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ORIGINAL ARTICLE

Observational Study

Prevalence of posttraumatic stress disorder following acute coronary syndrome and clinical characteristics of patients referred to cardiac rehabilitation

Ivana Sopek Merkaš, Nenad Lakušić, Zdenko Sonicki, Barbara Koret, Sandra Vuk Pisk, Igor Filipčić

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Abstract

BACKGROUND

Studies have demonstrated that patients who have experienced acute coronary syndrome (ACS) have an increased risk of developing posttraumatic stress disorder (PTSD) and experiencing worse survival outcomes than those who do not develop PTSD. Nevertheless, the prevalence rates of PTSD following ACS vary widely across studies, and it is noteworthy that in most cases, the diagnosis of PTSD was based on self-report symptom questionnaires, rather than being established by psychiatrists. Additionally, the individual characteristics of patients who develop PTSD after ACS can differ widely, making it difficult to

identify any consistent patterns or predictors of the disorder.

AIM

To investigate the prevalence of PTSD among a large sample of patients undergoing cardiac rehabilitation (CR) after ACS, as well as their characteristics in comparison to a control group.

METHODS

The participants of this study are patients who have experienced ACS with or without undergoing percutaneous coronary intervention and are enrolled in a 3-wk CR program at the largest CR center in Croatia, the Special Hospital for Medical Rehabilitation Krapinske Toplice. Patient recruitment for the study took place over the course of one year, from January 1, 2022, to December 31, 2022, with a total of 504 participants. The expected average follow-up period for patients included in the study is about 18 mo, and currently ongoing. Using self-assessment questionnaire for PTSD criteria and clinical psychiatric interview, a group of patients with a PTSD diagnosis was identified. From the participants who do not have a PTSD diagnosis, patients who would match those with a PTSD diagnosis in terms of relevant clinical and medical stratification variables and during the same rehabilitation period were selected to enable comparability of the two groups.

RESULTS

A total of 507 patients who were enrolled in the CR program were approached to participate in the study. Three patients declined to participate in the study. The screening PTSD Checklist-Civilian Version questionnaire was completed by 504 patients. Out of the total sample of 504 patients, 74.2% were men (n = 374) and 25.8% were women (n = 130). The mean age of all participants was 56.7 years (55.8 for men and 59.1 for women). Among the 504 participants who completed the screening questionnaire, 80 met the cutoff criteria for the PTSD and qualified for further evaluation (15.9%). All 80 patients agreed to a psychiatric interview. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders criteria. Among the variables analyzed, there was a noticeable difference in the percentage of theoretical maximum achieved on exercise testing between the PTSD and non-PTSD groups. Non-PTSD group achieved a significantly higher percentage of their maximum compared to the PTSD group (P = 0.035).

CONCLUSION

The preliminary results of the study indicate that a significant proportion of patients with PTSD induced by ACS are not receiving adequate treatment. Furthermore, the data suggest that these patients may exhibit reduced physical activity levels, which could be one of the possible underlying mechanisms in observed poor cardiovascular outcomes in this population. Identifying cardiac biomarkers is crucial for identifying patients at risk of developing PTSD and may derive benefits from personalized interventions based on the principles of precision medicine in multidisciplinary CR programs.

Key Words: Cardiac rehabilitation; Acute coronary syndrome; Posttraumatic stress disorder; Psychiatric interview; Multidisciplinary team; Cardiac biomarkers

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Core Tip: The preliminary results of the first large-scale study on a sample of cardiac rehabilitation (CR) patients with posttraumatic stress disorder induced by acute coronary syndrome indicate a significant number of patients who have a persistently increased risk of adverse events, and yet are still insufficiently recognized and treated. The study demonstrates that one possible mechanism of poorer outcomes is the avoidance of physical activity. A multidisciplinary approach involving cardiologists, psychiatrists, and psychologists is required for the identification and early intervention in these patients, and CR and comprehensive social support play a critical role.

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INTRODUCTION

There is evidence to suggest that mental health disorders such as chronic stress, anxiety, and depression are linked to adverse cardiovascular outcomes[1,2]. In particular, stress-related disorders, especially posttraumatic stress disorder (PTSD)[3,4], have been identified as independent risk factors for acute cardiac events[5-7]. There are presumed different interaction mechanisms through which PTSD is associated with cardiovascular diseases. These include psychological (ability to adapt to stress, personality profile, personal traits, social interactions), behavioral (smoking, alcohol, diet, sleep disorders, adherence to prescribed therapy), and biological factors (neuroendocrine dysfunction involving metabolic syndrome, hypothalamic-pituitary-axis dysfunction, inflammation, renin-angiotensin system dysregulation, autonomic nervous system dysfunction)[7-9].

