Short Communication

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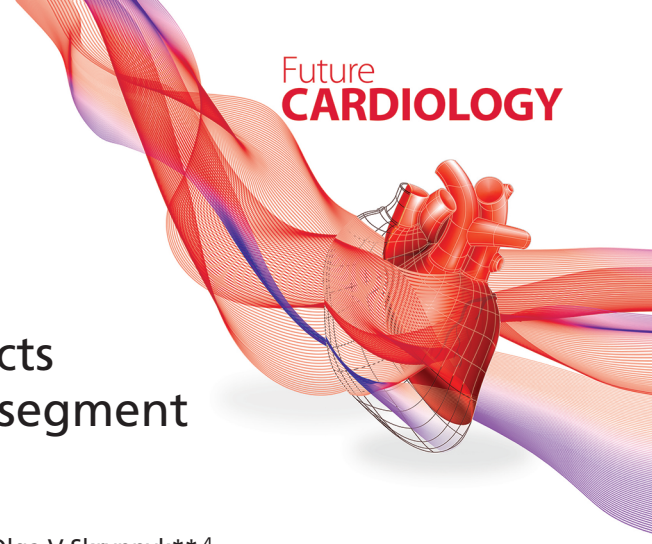

Subclinical emotional distress predicts 6-month clinical outcomes after ST-segment elevation myocardial infarction

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Aim: To investigate associations between subclinical distress and 6-month clinical outcomes after ST-segment elevation myocardial infarction (STEMI). **Materials & methods:** The case–control study involved 144 STEMI patients (72 STEMI having subclinical emotional disturbances were included to the case group and 72 STEMI individuals matched with age, sex and cardiovascular risk factors were enrolled to the control group). The primary end point was the combination of 6-month events including CV death, recurrent angina, newly diagnosed heart failure and re-hospitalization. **Results:** The emotional distress predicted out-hospital combined end point (odds ratio [OR] = 2.48; 95% CI: 1.12–5.33; p = 0.034). Other independent predictors of out-hospital end point were Type 2 diabetes mellitus (OR = 1.10; 95% CI: 1.02–1.23; p = 0.048), thrombolysis in myocardial infarction score <6 units (OR = 0.86; 95% CI: 0.67–0.92; p = 0.001) and the number of culprit vessels (OR = 1.19; 95% CI: 1.02–1.34; p = 0.002). **Conclusion:** Premorbid emotional distress independently predicted 6 month combined clinical end point in STEMI patients.

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Keywords: anxiety • clinical outcomes • depression • emotional distress • percutaneous coronary intervention • STEMI • stress

ST-segment elevation myocardial infarction (STEMI) is associated with a high level of mortality, while reperfusion therapy including complete percutaneous coronary intervention (PCI) and thrombolytic therapy had sufficiently improved the survival rate [1]. After implementation of early PCI, the in-hospital mortality rate has declined up to 4–7%, although in numerous of developing countries average of this parameter remained to be within 10–14% [2]. There are no predictive scores to identify post-STEMI patients after successful PCI at high risk of recurrent major adverse cardiovascular (CV) events [3]. Previous clinical studies have shown the predictors for clinical outcomes in STEMI were smoking, older age, hypertension, heart failure (HF), atrial fibrillation, increased circulating levels of brain natriuretic peptide, D-dimer, serum uric acid and high values of thrombolysis in myocardial Infarction (TIMI) score [4–6]. There is a large number of evidence regarding of the impact of anxiety and depression on the occurrence and worsening of CV diseases including STEMI [7]. The emotional distress including anxiety and depression was associated with poor survival and major adverse CV events in STEMI patients [8].

In fact, the nature of the relationship of the premorbid and postmorbid mental and somatic state remains insufficiently studied but acquires relevance [9,10]. For instance, there is strong relationship between premorbid bipolar disorders and endothelial dysfunction and arterial stiffness in STEMI patients [11]. There was a significant relation between a risk of unplanned re-admission to the hospital and depression in patients with after STEMI [12].

