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Source / Izvornik: **Mediterranean journal of clinical psychology, 2022, 10, 1 - 30**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.13129/2282-1619/mjcp-3415

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:874896

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Download date / Datum preuzimanja: **2024-07-31**

Repository / Repozitorij:

Repository of the University of Rijeka, Faculty of Medicine - FMRI Repository

Mediterranean Journal of Clinical Psychology

ISSN 2282-1619

MJCP

Volume 10, n 3, 2022

Health Psychology

Psychological, Medical and Laboratory Predictors of Cardiac Anxiety in Patients with Heart Failure During the COVID-19 Pandemic

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Abstract

Objective: The aim of the study was to identify predictors of heart-focused anxiety in patients with heart failure. A better understanding of such predictors may help in detecting the comorbidity underlying heart-focused anxiety and identifying patients who need psychological help.

Methods: In order to account for multiple sources of heart-focused anxiety, we included psychological, lifestyle, and medical/laboratory predictors. The study involved 148 patients, of whom 74 had a leading diagnosis of worsening heart failure and were hospitalized during the COVID-19 epidemic. A second group of 74 patients suffering from cardiovascular diseases without a diagnosis of acute heart failure, were examined in various out-patient cardiology clinics. The sample consisted of 37.8% females and 62.2% males, with an average age of 63.35 years. The patients completed the Cardiac Anxiety Questionnaire, the Generalized Anxiety Disorder scale, the Patient Health Questionnaire, and the Intolerance of Uncertainty Scale.

Results: Patients with heart failure with higher levels of depression and intolerance of uncertainty had higher overall levels of heart-focused anxiety, higher levels of fear about chest and heart sensations. Older patients with higher levels of depression had higher levels of activity avoidance, especially activities believed to elicit cardiac symptoms. Cardiac patients with higher level of anxiety and with anaemia as comorbidity had higher levels of heart-focused attention and monitoring of cardiac activity.

Conclusion: In patients with heart failure, the presence of heart-focused anxiety significantly reduces the quality of life, leads to avoidant behaviours, and is associated with anxiety and depressive symptoms. These patients are more likely to seek medical help and specialist services, but the need for psychological help is very rarely recognized.

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Keywords:
Heart failure; Heart-focused anxiety; Anaemia; Anxiety; Depression; Intolerance of uncertainty.

Received: 5 April 2022
Accepted: 29 November 2022
Published: 28 December 2022

Citation: Pokrajac-Bulian, A., Zaninović Jurjević, T., Dvornik, S., Vodopija-Krstanović, I., Ružić, A. (2022). Psychological, Medical and Laboratory Predictors of Cardiac Anxiety in Patients with Heart Failure During the COVID-19 Pandemic. *Mediterranean Journal of Clinical Psychology 10*(3). https://doi.org/10.13129/2282-1619/mjcp-3415

1. Introduction

Psychological factors have been recognized as important contributors to the aetiology and maintenance of chronic diseases (Conversano & Di Giuseppe, 2021; Merlo, 2019; Shahar, 2021). This has led to an increase in research on psychological correlates of various chronic illnesses, such as cardiovascular disease (D'Antoni, 2021; Kukić & Pokrajac-Bulian, 2022; Sheikh et al., 2019), diabetes mellitus (Marchini et al., 2018; Martino et al., 2019), gastrointestinal disorders (Kano et al., 2018), skeletal muscle and rheumatic disease (Marchi et al., 2019), as well as neuropsychological problems (Conversano et al., 2020; Merlo et al., 2020). Given that psychological and organic issues are intercorrelated, a comprehensive understanding of chronic medical conditions should consider all aspects of the illness (Yoo & Ryff, 2019). The benefits of psychological interventions in medical settings are that it can increase patient adherence to the prescribed medical regimes (World Health Organisation, 2003), increase the use of functional coping strategies (Büssing et al., 2010), reduce the denial of symptoms (White et al., 2016), increase more adaptive health behavior (Spitzer et al., 2022), and reduce postsurgical hospital length of stay (Siddique et al., 2021). It has been shown that psychological tretements can reliably reduce medical costs (Chiles et al., 1999) and eliminate human suffering from a wide range of medical disorders.