Furthermore, there is a growing recognition of acute coronary syndrome (ACS) as a potential precipitating event for PTSD[10-12], which is now increasingly acknowledged as a medical issue, prompting questions about its prevalence and clinical implications. It has been observed that patients who develop PTSD following an ACS have a higher risk of experiencing recurrent myocardial infarction (MI) and higher mortality rates[5,11,13]. A meta-analysis from 2012 reported a 12% prevalence of significant PTSD symptoms following ACS[11], while a 2021 systematic review found a prevalence range of 3% to 19%[13]. It's worth noting that the higher prevalence rates were observed when PTSD was assessed through self-report questionnaires compared to clinical diagnostic interviews conducted by a psychiatrist who made the diagnosis.

Reports on the characteristics of individuals who develop PTSD after ACS vary greatly, and there is no consensus on the specific demographic or biological risk factors that contribute to its development. In the systematic review from 2021 the authors reported several risk factors for PTSD following MI, including female gender, younger age and prior history of psychiatric disorders[13]. However, the individual characteristics of those who develop PTSD after ACS can differ widely, making it difficult to identify any consistent patterns or predictors of the disorder. Identifying patients at risk for persistent and severe ACS-induced PTSD based on demographic, biological and psychological factors could facilitate the implementation of early preventive measures[14].

While there is a significant correlation between PTSD and acute cardiac events, research on PTSD development following ACS is not as advanced. As a result, mechanisms of interaction are poorly understood. ACS-induced PTSD is associated with an increased risk of recurrence, but this risk is most prominent during the first year after the cardiovascular event, which is much shorter than the time frame required for many of the potential mechanisms linking PTSD to cardiovascular diseases[5]. Early identification and intervention are crucial, especially during this first year, when patients participate in cardiac rehabilitation (CR), which offers a unique opportunity for timely recognition and management of high-risk patients, potentially leading to improved outcomes.

MATERIALS AND METHODS

Study design

This ongoing observational, prospective, analytical case-control study presents preliminary findings on the number of patients who developed PTSD diagnosed by a psychiatrist after an ACS in a sample of patients undergoing CR, and their demographic, behavioral and biological characteristics compared to the control group.

Study subjects

This study enrolled patients who experienced ACS, with or without undergoing percutaneous coronary intervention (PCI), and who were participating in a 3-wk CR program at the at the Special Hospital for Medical Rehabilitation Krapinske Toplice, the largest CR center in Croatia. Patient recruitment for the study spanned a year (from January 1, 2022 to December 31, 2022), and the study ultimately included 504 participants. The expected follow-up period is approximately 18 mo and is currently ongoing. Inclusion criteria: Patients who have completed one month after an ACS (stressful event) before arriving at rehabilitation, both sexes, aged between 18 and 70 years. Exclusion criteria: Patients with a history of cardiac surgery, repeated MI, active psychiatric treatment, diagnosed psychiatric disorder or previously diagnosed PTSD from another cause, active malignancy, clinically unstable patients (acute heart failure, unstable coronary disease, acute infection), and patients who do not wish to participate in the study. Exclusion criteria are also applied to those who develop conditions that are defined as exclusion criteria during data collection, or those who no longer wish to participate in the study.

To identify patients with PTSD, a combination of self-assessment questionnaires and clinical psychiatric interviews were used. The initial screening of patients who agreed to participate in the study involved the use of the PTSD Checklist-Civilian Version (PCL-C) questionnaire[15,16]. For the purposes of this study, the recommended cutoff score for suggesting the possibility of PTSD based on the questionnaire was 30-35 points, given the civilian population. A combination of both scoring methods was employed, using a higher threshold score (35 points) and the requirement of a symptom pattern to

minimize the number of false positives. Participants who met the criteria based on the questionnaire underwent a clinical psychiatric interview, and those who were diagnosed with PTSD in accordance with Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification[17] by the psychiatrist were included in the group of patients with PTSD (Figure 1).

From the pool of study participants who did not receive a PTSD diagnosis, a subset of individuals was selected for further analysis based on clinically and medically relevant stratification variables such as age, gender, type of ACS [ST-elevation MI (STEMI), non-STEMI (NSTEMI), or unstable angina (UA)], who underwent rehabilitation during the same period. They form a second group of participants that matches the characteristics of those with a PTSD diagnosis, in order to enable comparability of the two groups.