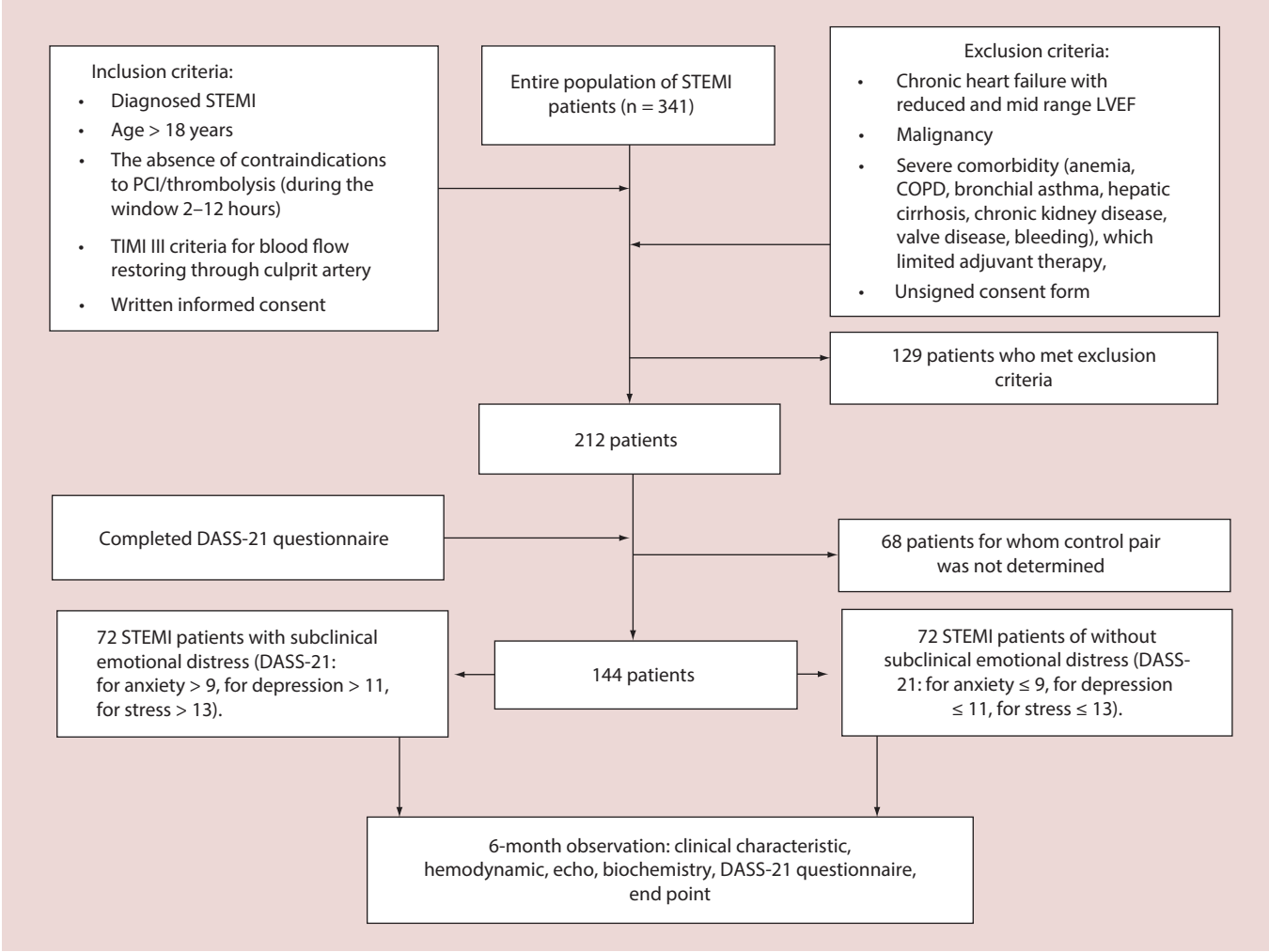

Figure 1. The study design: flow chart.
COPD: Chronic obstructive pulmonary disease; DASS-28: "Depression, Anxiety and Stress-21" questionnaire; LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; TIMI: Thrombolysis in myocardial infarction score.

The meta-analysis has revealed that both premorbid and postmorbid major depression influenced negatively on mortality among patients with STEMI [13]. However, there is limiting evidence regarding a role of asymptomatic premorbid emotional disorders in STEMI-related clinical outcomes [14]. Therefore, the mechanisms that ensure an interaction between psychological factors and progression on coronary atherosclerosis remain to be unclear [15]. The aim of the study was to investigate associations between subclinical level of anxiety, depression and stress with unfavorable events at 6-month observation after STEMI.

Materials & methods

We used a database consisted a total of 341 patients with confirmed STEMI who had admitted to intensive care unit of 'L.T.Malaya TNI NAMSU' from 2016 August to 2019 February (Figure 1). Acute STEMI was diagnosed according to European Cardiology Society (ECS) Guidelines (2017) [1]. From entire STEMI patient population (n = 341), according to inclusion and noninclusion criteria, we enrolled 212 STEMI individuals who were completely re-vascularized with PCI. Inclusion criteria were established acute STEMI required to be treated with PCI, age >18 years old. Exclusion criteria were previous myocardial infarction, established chronic HF, known malignancy, severe comorbidities.

