1–3].

Risk classification for mortality in patients with acute coronary syndrome (ACS) not only provides better management and follow-up, but also helps determine which patients are likely to benefit most from treatment [4].

Terminal QRS distortion hypothesis, also referred to as Grade 3 ischemia (G3I), is a strong indicator of in-hospital short-term mortality and the success of reperfusion in patients with STEMI [3,5].

Previous studies have shown that patients with G3I on admission ECG have poor in-hospital prognosis, poor response to fibrinolytic therapy, high mortality after primary percutaneous treatment and larger infarcts [6–10]. Additionally, it has also been shown that G3I is associated with high SYNTAX score and high no-reflow rates [11]. And also patients with G3I on admission ECG had worse left ventricular function and were more likely to develop complications during percutaneous intervention. More frequent LAD involvement and more widespread tissue damage, may in part, account for some of these results [12].

In the Global Registry of Acute Coronary Events (GRACE) trial, Eagle and colleagues followed a total of 102,341 patients with ACS for mortality for 10 years. These patients were registered in any of the

participating 247 centers in 30 countries. Greater than 70 years of age, history of MI, higher Killip class, increased heart rate, low blood pressure (BP), increased creatinine and cardiac biomarker levels and ST segment deviation were found to be associated with increased mortality rates. Data from this study were used to develop a scoring system, namely the GRACE scoring system, to estimate mortality rate in patients with ACS at 6 and 36 months [13,14]. This scoring system is recommended in many of the current ACS guidelines [15].

The association of G3I with long-term mortality and its correlation with the GRACE (version 2.0) risk score system has not yet been fully investigated. The aim of the current study is to investigate the effect of G3I on in-hospital and long-term mortality in patients with STEMI.

Material and methods

Study population

Patients older than 18 years who were diagnosed as STEMI in the cardiology clinic of Selçuk University Faculty of Medicine between January 2011 and January 2014 and who were admitted to the hospital within <24 h after the onset of symptoms were included in the study.

We used the European Society of Cardiology (ESC) guidelines to diagnose STEMI. We classified patients into two groups according to the presence or absence of G3I on the admission ECG and performed intra- and inter-group comparisons.

We obtained written informed consent from each participant in accordance with the Helsinki Declaration Principles.

Patients who had had >24 h of onset of chest pain, an ECG with left or right branch block, a history of previous MI or

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bypass operation, inverted T waves in leads with ST elevation, pacemaker rhythm or those with an ambiguous ECG were excluded from the study.

We investigated and documented risk factors for cardiovascular events, including age, sex, family history of coronary artery disease (CAD), current smoking status (defined as an adult who has smoked at least 100 cigarettes in his or her lifetime, both previous and active), hypertension (HT), hyperlipidemia (HL) (defined as the patients who needs treatment according to 2016 ESC/EAS Guidelines for the Management of Dyslipidemias), and diabetes mellitus (DM). We also recorded pre-procedural medications and Killip class on admission. Additionally, all patients underwent an echocardiographic examination before discharge. We used the bi-plan modified Simpson method to measure left ventricular ejection fraction (LVEF). Laboratory studies included measurement of routine biochemistry, lipid profile, hemogram, creatine kinase (CK), creatine kinase-MB (CK-MB), and troponin I. Finally, we calculated the GRACE scores and 36th-month GRACE mortality percentages of each patient from GRACE 2.0 calculator.

Long-term follow-up was done by hospital visits at 1, 3, 6, 12, 24, 36 months. The patients who were lost to follow up called by telephone and invited for control, missing ones excluded from the study (n: 71). Cause of deaths learned from the hospital registries. Patients whose cause of death could not be determined excluded from the study (n: 9).

Electrocardiographic evaluation

We obtained ECG from all patients who presented with STEMI within the first 12 h of symptom onset using the Nicoh Cohden Cardiofax 12-channel ECG device. We then divided patients into two groups based on the grade of ischemia, as defined by Birnbaum et al. [3]. G3I was defined as: absence of an S wave below the TP-PR isoelectric line in ≥ 2 leads that usually have a terminal S configuration (leads V1 to V3), or ST J-point amplitude $\geq 50\%$ of the R wave amplitude measured from the TP-PR baseline in ≥ 2 all other infarct-related leads (Fig. 1). Patients meeting the ST elevation criteria

but not the G3I criteria were classified as having grade 2 ischemia (G2I) (Fig. 2).