Data collection

The study obtained medical data through a patient's anamnesis, including their age, gender, lifestyle habits such as smoking and alcohol consumption, family history of cardiovascular disease (positive or negative), comorbidities such as hypertension, dyslipidemia, diabetes, and body mass index (BMI). Additionally, diagnostic tests were conducted during the three-week rehabilitation period to obtain data on important biological characteristics [laboratory testing, exercise stress test (ergometry), echocardiogram].

Follow-up

The expected average follow-up period of patients in the study is approximately 18 mo and is currently ongoing. Both groups of patients will be contacted (letter sent by post along with questionnaires and subsequently contacted by phone). They will complete the PCL-C scale again, a questionnaire on quality of life, medication adherence, and report any adverse cardiovascular events. In case it is not possible to contact the patient, data will be obtained from family members or primary care physician. After the end of the study, further analysis of the collected data will follow, and the obtained results and conclusions should direct attention to a subpopulation of patients in terms of precision medicine (identification of specific groups of patients).

Statistical analysis

We used the SPSS 29.0.0.0 statistical software package, setting significance level at $P < 0.05$ (2-tailed). For clarity, we present all data in original units (mean ± SD, ranges). For calculations of differences between groups, the student' t test, χ^2 test, Fisher's exact test and Mann Whitney test were used.

Ethical considerations

The study protocol was approved by the ethics committee of the Special Hospital for Medical Rehabilitation Krapinske Toplice. Data regarding patients were extracted from routine medical and treatment records. Patient identities have not been revealed. Written informed consent was obtained from every patient who agreed to participate in the study. All the methods followed the guidelines of the Declaration of Helsinki for medical research involving human subjects.

RESULTS

A total of 507 patients who were enrolled in the CR program were approached to participate in the study, out of which 3 patients refused to participate. The PCL-C questionnaire was completed by 504 patients. Of these, 74.2% (n = 374) were men and 25.8% (n = 130) were women. The mean age of all participants was 56.7 years (55.8 years for men and 59.1 years for women). Out of the 504 participants, 80 individuals met the cutoff criteria for PTSD on the screening questionnaire and qualified for further evaluation, representing 15.9% of the total sample. All 80 patients agreed to psychiatric interview. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to DSM-5 criteria (Figure 1, Table 1).

From 51 PTSD patients, 32 were male (62.7%) and 19 female (37.3%). The average age of male participants diagnosed with PTSD was 52.8 years (range 42-65), and for female it was 56.5 years (range 42-66). Of these PTSD patients, 39 suffered STEMI (76.5%), 12 NSTEMI (23.5%), and there were no cases of PTSD following UA (Table 2).

Patients' characteristic

This preliminary report of the study presents findings on the investigation of demographic, behavioral, and particularly biological factors, and examines the differences in individual characteristics between PTSD and non-PTSD group (which was formed based on clinically and medically relevant variables such as age, gender, type of ACS), and the results are summarized in the table (Table 3).

Among the variables included, the PTSD group had a significantly lower percentage of maximum exercise capacity achieved compared to the non-PTSD group (P = 0.03). No significant differences were

Table 1 All patients included in the study

General data	Value
Patients	504
Age	56.68 ± 7.82 (27-70)
Male patients	374 (74.21%)
Male patients age	55.85 ± 8.04 (27-70)
Female patients	130 (25.79%)
Female patients age	59.05 ± 6.6 (44-70)
PTSD patients after PCL-C questionnaire	80 (15.87%)
Diagnosed PTSD patients	51 (10.12%)

Data are given as mean ± SD (ranges) or values (percentages). PTSD: Posttraumatic stress disorder; PCL-C: Posttraumatic stress disorder Checklist-Civilian Version.

Table 2 Posttraumatic stress disorder/pairs included in the study

General data	Value
Patients in each group	51
Age	54.16 ± 6.64 (42-66)
Male patients	32 (62.75%)
Male patients age	52.78 ± 6.53 (42-65)
Female patients	19 (37.25%)
Female patients age	56.47 ± 6.32 (42-66)
STEMI	39 (76.47%)
NSTEMI	12 (23.53%)
UA	0 (0.0%)

Data are given as mean ± SD (ranges) or values (percentages). STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; UA: Unstable angina.

found in commonly observed comorbidities in cardiology patients such as hypertension, diabetes, dyslipidemia, and BMI.