A total of 144 STEMI patients treated with primary PCI with bare metal stent (COMMANDER, 'Alvimedica', Turkey) after completing DASS-21 questionnaire were selected to the study. Thrombolytic therapy (tenecteplase,

Boehringer Ingelheim Pharma, Germany) was performed prior to PCI, if needed. All STEMI patients have received adjuvant treatment according to current ESC recommendations [1].

Ethical declaration

All procedures performed in the study involving human participants were in accordance with the ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and approved by the local ethics committee (Protocol №8, 29 August 2016). All patients included in the study have given voluntary inform consent to participate.

Subclinical emotional disturbance evaluation

We used 'Depression, Anxiety and Stress-21" (DASS-21) questionnaire ((a) depression [DASS-Depression [DASS-D]], anxiety [DASS-Anxiety [DASS-A]], stress [DASS-Stress [DASS-S]]) to identify premorbid subclinical emotional distress [16]. The Depression Scale included symptoms that reflect dysphoric mood (sadness or uselessness futility), the Anxiety Scale included physical arousal, fear and panic attacks (trembling or pallor), and the Stress Scale was based on verification of tension, irritability and tendency to over-react to stressors. These symptoms were not evaluated by Beck Depression Inventory and Beck Anxiety Inventory [16]. All patients in the case cohort had subclinical emotional distress. Patients with recurrent depressive disorder (F 33.0-3) or depressive episode of different severity (F 32.0-3) generalized anxiety disorder (F 41.1) and mixed anxiety and depressive disorder (F41.2) according to the criteria for the International Classification of Diseases of the 10th revision (ICD-10) were not included in the study.

The score 9 points and more on the Anxiety Scale meant presence of anxiety. The score over 11 points on Depression Scale meant decrease in mood. A stressful situation assumed when the score more than 13 points on a corresponding scale. In 2–3 days, PCI emotionally stable patient was asked about psychological state that was prior to event and they filled out the questionnaire personally.

Case & control cohorts' determination

In total, 72 STEMI patients with subclinical emotional distress according to the DASS-21 questionnaire (anxiety >9 points, depression >11 points and stress >13 points) were included into the case group, and 72 STEMI patients who were matched to sex, age and CV risk factors but not having emotional distress according to the DASS-21 questionnaire (anxiety ≤9 points, depression ≤11 points and stress ≤13 points) were enrolled in the control group.

Sample size calculation

Sample size was calculated with the G-power calculator for Windows taking into account α-error = 0.05 and β-error = 0.2. Expected frequency of end points (composite of CV death, recurrent angina and newly diagnosed HF) was 14%, in-hospital mortality was 7.5%, sample size was calculated as 144 (72 comparable patients in each group) [17].

Coronary angiography

All STEMI patients underwent coronary angiography through radial or femoral vascular access at admission to the critical care unit. Digital x-Ray system 'Integris Allura' manufactured by Philips Healthcare (The Best, The Netherlands) was used. Successful coronary angiography was defined as residual stenosis <50% and TIMI grade 3 flow was determined.

Determination of risk factors & comorbidities

Hypercholesterolemia (HCE) was diagnosed according to ECS dyslipidemia guideline (2016) [18]. Hypertension was diagnosed according to ECS guideline on diagnostics and treatment of arterial hypertension (2018) [19]. HF was diagnosed according to ECS HF guideline (2016) [20].

Echo examination

Transthoracic echocardiography was performed on 'Aplio 500' (TUS-A500) TOSHIBA MEDICAL SYSTEMS CORPORATION (Japan). We measured left ventricular end diastolic volume, left ventricular end systolic volume, left ventricular ejection fraction (LVEF) using Simpson's method. Left ventricular global longitudinal strain (e`) and early transmitral velocity (E) were measured by Tissue Doppler Imaging technique and impulse transmitral Doppler regime, respectively.

Determination of STEMI prognosis

We used the TIMI score and GRACE score to validate prognostic capacity after STEMI [21,22].

SYNTAX score determination

SYNTAX score was used to assess the severity of coronary atherosclerotic lesions and it was calculated by experienced interventional cardiologist accordingly [23].

Determination of end points

The primary end point was combination of 6-month events including CV death, recurrent angina, newly diagnosed HF and re-hospitalization. CV death was ascertained by personal or phone contacting the family doctor or the hospital where the patient died. The diagnosis of recurrent angina required the presence of clinical signs/symptoms or electrocardiographic changes. The diagnosis of HF *de novo* has been established per current ESC clinical guideline [20]. Hospitalization was ascertained by direct or phone contact with the hospital reception where the patient was admitted.

Blood samples

Blood samples were collected prior to PCI and then immediately centrifuged. The serum was freezed with -70°C and stored in plastic tubes.

Troponin I (Tn I) concentrations were measured with chemo luminescent immunoassay (Humalyser 2000, Mannheim, Germany). The TnI level average was 0.5–50 ng/ml.