Statistical analysis

We used the SPSS 17 (SPSS Inc., Chicago, IL, USA) software for statistical analysis. We used the Chi-square test for the comparison of categorical variables and Student's *t*-test and Mann Whitney *U* test for the comparison of continuous variables. We also performed logistic regression analysis and Cox regression analysis using the forward stepwise method. Specifically, we used the Mann Whitney - *U* test to analyze the relationship between G3I and gender, HT, HL, DM, smoking, medication, complete atrioventricular (AV) block development, intra-aortic balloon pump (IABP) need and death; Kruskal-Wallis test to analyze the relationship between G3I and MI localization; and finally the logistic regression analysis to assess factors know to be associated with mortality in patients with STEMI such as age, gender, time of arrival, Killip class, DM, LVEF, CAD history, renal failure, cardiogenic shock, MI localization and GRACE score. The results were evaluated in the 95% confidence interval and we accepted *p*-values of 0.05 or less as statistically significant.

Results

A total of 216 patients (mean age: 60.9 ± 14.2 years, range: 25 to 89 years) were enrolled into the study. Patients admitted to the hospital within mean 4.4 ± 2 h after the onset of symptoms. Of these 170 (78%) were men and 46 (22%) women. The average age of male and female patients was 59.2 and 66.5, respectively.

While 59.7% of the patients were diagnosed with inferior MI, 40.3% had anterior MI and overall 17.1% of the patients had a history of CAD. 31.4% of the patients received fibrinolytic therapy, 61.1% underwent primary percutaneous intervention and 31.9% received Gp IIb/IIIa antagonist (tirofiban). Eighty-seven (40.2%) patients developed new heart failure, 15 (6.9%) needed IABP

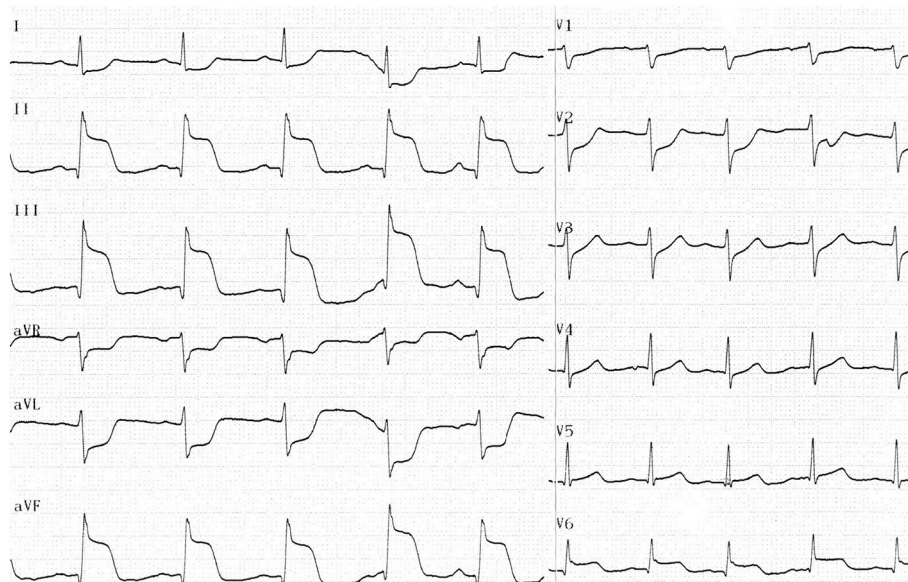


Fig. 1. Inferolateral (with posterior wall) myocardial infarction with terminal QRS distortion (G3I+) (J points emerge at $\geq 50\%$ of the R wave amplitude in leads II, III and aVF).



Fig. 2. Anteroseptal myocardial infarction without terminal QRS distortion (G3I–) (S wave persists in leads V1, V2 and V3).

support and nine (4.1%) required temporary cardiac pacemaker insertion due to complete AV block. Of all the deaths, 64.9% were due to cardiovascular events. Twenty-two (10.1%) patients died during hospitalization and 35 (18%) of the 194 discharged patients died during the 36-month follow-up period, summing up to a total death rate of 26.3% ($n = 57$) at 36-month follow-up. The mean GRACE risk score points of 216 patients on admission was 120 ± 34 .

Patients were grouped as G3I+ (QRS distortion positive: 93 patients; 43.0%) and G3I– (QRS distortion negative: 123 patients; 57.0%). There was no significant difference in the distribution of G3I between male ($n = 75$; 44.1%) and female ($n = 18$; 39%) patients ($p = 0.61$). Similarly, groups were well matched with regards to conventional CAD risk factors including DM, HT, HL, family history of CAD and smoking (Table 1).

Table 1

Basic characteristics and laboratory results of the patients enrolled into the study.