In the study, there were participants who underwent a second PCI as an elective procedure after an acute event and those who experienced cardiorespiratory arrest and other complications following MI. Within the PTSD group, 7 participants (13.7%) underwent an elective PCI during hospitalization due to MI, while in the non-PTSD group, the number was 12 (23.5%). Acute heart failure was reported as a complication of MI in one male participant from each group. Within the PTSD group, one participant had a complication of surgically treated ventricular septal defect, while in the non-PTSD group, one female participant experienced post-procedural atrial fibrillation that was successfully converted to sinus rhythm using amiodarone. In both groups, two patients experienced cardiac arrest and were successfully resuscitated. Complications occurring during the acute phase of ACS and repeated PCI did not prove to be significant risk factors for developing PTSD.

DISCUSSION

To our knowledge, this is the first study on a large sample of CR patients that investigates the prevalence of PTSD after ACS, characteristics of these patients, and possible factors important for clinicians to recognize such patients in a timely manner. Consistent with prior research, it has been demonstrated that the prevalence of PTSD is lower when diagnosed by a psychiatrist rather than relying solely on self- administrated questionnaires. The results confirm that the diagnosis of PTSD after ACS made by a psychiatrist is approximately 10%, which exceeds the prevalence reported in meta-analysis

Table 3 Characteristics of patients

Variable	PTSD	Non-PTSD	*P* value
BMI	29.09 ± 4.15 (21.9-41.9)	28.58 ± 4.15 (20.5-36.4)	0.5373
Smoking	31 (60.78%)	26 (50.98%)	0.3187
Alcohol use	0 (0.0%)	2 (3.92%)	0.495
Family history of cardiovascular diseases	23 (45.1%)	30 (58.82%)	0.1654
History of hypertension	26 (50.98%)	31 (60.78%)	0.3187
History of dyslipidemia	18 (35.29%)	19 (37.25%)	0.8368
History of diabetes	10 (19.61%)	7 (13.73%)	0.4254
LDL	2.15 ± 0.8 (1.1-4.5)	2.28 ± 0.64 (0.9-3.3)	0.3481
LVEF	53.27 ± 10.81 (25-75)	55.78 ± 9.12 (30-76)	0.2078
LVDd	52.2 ± 10.81 (43-66)	50.78 ± 9.12 (41-68)	0.2462
Theoretical maximum percentage in exercise test	88.55 ± 13.35 (46-114)	94.24 ± 13.58 (44-124)	0.0354
WATT in exercise test	126.96 ± 39 (50-200)	132.65 ± 47.83 (50-225)	0.512
METs in exercise test	6 ± 1.36 (2.8-9.89)	6.3 ± 1.45 (3.5-9.29)	0.2754
MPRH percentage in exercise test	76.76 ± 11.02 (54-103)	79.04 ± 9.76 (54-103)	0.2726
PCI in second act	7 (13.73%)	12 (23.53%)	0.2035
Positive exercise test	4 (7.84%)	4 (7.84%)	-
Acute complications	2 (3.92%)	2 (3.92%)	-
Arrest	2 (3.92%)	2 (3.92%)	-

Data are given as mean ± SD (ranges) or values (percentages). BMI: Body mass index; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; LVDd: Left ventricular diastolic diameter; METs: Metabolic equivalents; MPHR: Maximal predicted heart rate; PCI: Percutaneous coronary intervention.

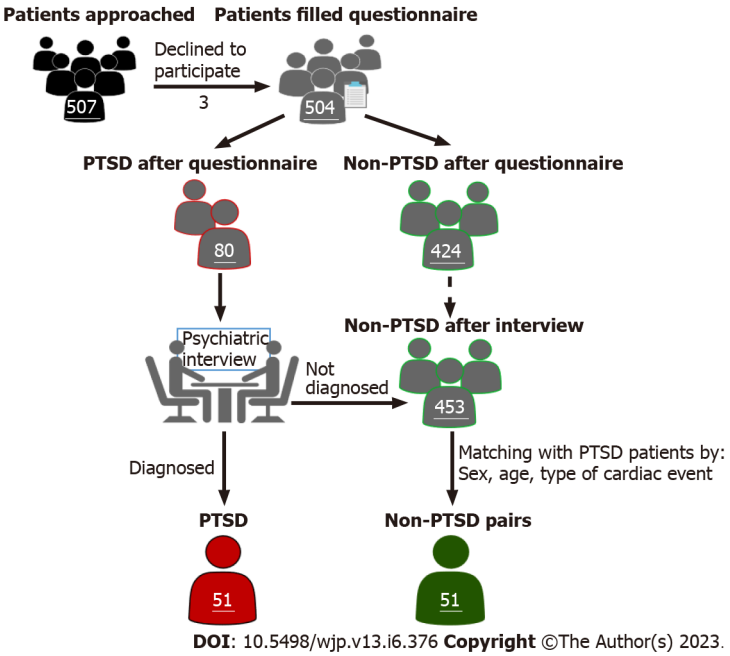

Figure 1 Algorithm for patient selection. PTSD: Posttraumatic stress disorder.