The lipid profile was measured by direct enzymatic method (Roche P800 analyzer, Basel, Switzerland). The intra-assay and interassay coefficients of variation were <5%.

Statistics

The Statistical Package for the Social Sciences (IBM SPSS software version 23.0 for Windows, NY, USA) was used for analyses. All data were assessed for normal distribution of their values using the Kolmogorov–Smirnov test. Data are presented as mean ± SD or median and interquartile range depending a type of distribution. Categorical variables are presented as frequencies (n) and percentages (%).The intergroup differences and quantitative values were determined with Mann–Whitney or Wald–Wolfowitz criteria and the $\chi 2$ and exact F Fisher tests. Spearman's rank test was used to relationship between the severity of emotional distress and age, gender, CV risk factors. Optional logistic regression was used to analyze the influence of multiple factors in STEMI population. Odds ratio was calculated for combined end point and *de novo* HF in case cohort versus control cohort. All differences were considered statistically significant with two-tailed $p < 0.05$.

Results

Basic characteristics of STEMI patients are presented in Table 1. The entire population of the STEMI patients consists from predominantly male (75.0%) with age average of 59 years (from 49 to 71 years) and several CV risk factors, such as hypertension (81.3%), Type 2 diabetes mellitus (T2DM) (19.4%), HCE (64.6%) and abdominal obesity (37.5%). There were not significant differences between both patients' cohort in demographic, CV risk factors, lipid profile and serum peak Tn I levels.

There were significant differences between both groups in all categories of DASS-21. For instance, DASS-21A 10.3 (9.0–11.0) and 6.8 (3.0–9.0), respectively ($p = 0.049$); DASS-21D 9.4 (9.0–10.0) and 5.7 (3.0–8.0), respectively (0.042); DASS-21S 10.7 (9.0–12.0) and 5.9 (2.0–9.0), respectively ($p = 0.038$).

Table 2 reports hemodynamic performances, STEMI localization, STEMI risk scores, the number of injured coronary arteries in patients who were enrolled in the study. In fact, entire population of STEMI patients was constructed from individuals with global LVEF >40% (average of 41–62%), ECG criteria of anterior localization of MI (52.8%), predominantly one or two vessels injury (43.8 and 32.6%, respectively) with involvement of left artery descending (68.8%) and right coronary artery (56.2%). STEMI risk scores have revealed mild-to-moderate risk of poor clinical outcomes and moderate severity of atherosclerosis changes. We did not find significant differences between both patients' cohorts in hemodynamic, STEMI localization, STEMI risk scores, concomitant medications, while frequency of two coronary artery injury was figured frequently in the control cohort compared with case cohort.

Table 1. Basic characteristic of ST-segment elevation myocardial infarction patients enrolled in the study depending on emotional disturbances.

	Entire STEMI population (n = 144)	Case (n = 72)	Control (n = 72)	χ^2, p-value
Age (years), mean (SD)	59.25 ± 9.33	59.91 ± 9.18	58.11 ± 9.65	0.222
Male, n (%)	108 (75.0%)	49 (68.1%)	59 (81.9%)	3.70, p = 0.054
Female, n (%)	36 (25.0%)	23 (31.9%)	13 (18.1%)	
Hypertension, n (%)	117 (81.3%)	58 (80.6%)	59 (81.9%)	0.05, p = 0.831
T2DM, n (%)	28 (19.4%)	16 (22.2%)	12 (16.7%)	0.71, p = 0.399
Smoking, n (%)	66 (45.8%)	28 (38.9%)	38 (52.8%)	2.80, p = 0.094
HCE, n (%)	93 (64.6%)	46 (63.9%)	47 (65.3%)	0.03, p = 0.862
BMI >30 kg/m^2, n (%)	54 (37.5%)	27 (37.5%)	27 (37.5%)	1.0
Peak TnI, ng/ml	18.90 [10.70–89.91]	18.48 (10.53–87.63)	19.56 (13.77–99.63)	0.645
TC, mmol/l	5.11 ± 1.17	5.25 ± 1.45	4.97 ± 1.22	0.283
HDL, mmol/l	1.18 ± 0.56	1.23 ± 0.74	1.13 ± 0.37	0.309
LDL, mmol/l	3.61 ± 1.22	3.23 ± 1.37	2.92 ± 1.01	0.234
TG, mmol/l	1.94 ± 1.10	1.89 ± 1.33	2.02 ± 1.06	0.152
GFR, ml/min	74.23 ± 15.44	70.79 ± 18.11	76.85 ± 21.68	0.112

GFR: Glomerular filtration rate; HCE: Hypercholesterolemia; SD: Standard deviation; STEMI: ST-segment elevation myocardial infarction; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides; TnI: Cardiac troponin I.