Basic Characteristics and Laboratory Results	G3I+ (n: 93)	G3I– (n: 123)	p Value
Age (years)	62	59	0.07
Gender (male), n (%)	75 (80.6)	95 (77)	0.61
DM, n (%)	15 (16.1)	26 (21.1)	0.38
HT, n (%)	44 (47.3)	49 (29.8)	0.33
Smoking, n (%)	66 (70.9)	85 (69.1)	0.88
CAD history, n (%)	14 (15.0)	23 (18.6)	0.58
HL, n (%)	14 (15.0)	15 (12.1)	0.55
Systolic BP (mm Hg)	110 ± 25	122 ± 23	<0.001
Diastolic BP (mm Hg)	67 ± 15	74 ± 13	<0.001
MI localisation – anterior, n (%)	44 (47.3)	43 (34.9)	0.07
LVEF on admission (%)	41 ± 8	45 ± 9	0.30
Creatinine, mg/dl	1.0 ± 0.31	0.9 ± 0.26	0.01
LDL-cholesterol, mg/dl	122 ± 37	126 ± 36	0.40
HDL-cholesterol, mg/dl	35.7 ± 9	35.4 ± 8	0.79
Triglyceride, mg/dl	166 ± 107	181 ± 109	0.42
CKMB, U/L	58 ± 9	32 ± 5	0.02
Troponin I, ng/ml	7.4 ± 0.9	5.5 ± 0.7	0.04
36th month Creatinine, mg/dl	0.95 ± 0.21	0.95 ± 0.29	0.99
36th month LDL-cholesterol, mg/dl	98 ± 38	107 ± 41	0.29
36th month HDL-cholesterol, mg/dl	35.9 ± 8.1	36.8 ± 7.9	0.56
36th month triglyceride, mg/dl	177 ± 13	185 ± 13	0.71
GRACE risk score (points)	133 ± 36	111 ± 29	<0.001
36-month GRACE mortality risk (%)	38 ± 30	23 ± 21	<0.001

HDL: high density lipoprotein, LDL: low density lipoprotein.

The number of patients who received fibrinolytic therapy, who underwent primary PCI and who received Tirofiban infusion did not differ between the groups ($p = 0.55$, $p = 0.26$, $p = 1$; respectively). The number of patients who required IABP insertion (12.9% vs. 2.4%; $p < 0.001$) and the number of patients with new onset heart failure (53.7% vs. 30%; $p < 0.001$), however, was significantly higher in the G3I+ group (both include heart failure with preserved LVEF and heart failure with reduced LVEF).

G3I was present in 67 of 183 (36.6%) patients with Killip Class I, 18 of 22 (81.8%) patients with Class II, 6 of 9 (66.6%) patients with Class III, and 2 of 2 (100%) patients with Class IV. The differences between the groups were all significant ($p < 0.001$).

There was no significant difference between groups with regards to complete AV block development (Total 10 patients; 6 patients at G3I– group, 4 patients at G3I+ group), the need for transient pacemaker insertion, the need for additional percutaneous intervention, and urgent coronary bypass surgery ($p > 0.05$). Inferior MI localization was significantly higher in complete AV block development ($p < 0.05$).

Troponin I (7.4 ± 0.9 ng/ml vs. 5.4 ± 0.7 ng/ml; $p = 0.04$), (normal range is between: 0.02–0.06 ng/ml) and CKMB (58 ± 9 U/l vs. 32 ± 5 U/l; $p = 0.02$), (normal range is between: 0–24 U/l) levels on admission were higher in the G3I+ group. GRACE scores and percentages were highly correlated with the presence of G3I both at GRACE risk score (points) and 36-month death risk (%) analysis (133 ± 36 vs. 111 ± 29 ; $p < 0.001$ and $38\% \pm 30\%$ vs. $23\% \pm 21\%$; $p < 0.001$, respectively) (Table 1).

Age, time from symptom onset to admission, cholesterol values and 36th month cholesterol values did not significantly differ between the groups. The systolic (110 ± 25 vs. 122 ± 23 , respectively; $p < 0.001$) and diastolic (67 ± 15 vs. 74 ± 13 , respectively; $p < 0.001$) blood pressures were significantly lower in patients at G3I+ group. Patients in the G3I+ group had higher creatinine ($p = 0.01$) and lower LVEF ($p = 0.01$) on admission.

Table 2

Long term clinical outcomes of patients G3I+ and G3I–.