[11] and literature review[13], but similar prevalence has been reported[18]. If only a self-reported questionnaire is used to assess the PTSD symptoms, reported prevalence can be up to 16%. These findings highlight the significant impact of this clinical disorder on a substantial group of patients who

are often underdiagnosed and at increased risk for poor clinical outcomes.

The biological mechanisms in PTSD have been extensively reviewed and could potentially contribute to the modification of cardiac and vascular functions, ultimately leading to the development of cardiovascular events[19,20]. These mechanisms involve a complex set of pro-inflammatory, pro-atherogenic, pro-ischemic, neuro-hormonal, metabolic, and immune reactions. As presented in the table, numerous biological factors were examined regarding the ACS-induced PTSD (Table 3). While no significant differences were found in commonly observed comorbidities (hypertension, diabetes, dyslipidemia, BMI) as well as in left ventricular ejection fraction, the study introduced a novel approach by using results from an exercise stress test which showed a significant difference between the two groups. A standardized protocol is used to measure the maximum amount of oxygen an individual can consume during exercise (VO_2max) and to estimate the maximum watts a patient should attain during the exercise test[21]. The non-PTSP group achieved a significantly higher percentage of their theoretical maximum compared to the PTSP group. Recent research shows that patients with PTSD following ACS may avoid physical activity if they experience cardiac symptoms such as dyspnea and tachycardia, which can be reminiscent of the traumatic event[22]. Our study further confirms that this could be an underlying mechanism that contributes to the negative prognosis of patients with ACS-induced PTSD.

Complications related to ACS, repeated PCI, and even cardiac arrest during the acute phase did not show a significant association with the development of PTSD. However, previous study demonstrated that cardiac arrest-induced posttraumatic symptoms are linked to an increased risk of mortality and cardiovascular disease[23].

A recent meta-analysis provides further support evidence that the presence of PTSD is a risk factor for the subsequent development recurrent cardiac events, such as MI[24]. Due to the significant prevalence of PTSD after ACS, which was confirmed in this study, further research is needed to identify the mediating factors involved in the direct association between PTSD and the subsequent occurrence of adverse cardiovascular events in more precise medical terms.

The latest study highlights the increasing acknowledgement of the importance of social support and the role of CR, emphasizing comprehensive, multidisciplinary approach and early intervention has the potential to exert a favorable effect on the outcomes of these patients[25]. Early psychological assessment and intervention in ACS patients is important, and the inclusion of psychological interventions can improve patients' attendance and adherence to CR programs[26,27]. Therefore, it is essential not to downplay the role of such interventions following ACS. Recent studies suggest that mental health conditions may not be a barrier to CR and that CR may provide an opportunity for greater mental health care and support[28]. Therefore, a CR program with a multidisciplinary team including cardiologists, psychiatrists, and psychologists could be considered as a potential early intervention site, and by combining medical treatment, lifestyle modifications, and psychosocial support, patients may benefit from a more holistic approach to their care, which could lead to improved quality of life, reduced morbidity, and better long-term adherence to lifestyle changes.

Study advantages

The present study is the first large-scale study among rehabilitation patients, excluding patients with a preexisting psychiatric diagnosis (which is not the case in most previous studies, and it is important in explaining pathophysiology) or a history of MI, focusing on a more precise description of PTSD as a secondary risk factor in cardiology patients and revealing possible mechanism of interactions. One of the strengths of the study is also the use of psychiatrist-based diagnosis. By identification of potentially important biomarkers, it may be possible to predict which subgroup of patients is at a higher risk for developing PTSD after an ACS.

Study limitations

This is a preliminary report of an ongoing study, with patients still under follow-up. Some biological markers have not yet been included in the analysis, and comprehensive data analyses will be performed once all data is collected. We do not yet have information on whether all enrolled patients will remain in the follow-up and if we will have complete data for all patients by the end of the study.