Cardiovascular disease (CVD) is a collective term for a range of disorders (Mensah et al., 2019; Timmis et al., 2022). These disorders are associated with death and disability resulting from 11 cardiovascular causes, led by ischaemic heart disease (IHD), stroke, and hypertensive heart disease, as well as disability due to heart failure (Mensah et al., 2019). The incidence of CVD in Croatia is 674 per 100,000 inhabitants, and in 2019, the prevalence was 6 732 per 100,000 inhabitants (age adjusted) (Timmis et al., 2022). CVD remains the most common cause of death in European Society of Cardiology (ESC) member countries, and IHD is the most common cause of CVD death accounting for 38% of all CVD deaths in females and 44% in males. Stroke is the second most common cause of CVD deaths, accounting for 26% of all CVD deaths in females and 21% in males (Timmis et al., 2022).

Heart failure (HF) is a clinical syndrome consisting of cardinal symptoms that may be accompanied by signs caused by a structural and/or functional abnormality of the heart (Mcdonagh et al., 2021). It is a major public health problem, globally affecting 1-2% of the adult population in developed countries (Conrad et al., 2018). It is estimated that 26 million adults worldwide are living with HF (Aggelopoulpou et al., 2017), more than 10% of those >70 years-old (Bui et al., 2011; Fonseca, 2017; Tian & Chen, 2016), and 15 million people in Europe suffer

from HF (Kell et al., 2015). In Croatia, five of the 10 leading causes of death are the consequences of CVD, among which is HF (Kralj & Brkić Biloš, 2013).

CVD outcomes depend on many factors, including depression and anxiety, both of which are linked to major adverse cardiac events, rehospitalisation and death, independent of traditional risk factors (Pedersen et al., 2017). Depression is common in patients with HF ranging from 11 to 25% in outpatients, and 35 to 70% in hospitalised patients (Rutledge et al., 2006). In a recent study, it was found that depression affects 20% of patients with HF and is severe in half of them (Mcdonagh et al., 2021; Sbolli et al., 2020). Co-morbid depressive disorder is a predictor of mortality, rehospitalisation and worsening HF; therefore, it represents an additional factor of deterioration and maintenance of HF (Jünger et al., 2005), but often remains unnoticed in routine patient care. Some reports suggest that increasing depressive symptoms may worsen (Sherwood et al., 2011) and remission from depression may improve cardiovascular outcomes (Jiang et al., 2011). In a prospective study of nearly 2 million healthy adults, depression was prospectively associated with an 18% increased risk of HF development over the subsequent seven years (Daskalopoulou et al., 2016). In a meta-analysis of eight studies examining the prospective associations between depressive disorder, elevated depressive symptoms and HF outcomes, Rutledge and colleagues found that depressive symptoms and depressive disorder led to a 2-time increased risk of death or cardiac events (Rutledge et al., 2006). Depression is also related to the severity of HF symptoms, baseline functional status, including limitation in activities of daily living and dyspnoea at rest are strongly related to depression (Vaccarino et al., 2001). Its occurrence is higher in women and it is associated with worse clinical status and a poor prognosis (Jha et al., 2019; Sbolli et al., 2020).

Although there is considerably less research on anxiety than on depression in HF patients, existing evidence suggests that the prevalence of anxiety may be as high as 63%, depending on the subgroup of HF patients studied (De Jong et al., 2004). As many as 40% of HF patients may suffer from major anxiety, and overall anxiety levels are 60% higher than levels seen in healthy elders (Denollet & Brutsaert, 1998). In a posttraumatic stress disorder (PTSD) prospective study, a diagnosis of PTSD at enrolment conferred a 47% increased risk of incident HF over seven years (Roy et al., 2015). This raises the possibility that anxiety disorders may pose a significantly greater risk to cardiac health than anxiety symptoms alone, which is consistent with prior research findings that anxiety disorders confer a much higher risk of adverse cardiac outcomes in coronary disease than anxiety alone (Celano et al., 2015).

The pathophysiological mechanisms that link depression, anxiety, and HF are very complex. Depression and anxiety affect biological processes of cardiovascular function in patients with HF by altering neurohormonal functions via activation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic dysregulation, and activation of cytokine cascades and platelets. HF patients with depression or anxiety may exhibit a continued cycle of HF progression, increased depression, and increased anxiety (Chapa et al., 2014). Both patients with decompensated HF and patients with depression/anxiety have increased levels of norepinephrine and epinephrine (Cameron et al., 2004; Chapa et al., 2014). Emerging evidence on norepinephrine in depression indicates that hormones have a determinant role in regulating cognition, motivation, and intellect, providing the fundamentals for social relationships (Moret & Briley, 2011). Dysregulation of the autonomic nervous system is a predictor of progression of HF mortality and sudden cardiac death (Landolina et al., 2008). Decreased heart rate variability is associated with increased severity of HF and increased dysrhythmia in patients with depression and anxiety (Cameron et al., 2004). Increased activation of the HPA axis, autonomic dysregulation, release of aldosterone and activation of the renin-angiotensin-aldosterone system, and cytokine cascades occur in patients with HF who are depressed or anxious. Because of the combined effects of emotional distress and HF, patients with HF who are depressed or anxious may be at greater risk for progression of cardiac diseases than patients who are not depressed or anxious (Chapa et al., 2014).