Therefore, at least 27% patients of entire population were found having in-hospital complications including acute HF (II-III/IV Killip class of HF was 9.2%/2.1%). Individuals who were included in the case cohort had higher frequency of onset of II-III Killip class of HF than patients from control cohort. Additionally, combined end point was reported in quarter of patients form entire cohort, and *de novo* HF was the only cause that significantly distinguished case cohort from control cohort.

Correlation between the severity of emotional distress & age, gender, CV risk factors

There were no relations between severity of emotional distress and age and gender in the entire cohort, as well as in both patients' cohorts. There were significant relations between severity of emotional distress and presentation of T2DM (r = 0.36; p = 0.026).

Univariate & multivariate logistic regression analysis of out-hospital combined clinical end point

The independent risk factors affecting out-hospital combined clinical end point were defined by logistic regression analysis. Unadjusted univariate logistic regression analysis has yielded age (odds ratio [OR] = 1.29; 95% CI: 1.02–2.77; p = 0.044), T2DM (OR = 1.18; CI: 1.08–1.32; p = 0.036), heart rate (OR = 1.13; OR = 1.02–1.27; p = 0.048), LVEF (OR = 1.09; CI: 1.03–1.14; p = 0.046) the number of culprit vessels (OR = 1.23; CI: 1.10–1.47; p = 0.003), emotional distress (OR = 2.56; 1.18–5.90; p = 0.002) and TIMI <6 units (OR = 0.70; CI: 0.62–0.84; p = 0.002) significantly predicted out-hospital combined end point. Unadjusted multivariate logistic regression analysis has shown that T2DM (OR = 1.10; CI: 1.02–1.23; p = 0.048), the number of culprit vessels (OR = 1.19; CI: 1.02–1.34; p = 0.002), emotional distress (OR = 2.48; 1.12–5.33, p = 0.034) and TIMI <6 units (OR = 0.86; CI: 0.67–0.92; p = 0.001) were independent predictors for combined end point.

After adjusting for known multiple clinical prognostic factors, such as age, male gender, smoking, T2DM, heart rate, LDL cholesterol, peak Tn I level, LVEF, severity of STEMI, the number of culprit vessels, emotional distress remained the predictor of out-hospital combined end point (OR = 2.48; 95% CI: 1.12–5.33; p = 0.034). Consequently, we found that the only the total score index of the DASS-21 related to combined clinical end point, but any component of the questionnaire did not. (Table 3). In fact, the emotional distress influenced significantly on the development of HF for 6 months of follow-up (OR = 3.75; 95% CI: 1.12–10.61; p = 0.039).

Kaplan–Meier analysis of out-hospital combined clinical end point in patients with & without subclinical emotional distress

Kaplan–Meier curves have exhibited a prominent divergence which appeared to be significance to the end of the study (Figure 2). In fact, the lowest number of accumulated combined clinical end points were found in patients

Table 2. Hemodynamic performances, ST-segment elevation myocardial infarction localization, ST-segment elevation myocardial infarction risk scores and the number of injured coronary arteries in patients enrolled in the study.