CONCLUSION

This study is one of the largest cohorts to investigate the incidence of PTSD after ACS, and it is the first to consider the role of CR in this context, with the diagnosis made by a psychiatrist using the DSM-5 classification system. The preliminary findings of the study reports on substantial group of patients with PTSD induced by ACS (10.1%) and suggest that they may avoid physical activity, which could be one of the underlying mechanisms of the worse cardiovascular outcomes observed in this population. It is imperative to identify potential cardiac biomarkers that could aid in detecting increased cardiac risk in patients with secondary risk factor - ACS-induced PTSD, as current research in this area is limited. Further research is necessary, as there is significant potential value in identifying prognostically useful cardiac biomarkers to predict and prevent the onset of recurrent cardiovascular events and higher

morbidity and mortality rates in this group of patients.

After completing the follow-up period of the present study and conducting complex statistical analyses of all collected data, it may be possible to identify a specific subset of patients who are at risk of developing PTSD and may derive benefits from personalized interventions based on the principles of precision medicine. In this individualized approach, CR with a multidisciplinary team and the development of specific therapeutic and rehabilitation strategies can play a key role in improving quality of life and reducing overall mortality of this vulnerable and previously under-recognized subgroup of patients.

ARTICLE HIGHLIGHTS

Research background

Acute coronary syndrome (ACS) can be a stressor in the development of posttraumatic stress disorder (PTSD). Patients with PTSD after ACS have worse survival outcomes, and studies report different prevalence rates of PTSD following ACS. It is challenging to identify these patients and prevent their unfavorable outcomes.

Research motivation

Clinicians and cardiologists who deal with cardiac rehabilitation (CR) are increasingly noticing patients with elements of PTSD after ACS. The problem is their poorer outcomes, and CR with a multidisciplinary team (cardiologist, psychiatrist, psychologist) can be a place for early detection and intervention in these patients.

Research objectives

In this study we aim to investigate the prevalence of PTSD after ACS in patients undergoing CR and their demographic, behavioral, and biological characteristics. Identifying patients at risk for persistent and severe ACS-induced PTSD based on these characteristics could facilitate the implementation of early preventive measures.

Research methods

This is an ongoing prospective analytical case-control study. The study includes patients who have experienced ACS and are enrolled in a 3-wk CR program. A group of patients with PTSD diagnosis was identified using self-assessment questionnaires for PTSD criteria and clinical psychiatric interviews, and a control group was formed based on clinically relevant variables to enable comparison of these patient groups. Medical data were collected, and diagnostic tests were conducted to obtain data on important biological characteristics [laboratory testing, exercise test (ergometry), echocardiogram]. The expected average follow-up period for patients included in the study is approximately 18 mo.

Research results

Of 504 patients completed PTSD Checklist-Civilian Version questionnaire and 80 (15.9%) met the cutoff criteria for the PTSD and qualified for further evaluation by psychiatrists. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders criteria. Among the variables analyzed, there was a noticeable difference in the percentage of theoretical maximum achieved on exercise testing between the PTSD and non-PTSD groups. Non-PTSD group achieved a significantly higher percentage of their maximum compared to the PTSD group (P = 0.035).

Research conclusions

This study found a significant proportion of patients with PTSD induced by ACS (10.1%), and these patients are under-recognized and not appropriately treated. The study also found that patients with PTSD achieved a lower theoretical maximum on exercise testing, suggesting that they may avoid physical activity, which could be one of the underlying mechanisms for the worse cardiovascular outcomes observed in this subpopulation of patients.

Research perspectives

Early identification of patients with ACS-induced PTSD and intervention are crucial, and CR provides a unique opportunity for timely recognition and management of high-risk patients, potently leading to improved outcomes. Future research could focus on identifying possible cardiac biomarkers to detect patients at risk of developing PTSD after ACS and apply personalized interventions based on the principle of precision medicine. Multidisciplinary CR programs may be particularly effective in addressing the complex needs of patients with ACS induced PTSD.

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FOOTNOTES

Author contributions: Sopek Merkaš I conducted research and wrote first version of the manuscript; Lakušić N and Sonicki Z designed the study and corrected the manuscript; Sonicki Z is involved in analytical tools; Koret B and Vuk Pisk S diagnosed PTSD, contributed in literature review and data processing; Lakušić N, Sonicki Z, and Filipčić I served as scientific advisors, literature review and participate in making critical revisions related to the important intellectual content.

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