People with heart disease can also have a specific type of anxiety called heart-focused anxiety (HFA). It reflects a specific pattern of anxiety symptoms, with a focus on the fear of cardiac-related sensations and their expected harmful consequences (e.g., life-threatening arrhythmia or sudden cardiac death). It leads to ongoing worries about heart-function, avoidance of activities believed to trigger cardiac symptoms, and recurrent medical help seeking behaviour (Eifert et al., 2000a). The identification of HFA in patients with cardiac disease is a challenge as anxiety-related and heart disease-related symptoms partly overlap (e.g., chest pain, palpitations, or dyspnoea). Consequently, undiagnosed patients with HFA cannot be referred to psychological care but have to remain in medical care (Van Beek et al., 2016).

The prevalence of anxiety and depression in HF patients is well supported by research; however, during the COVID-19 pandemic, there was an increase in psychological disorders in general, and especially in people suffering from chronic health diseases. Research shows that patients with HF belong to a particularly vulnerable group of cardiac patients due to frequent exacerbations of the disease and the frequent need for rehospitalisation. The symptoms of HF

can be very dramatic and the breathing difficulties and fear of death experienced by patients are an additional indicator of the severity of this disease. During the COVID-19 pandemic, HF patients delayed their appointments, found it harder to reach their family physicians, which ultimately led to later hospitalizations when the condition was already severely impaired, and the chances of remission were reduced. The fear of HF was accompanied by fear of COVID-19, which resulted in poor patient cooperation and worsening of symptoms, requiring additional staff engagement during inpatient treatment of these patients. Other mental health concerns include mental distress, grief and bereavement, loss/separation from family, shame, guilt, helplessness, medical mistrust and inclination towards conspiracies, panic attacks, stress, anxiety, depression, loneliness, suicidal ideation, mood problems, sleep problems, worry, denial, ambivalence, uncertainty, frustration, anger, fear, stigmatization, marginalization, xenophobia, and mass hysteria have also been reported worldwide (Flouda et al., 2020; Mukhtar, 2020; Mukhtar & Mukhtar, 2020). This clearly shows that clinical psychologists have a crucial role in conducting psychoeducation and in assessing, preventing, and treating mental health conditions in medical settings. Clinical psychologists have to shoulder the complex burden of dealing with mental health conditions embedded within a purely medical context. This challenges psychologists to acquire and use a wide range of clinical, cognitive, and interpersonal skills (Shahar, 2021). The COVID-19 pandemic has caused major changes in the lives of millions of people around the world. The spread of the virus, which is taking place at a high speed, the increase in the number of COVID patients, and the vast availability of information in the media, are causing distress and creating a climate of uncertainty and fear. Intolerance of uncertainty (IUC) is "a bias that determines how someone processes uncertain situations" (Dugas et al., 2005). People with a higher IUC believe that uncertainty is stressful, negative and disturbing, and that it should be avoided. In situations of threat and uncertainty, these people are particularly affected, leading to difficulties in their daily functioning (Buhr & Dugas, 2002). In the last three decades, numerous studies have examined IUC and several cognitive models that correlate IUC to various forms of anxiety have been established; however, previous studies have not dealt with IUC and heart disease patients who have a specific anxiety disorder, such as HFA.

The aim of these study was to identify predictors of heart-focused anxiety in a sample of patients with HF. A better understanding of such predictors may help in detecting the comorbidity underlying HFA and identifying patients who need psychological help. In order to account for multiple sources of HFA, we included psychological, lifestyle, and medical/laboratory predictors. In addition to the most commonly studied depressive and anxiety symptoms, this research aims to analyse whether IUC is one of the risk factors for developing HFA in the

context of the COVID-19 pandemic, which particularly increases uncertainty for vulnerable patients with HF.