Data	Entire STEMI population (n = 144)	Case (n = 72)	Control (n = 72)	χ^2, p-value
Hemodynamic performances				
HR, per min	76 ± 15	77 ± 14	74 ± 17	0.192
SBP, mmHg	135 ± 16	137 ± 18	131 ± 15	0.157
DBP, mmHg	81 ± 12.53	81 ± 12.56	78 ± 12	0.122
LV EDV, ml	136 ± 12	136 ± 13	138 ± 13	0.672
LV ESV, ml	64 ± 12	65 ± 13	63 ± 15	0.430
LV EF, %	53 ± 9	51 ± 8	54 ± 7	0.142
E/e` ratio, unit	11 ± 4	12 ± 5	11 ± 4	0.116
STEMI localization				
Anterior MI, n (%)	76 (52.8%)	39 (54.2%)	37 (51.4%)	0.11, p = 0.74
Posterior MI, n (%)	68 (47.2%)	33 (45.8%)	35 (48.6%)	
One vessel injury, n (%)	63 (43.8%)	29 (40.3 %)	34 (47.2%)	0.71, p = 0.401
Two vessel injury, n (%)	47 (32.6%)	24 (33.3%)	23 (31.9%)	0.03, p = 0.86
Three and more vessel injury, n (%)	33 (22.9%)	19 (26.4%)	14 (19.4%)	0.98, p = 0.32
Amount of stenosis	2.35 ± 1.24	2.39 ± 1.44	2.32 ± 1.68	p = 0.79
LAD, n (%)	99 (68.8%)	54 (75%)	45 (62.5%)	2.62, p = 0.11
RCA, n (%)	81 (56.2%)	43 (59.7%)	38 (52.8%)	0.71, p = 0.40
LCX, n (%)	55 (38.2%)	29 (40.3%)	26 (36.2%)	0.26, p = 0.607
LCA, n (%)	8 (5.6%)	6 (8.3%)	2 (2.8%)	0.14, p = 0.138
STEMI risk scores				
TIMI risk score, point	6 (4–7)	6 (4–7)	6 (4–8)	0.96
Total SYNTAX score, point	27.54 ± 6.41	28.7 ± 6.15	25.65 ± 8.82	0.134
Total GRACE score, points	150 (120–172)	143 (117–170)	152 (119–176)	0.294
PCI and concomitant medications				
Primary PCI, n (%)	105 (7.29%)	53 (73.6%)	52 (72.2%)	0.04, p = 0.851
Trombolysis+PCI, n (%)	39 (27.0%)	19 (26.4%)	20 (27.8%)	0.04, p = 0.851
β-adrenoblockers, n (%)	123 (85.4%)	59 (81.9%)	64 (88.9%)	0.89, p = 0.345
ACEiI / ARAII, n (%)	139 (96.5)	69 (95.8%)	70 (97.2%)	p = 0.500
Clopidogrel or ticagrelor, n (%)	144 (100%)	72 (100%)	72 (100%)	p = 1.00
Statins, n (%)	144 (100%)	72 (100%)	72 (100%)	p = 1.00
MCR antagonists, n (%)	16 (11.1%)	7 (9.7%)	9 (12.5%)	0.07, p = 0.791
The number of in-hospital complications				
Total number, n (%)	40 (27.8%)	24 (33.3%)	16 (22.2%)	2.22, p = 0.137
II-III Killip class of HF, n (%)	13 (9.2%)	10 (13.9%)	3 (4.2%)	R = 0.0389
IV Killip class of HF, n (%)	3 (2.1%)	1 (1.4%)	2 (2.7%)	R = 0.500
6 month end points				
Recurrent angina, n (%)	11 (7.6%)	6 (8.3%)	5 (6.9%)	p = 0.608
De novo HF, n (%)	17 (11.8%)	13 (18.1%)	4 (5.6%)	p = 0.039
Hospitalization, n (%)	7 (4.9%)	4 (5.6%)	3 (4.2%)	p = 0.500
Death, n (%)	1 (0.7%)	1 (1.4%)	0	p = 0.500
Combined end point, n (%)	36 (25.0%)	24 (33.3%)	12 (22.2%)	3.85, p = 0.0343

ACEi: Angiotensin converting enzyme inhibitor; ARAII: Antagonists of receptors to angiotensin-II; DVP: Diastolic blood pressure; E: Early diastolic transmitral blood flow; e': Longitudinal strain; HF: Heart failure; HR: Heart rate; LAD: Left artery descending; LCA: Left coronary artery; LCX: Left circumflex coronary artery; LVEF: Left ventricular ejection fraction; LV EDV: Left ventricular end diastolic volume; LV ESV: Left ventricular end systolic volume; MCR: Mineralocorticoid receptor; MII: Myocardial infarction; PCI: Percutaneous coronary intervention; RCA: Right coronary artery; SBP: Systolic blood pressure; STEMI: ST segment elevation myocardial infarction; TIMI: Thrombolysis in myocardial Infarction score.

Table 3. Univariate and multivariate analysis of out-hospital combined clinical end point.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.29	1.02–2.77	0.044	1.12	1.00–1.42	0.34
Gender (Male)	1.48	0.79–3.55	0.22	-		
Smoking (present vs absent)	1.07	1.00–1.18	0.066	-		
Hypertension (present vs absent)	1.02	0.94–1.08	0.82	-		
T2DM (present vs absent)	1.18	1.08–1.32	0.036	1.10	1.02–1.23	0.048
BMI ($\geq$30 kg/m^2 vs <30 kg/m^2)	1.04	0.98–1.08	0.84	-		
Heart rate	1.13	1.02–1.27	0.048	1.07	1.00–1.16	0.058
LDL-C	1.05	1.00–1.10	0.26	-		
Peak troponin I level	1.04	1.00–1.07	0.76	-		
LVEF	1.09	1.03–1.14	0.046	1.06	1.00–1.10	0.063
Number of culprit vessels	1.23	1.10–1.47	0.003	1.19	1.02–1.34	0.002
Emotional distress (present vs absent)	2.56	1.18–5.90	0.022	2.48	1.12–5.33	0.034
TIMI <6 units	0.70	0.62–0.84	0.002	0.86	0.67–0.92	0.001

LDL-C: LDL-cholesterol; LVEF: Left ventricular ejection fraction; OR: Odds ratio; T2DM: Type 2 diabetes mellitus; TIMI: Thrombolysis in myocardial Infarction score.