Clinical Outcomes	G3I+ (n: 93)	G3I– (n: 123)	p Value
Heart Failure, n (%)	50 (53.7)	37 (30.0)	<0.001
Total mortality, n (%)	33 (35.4)	24 (19.5)	0.01
In hospital mortality, n (%)	16 (17.2)	6 (4.8)	<0.001
Cardiovascular mortality, n (%)	24 (27.7)	13 (11.4)	<0.001

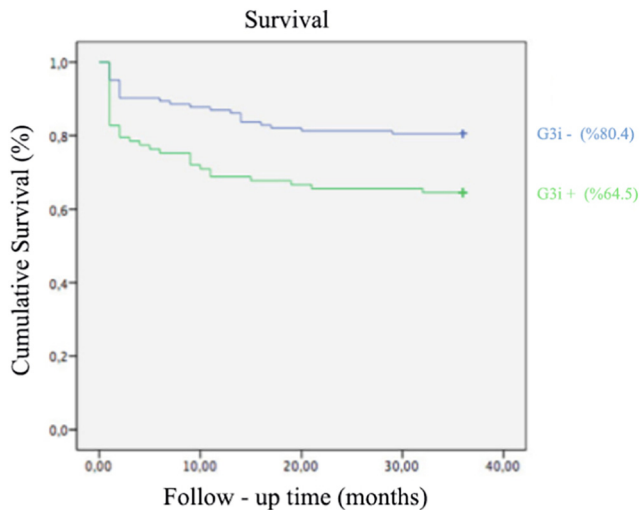


Fig. 3. Kaplan-Meier curve (At 36 month, the G3I– group has 24 deaths and 99 surviving patients. The G3I+ group has 33 deaths and 60 surviving patients).

In-hospital mortality rate (17.2% vs 4.8%, respectively; $p < 0.001$) and the overall mortality rate at 36-month follow-up (35.4% vs 19.5%; $p = 0.01$) was significantly higher in patients in the G3I+ group. When all deaths were examined, at G3I+ group, 24 of 33 (72.7%) deaths were cardiovascular death. At G3I– group, 13 of 24 (54.1%) deaths were cardiovascular death (Table 2). Cardiovascular mortality was higher in the G3I+ group ($p < 0.001$).

Multiple logistic regression analysis revealed that only higher age ($p = 0.002$) was independently associated with G3I.

The Kaplan-Meier curve revealed that mortality rate remained higher in the G3I+ group throughout all time periods during follow-up (Fig. 3).

Discussion

The occurrence of G3I has been shown to be independent of the duration of ischemia, and its prevalence in patients with STEMI ranges between 19% to 53% [2,8,9,16].

The association of G3I and long-term mortality in STEMI patients remains unclear and its correlation with the GRACE score system is not studied before.

In the current study, we investigated the relationship between G3I and variables known to be associated with mortality in STEMI such as age, DM, LVEF, time to treatment, previous MI story, Killip classification, renal failure, cardiogenic shock, and treatment

modality. Among these, only advanced age was found to be significantly and independently associated with the G3I occurrence. We found that G3I could be used as a predictor of in-hospital mortality and mortality at 36 months. We also observed a high correlation between G3I and the GRACE score and 36-month GRACE death risk percentages. This is one of the other remarkable findings of our study.

Eight independent parameters were used to calculate the GRACE risk score. These include age, heart rate, systolic BP, renal function (serum creatinine level), congestive heart failure (Killip class/diuretic usage), ST-segment deviation on admission ECG, cardiac arrest at admission and elevated cardiac necrosis biomarkers (troponin). When these eight parameters forming the GRACE risk score were examined the association with the G3I+ and G3I– groups, it was seen that the systolic BP was lower and the heart rate, creatine and troponin levels were higher in the G3I+ group. The Killip class was found to be significantly higher. The number of patients with cardiac arrest on admission was higher in the G3I+ group. Age and the number of patients with ST segment deviation on admission ECG (because all patients are STEMI) did not differ significantly between both groups (Table 3).

The Kaplan Meier curve demonstrated that G3I is a strong prognostic indicator of mortality. Taken together, our results demonstrate that QRS morphology may be used to identify patients at high risk for in-hospital and long-term mortality. These patients should be closely monitored to reduce mortality rates. We also found that QRS morphology was significantly correlated with cardiogenic shock and heart failure development but not with the length of hospital stays.

The prognosis of STEMI is closely associated with early risk stratification. In our study, we found that G3I is related to 36-month mortality. In many studies, it has been shown that G3I is associated with high SYNTAX score and high no-reflow rates [11,15]. In addition, Yang et al. showed that patients with anterior MI and G3I had larger infarct areas [17].

In a review that included studies performed by several independent groups in Israel, the United States, Spain, Italy, Scandinavia, Turkey, Korea and Japan Birnbaum et al. showed that patients with G3I on admission ECG had larger infarct size, less myocardial salvage and poorer clinical outcomes [5]. Our study supports that these results will be similar in long-term follow-ups.