2. Methods

2.1. Study design and participants

The study involved 148 patients, of whom 74 were consecutively admitted to the hospital for acute heart failure (AHF), characterized by rapid or gradual onset of symptoms and/or signs of HF, leading to an unplanned hospital admission or an emergency department visit (Mcdonagh et al., 2021). In our study group, the leading clinical presentation was acute decompensated heart failure (ADHF). We used the clinical signs and symtpoms, ECG, echocardiography and plasma NT-proBNP in diagnostic workout according to the ESCARDIO guidelines (Mcdonagh et al., 2021). The patients with acute pulmonary edema and cardiogenic shock were excluded. The New York Heart Association (NYHA) functional classification was used to grade clinical severity at hospital admission (Caraballo et al., 2019). The patients were hospitalized at the Clinic for Cardiovascular Diseases of the Clinical Hospital Center Rijeka (KBC) in Croatia during the COVID-19 epidemic. A second group of 74 patients suffering from cardiovascular diseases without a diagnosis of acute HF, such as arterial hypertension and chronic IHD, were examined in various out-patient cardiology clinics in the Primorje-Gorski Kotar County (PGŽ) in Croatia. Only 7 respondents refused to participate in the survey (4.73% of the total sample). The sample consisted of 37.8% females and 62.2% males, with an average age of 63.35 years (SD = 13.30) and an age range from 27 to 89 years (Table 1).

Table 1. Descriptive statistics for variables included in the study

Variable	N or M	SD	Min-Max
Male (%)	92 (62.2)	-	-
Female (%)	56 (37.8)	-	-
Hospital patients (%)	74 (50)	-	-
Out-patients (%)	74 (50)	-	-
Age	63.35	13.30	27 - 89
NYHA class*			
II (%)	9 (14.5)	-	-
III (%)	42 (67.7)	-	-
IV (%)	11 (17.7)	-	-
Laboratory values			
NT-proBNP	7441.96	9388.02	24 - 62239
eGFR	64.34	24.41	17 - 131
cTnT	61.82	100.14	0 - 745
Haemoglobin	133.90	21.10	86 - 178
MPV	9.25	1.01	6.90 - 12.20
Leukocytes	8.90	3.28	3.1 - 19.2
Glucose	8.00	3.50	4.3 - 20.9

AST	40.50	95.51	5 - 675
ALT	50.41	136.89	8 - 1051
ALP	96.52	57.86	31 - 298
hs_CRP	28.66	54.18	90 - 351
CAQ			
Total	1.54	0.76	0 - 3.28
Fear	1.62	0.88	0 - 3.75
Avoidance	1.60	1.01	0 - 4
Attention	1.34	0.79	0 - 3.20
Anxiety	5.39	5.13	0 - 21
Depression	6.75	5.17	0 - 22
IUC	29.30	10.52	12 - 58

Note. M: Mean, SD: Standard Deviation, Min: Minimum, Max: Maximum, NYHA class*: New York Heart Association classification, only for n=62 patients; NT-proBNP: N-Terminal pro-Brain Natriuretic Peptide in pg/ml, eGFR: estimated Glomerular Filtration Rate in ml/min per 1.73 m2, MPV: mean platelet volume, CAQ: Cardiac Anxiety Questionnaire, IUC: Intolerance of Uncertainty

The body mass index (BMI) of participants ranged from 19.53 to 52.08 kg/m2 with 25.3% of normal weight, 41.4% patients with overweight, and 33.3% patients with obesity. There were no significant differences in the BMI of HF (hospitalized) and out-patients, but they did differ significantly in age and the number of comorbid diagnoses (Table 2).

Table 2. Characteristics of the participants enrolled in the study

Variables	Hospital (HF) patients (N=74)		Out-patients (N=74)		*t*	*p*
	M	*SD*	*M*	*SD*		
Age (years)	68.80	11.63	57.91	12.69	5.44	.00
BMI (kg/m^2)	29.26	6.25	26.74	3.32	1.46	.15
Number of comorbid conditions	2.64	1.41	1.28	1.08	6.53	.00

Note: Hospital patients: patients with heart failure, Out-patients: patients with other CVD

The Medical Ethics Committee of the participating Hospital approved the study protocol [1]. The study was conducted in accordance with the Declaration of Helsinki, and all the patients received written and oral information about the study and provided written informed consent. The research was funded by the University of Rijeka [2]. The participants in the study were subjected to a specialists' cardiological examination, routine laboratory examination, and completed a set of psychological questionnaires. The participants were examined between January and April 2021, during the third wave of the COVID-19 pandemic.

[1] Etical number: Kl. 003-05//20-1/152; Ur. br.: 2170-29-02/1-20-2 (19th December 2020)
[2] UNIRI COVID-19 project 970100002: *Psychological changes of patients with acute chronic heart failure during the COVID-19 epidemic*

2.2. Measures

In the first part of the study, the patients completed a set of standardized psychological questionnaires during their hospitalization for HF or during their out-patient cardiovascular examination. The introductory page of the questionnaire informed the patients that the study was about their HF or other CVD. Clinical data were collected from patients' medical records at the time of hospitalization or cardiovascular examination in the out-patient cardiology clinic.