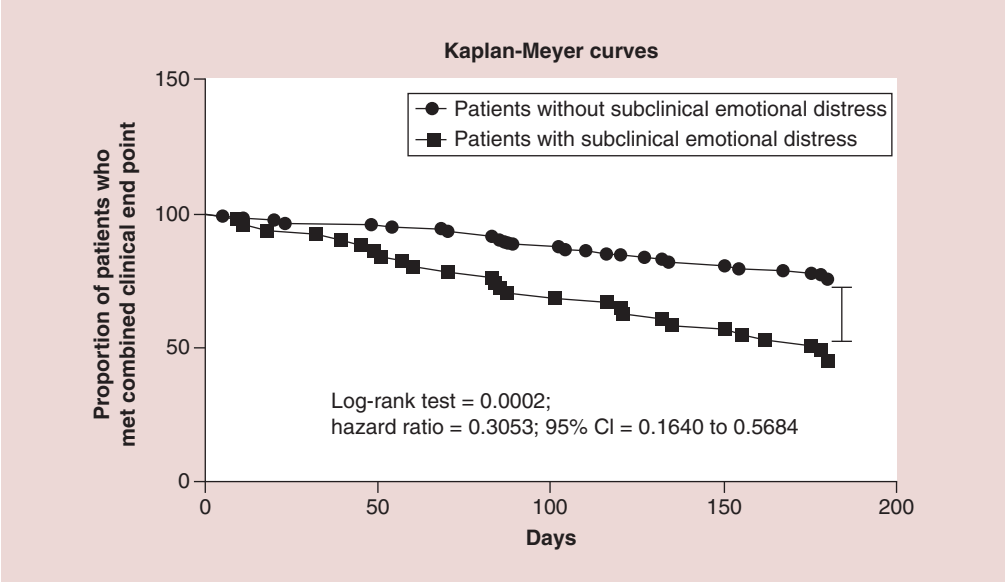

Figure 2. Kaplan–Meier curves in patients with and without pre-ST-segment elevation myocardial infarction subclinical emotional distress.

without subclinical emotional distress, whereas presentation of emotional distress was associated with the worst clinical outcome (HR = 0.3053; 95% CI: 0.164–0.5684; p = 0.0002).

Thus, STEMI patients who were enrolled in the study having emotional distress have exhibited sufficiently worse clinical outcomes that those who had no emotional distress.

Discussion

The results of the study have revealed that pre-STEMI emotional stress may have a negative impact on long-term clinical outcomes after PCI. Although pre-STEMI major depression has previously determined as predictor of a

risk of in-hospital death in the STEMI patients [24,25], we reported first that subclinical emotional distress may be an independent predictor of poor clinical outcomes after STEMI and that this was associated with increased a risk of *de novo* HF onset. There is a large body of evidence regarding a value of moderate-to-severe depression in 30-day re-admission after STEMI [26] and prognosis of myocardial infarction [27]. Therefore, there are close associations between comorbid depression and severity of stable coronary artery disease, advance in HF, atrial fibrillation and recurrent ischemia [28–31].

We hypothesized that some physiological factors, such as subclinical emotional stress, may influence on vasculature and endothelium through several molecular mechanisms and thereby accelerate atherosclerosis, mediate low-grade microvascular inflammation, and induce endothelial dysfunction, which are known factors involved in the pathogenesis of myocardial dysfunction HF. Indeed, there are findings that support an idea that depression and anxiety are able to influence on endothelium indirectly via modulation of the circulating levels of proinflammatory cytokines, such as C-reactive protein, IL-1, IL-6, TNF-α and others [32–34]. Noted that these data were found in patients with known major depression and, however, this evidence cannot be extrapolated to other populations including subclinical emotional distress patients. Interestingly, previous clinical studies have shown that successful PCI might positively influence on post-STEMI survival and urgent re-admission through decreasing of the levels of depression, anxiety and panic agoraphobia rating scales [35–37]. However, we unleashed that subclinical pre-STEMI emotional distress remained a certain coronary risk factor that mediates post-STEMI clinical outcome. Although recent studies STEMI women demonstrated an elevated risk of having anxiety and/or depression disorder compared with men [37,38], we did not confirm similar issue. Therefore, the gender proportion among the STEMI patients having subclinical emotional distress and those who did not this disturbance was similar. Additionally, some investigators have reported that the severity of depression strongly correlated to the number of traditional CV risk factors including HCE, hypertension and T2DM. Moreover, it was not clear whether depression and anxiety can directly influence on the post-STEMI outcomes beyond conventional risk factors [39]. We have determined that subclinical emotional distress became discriminative value even after adjusting to CV risk factors including age, gender and T2DM. We also found that the Kaplan–Meier curves have demonstrated steady divergence between patients' cohorts and the number of combined clinical end point accumulation was sufficiently lower in the patients without pre-STEMI subclinical emotional distress than those who had. However, there is limited evidence regarding pre-STEMI emotional distress on post-STEMI clinical outcomes. Majority studies have revealed a relationship between post-STEMI depression and post-STEMI outcomes. In fact, we report first that there is a phenomenon of pre-STEMI subclinical emotional distress that can directly effect on post-STEMI outcomes in patients with complete revascularization with PCI, while it was been expected otherwise.