Buber and colleagues have shown that G3I could be one of the strongest independent predictors of the no-reflow and post-thrombolytic rescue PCI ratios [18]. Weaver and colleagues and Rommel and his colleagues also found that patients with G3I had larger microvascular damage detected on cardiac Magnetic Resonance Imaging studies [19,20]. In another cardiac Magnetic Resonance Imaging study, Valle-Caballero and colleagues found that G3I on pre-reperfusion ECG in two or more leads is independently associated with larger myocardium at risk and infarct size in the setting of primary angioplasty-reperfusion anterior STEMI [21].

Tanriverdi et al., in a prospective study conducted on 316 STEMI patients, found that patients with G3I on admission ECG had less benefit from fibrinolytic therapy as compared with those without G3I [6].

The Thrombolysis in Myocardial Infarction 4 (TIMI 4) trial revealed that patients with G3I were older, had more anterior STEMI, less often pre-infarction angina and higher rates of mortality than patients without G3I. The combined weighted endpoint of death, re-infarction, heart failure, or LVEF was higher in patients with G3I.

Bigi et al. compared LVEF between patients with and without G3I and found that while there was no significant difference at discharge, LVEF was significantly lower in patients with G3I at 6-month follow-up [22].

Table 3
Association with GRACE risk score parameters and G3I.

Grace score parameters	G3I+ (n: 93)	G3I– (n: 123)	p Value
Age (years)	62 ± 15	59 ± 14	0.07
Heart rate (bpm)	103 ± 28	88 ± 17	<0.001
Systolic BP (mm Hg)	110 ± 25	122 ± 23	<0.001
Creatinine (mg/dl)	1.0 ± 0.31	0.9 ± 0.26	0.01
Heart failure, Killip ≥II, n (%)	26 (27.9)	7 (5.6)	<0.001
Troponin I (ng/ml)	7.4 ± 0.9	5.5 ± 0.7	0.04
ST deviation on admission ECG (%)	100	100	1
Cardiac arrest on admission, n (%)	9 (9.6)	4 (3.2)	<0.001

These studies have suggested a mechanistic link between G3I and poor outcomes. As similar with the results of these studies, the long-term mortality rates were higher in patients with G3I+ than in patients with G3I– in our study, too.

Garcia-Rubira et al., in a study performed on 634 patients with STEMI reported that the presence of G3I in elderly patients was associated with adverse outcomes. They found that G3I was more prevalent in patients older than 75-years of age and that increased in-hospital mortality was associated with G3I only in these patients [23]. In addition, in our study, multiple logistic regression analysis revealed that only age was independently associated with G3I.

Tang et al. found that GRACE risk score accurately predicts long-term mortality and accurately discriminated survivors from non-survivors over the longer term (up to 4 years) in all ACS patients (n: 1143). The GRACE Risk Score worked for all ACS patients at all time points with C index >0.75 [24]. Our results validate GRACE Risk Score as a useful tool in the risk stratification of patients with STEMI.

Nigel et al., in a study, found that the presence of low QRS voltage in the ECG of patients with ACS may provide increased prognostic benefit for in-hospital mortality and re-infarction beyond the established GRACE risk score variables [25]. In our study, we observed that G3I on admission ECG can predict long-term mortality alone, independent of all variables on the GRACE risk score.

The ECG deviation is a variable in the GRACE risk scoring system, but the G3I n is not a separate parameter. In future studies, it should be investigated that the presence of G3I at the time of admission in STEMI patients may give additional predictive power to the GRACE risk score. We think that assessing the presence of G3I may increase the accuracy of the GRACE risk score to predict long-term mortality.

In contrast to our findings, in a retrospective analysis conducted on patients with ACS, Zalenski et al. showed that the presence of G3I was not associated with 2-year mortality. The study, however, was criticized on several grounds. First, it involved patients both with (69.4%) and without (30.6%) STEMI. Second, researchers failed to report whether patients with high-risk non-STEMI (e.g. diffuse ST depression with ST elevation in aVR) were included. And finally, data on reperfusion therapy and duration of symptoms was missing [26].

To the best of our knowledge, this is the first study in the literature to assess the association between G3I and long-term mortality as well as its correlation with the GRACE score system. We think that the G3I, which is highly correlated with the GRACE risk score and easily detectable, can be used as a practical and straightforward method to predict long-term mortality. As a result of future investigations, in patients with STEMI, G3I may be added as a value on top of GRACE risk score. Further studies with larger sample size should be conducted to confirm our findings.

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