The exact molecular mechanism that mediates emotional disturbances to coronary events and HF still remains unclear. We suggest that post-STEMI patients after success in PCI could be incomplete adhere to concomitant medications including statins and antiplatelet drugs, the effects of which on long-term prognosis have established. Yet, we cannot rule-out a negative effect of microvascular obstruction after PCI, and pre-STEMI emotional distress can be related to innate mechanisms of development of endothelial dysfunction, such as deficiency of endogenous production of brain-derived neurotrophic factor and VEGF [40,41]. Probably, T2DM could influence a negative impact on the microvascular inflammation through increase in reactive oxygen species that throughout microvascular dysfunction leads to worse clinical outcomes in post-STEMI individuals. Additionally, subclinical microvascular obstruction in post-STEMI patients can be clinically silent and corresponds to abnormalities on ECG, such as inverted T waves, persistence of ST-segment depression, prolongation of QT intervals, premature contraction and salvo complexes/nonsustained tachycardia episodes [42,43]. Although these factors were widely described, we did not find close association between clinical combined end point and ECG abnormalities amid post-STEMI patients after completed revascularization in follow-up period, but emotional distress was found to be independent predictor of poor outcome. Another factor that could contribute to a relationship between subclinical emotional distress and post-STEMI outcome is persistent masked major depression that was not being able to determine with questionnaire completion at the screening [44]. However, the main cause of finding received in the investigation requires to be evaluated in the large clinical study.

Study limitations

The study has several limitations. The first limitation is small sample size, while the period of the screening was 2.5 years (from August 2016 to February 2019). It was difficult to obtain clear information regarding pre-STEMI emotional status in patients after STEMI treated with PCI. Moreover, each STEMI patient had been consulted by

psychiatrist, who had excluded major depression at the screening and serious emotional disturbance playing down the value of appropriate information collected at baseline. This was the second limitation. Additionally, this was the single center study and it was not adjudication of the end point by an external agency.

Conclusion

We found that pre-STEMI subclinical emotional distress may be a predictor the 6 month poor clinical outcomes.

Summary points

Background

- Subclinical emotional stress may accelerate microvascular inflammation and induce endothelial dysfunction that leads to poor prognosis amid patients with ST-segment elevation myocardial infarction (STEMI). The aim of the study was to investigate associations between pre-STEMI subclinical distress and 6-month clinical outcomes in post-STEMI patients.

Methods

- The case–control study involved 144 STEMI patients (72 STEMI having subclinical emotional disturbances were included to the case group and 72 STEMI individuals matched with age, sex and cardiovascular risk factors were enrolled to the control group. The primary end point was combination of 6 month events including cardiovascular death, recurrent angina, newly diagnosed heart failure (HF) and re-hospitalization.

Results

- The combined end point was reported in 25% of patients form entire cohort, and HF was the only cause that significantly distinguished case cohort from control cohort. The emotional distress remained the predictor of out-hospital combined end point (odds ratio [OR] = 2.48; 95% CI: 1.12–5.33; p = 0.034). Other independent predictors of out-hospital end point were Type 2 diabetes mellitus (OR = 1.10; 95% CI: 1.02–1.23; p = 0.048), thrombolysis in myocardial infarction score (TIMI) <6 units (OR = 0.86; 95% CI: 0.67–0.92; p = 0.001) and the number of culprit vessels (OR = 1.19; 95% CI: 1.02–1.34; p = 0.002). The emotional distress influenced significantly on the development of HF for 6 months (OR = 3.75; 95% CI: 1.12–10.61; p = 0.039).

Conclusion

- Premorbid emotional distress together Type 2 diabetes mellitus, thrombolysis in myocardial infarction score, the number of culprit vessels predicted 6-month combined clinical end point in post-STEMI patients treated by percutaneous coronary intervention. Post-STEMI patients with pre-STEMI emotional distress had higher risk of HF *de novo*.

Author contributions

Conception and design: OV Petyunina; Writing of the article: OV Petyunina, MP Kopytsya and AE Berezin; Critical revision of the article: AE Berezin; Psychiatric counseling: OV Skrynnik.

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