Socio-demographic characteristics, which included age and gender, and were collected by means of purpose-designed questions in the baseline questionnaire.

Heart-focused anxiety was assessed by the Croatian version of the Cardiac Anxiety Questionnaire (CAQ) (Pokrajac-Bulian & Ambrosi-Randić, 2020), a self-report measure consisting of 18 items. The CAQ assesses overall heart-focused anxiety and three component scores representing distinct symptoms: fear of heart related sensations, (8 item; e.g., *Even if tests come out normal, I will still worry about my heart*); avoidance of activities believed to elicit cardiac symptoms (5 items; e.g. *I avoid exercise and other physical work*); and heart-focused attention and monitoring (5 items; e.g. *I pay attention to my heartbeat*). Each item is rated on a five-point Likert-scale (values from 0 to 4). Scoring on each scale is calculated by means (range 0 to 4) with higher scores reflecting higher levels of HFA. This scale demonstrates acceptable psychometric properties with Cronbach's α coefficients from .70 to .88 for each scale and for CAQ total .90.

Anxiety symptoms were measured using the 7-item Generalized Anxiety Disorder scale (GAD-7) (Spitzer et al., 2006). Each item asks the individual to rate the severity of his or her symptoms over the past two weeks (e.g., *Over the last 2 weeks, how often have you felt nervous, anxious or on edge?*). Items on this scale are rated on a four points Likert scale, and response options include "0 - *not at all*", "1 - *several days*", "2 - *more than half the days*" and "3 - *nearly every day*". GAD-7 total score for the seven items ranges from 0 to 21. Scores of 5, 10, and 15 represent cut-off points for mild, moderate, and severe anxiety, respectively. The GAD-7 is a reliable and valid scale, with a cut-off value of ≥ 10 to classify patients with clinically relevant anxiety symptoms (Spitzer et al., 2006). Cronbach's alpha was .89 in this sample.

Depressive symptoms were measured with the 9-item Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). The items of this questionnaire mirror each of the 9 DSM-IV depression criteria, with items evaluated on a 4-point Likert scale, and response options include "0 - *not at all*", "1 - *several days*", "2 - *more than half the days*" and "3 - *nearly every day*" (e.g., *Little interest or pleasure doing things.*). PHD-9 total score for the nine items ranges from 0 to 27. A cut-off score ≥ 10 was used to classify patients with clinically relevant symptoms of depression. The PHQ-9

is a reliable and valid measure of depressive symptoms (Kroenke et al., 2001). Cronbach's alpha was .86 in the current sample.

Intolerance of uncertainty was measured with the short version of the Intolerance of Uncertainty Scale (IUC-12) (Carleton et al., 2007). This 12-item scale assesses reactions to uncertainty, ambiguous situations, and the future. Items are scored on a Likert scale ranging from "1 - *not at all characteristic of me*" to "5 - *entirely characteristic of me*", yielding possible scores from 12 to 60. IUC-12 scores should be based on a simple sum of items, with the total score being used for evaluating a general intolerance of uncertainty (Carleton et al., 2007). Cronbach's alpha was .90 in the current sample.

2.3. Medical and laboratory assessment

Clinical data were collected from patients' medical records at the time of hospitalization or during cardiovascular examination of the outpatients in the cardiology clinic.

Clinical characteristics included New York Heart Association (NYHA) functional class, heart failure aetiology, left ventricular ejection fraction (LVEF), atrial fibrillation, and recording of comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, renal disease, and anaemia. Information on *lifestyle characteristics* (i.e., BMI, smoking status) were obtained from patients' medical records.

For the hospitalized HF patients, routine laboratory examinations were made at the beginning of the hospitalization using standard laboratory methods. During cardiovascular examination in the cardiology clinic laboratory test results were collected from the outpatients. Laboratory examinations included routine haematology and biochemistry analyses, and for hospitalized patients' cardiology tests as N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), cardiac troponin T (cTnT) were performed.

2.4. Data Analysis

The statistical analysis was conducted with IBM SPSS Statistics, version 22 (Field, 2005). The descriptive statistics show means and standard deviations for metric variables and frequencies for categorical variables (Table 1). First, we tested significant correlations between the CAQ scores (total, fear, avoidance, focus attention) and the set of predictor variables (psychological, lifestyle, and medical/laboratory) using Pearson correlations. Second, we used hierarchical regression analyses to predict CAQ scores with the predictors that showed significant correlations with CAQ scales in order to determine the effect of each predictor on the outcome while controlling for the influence of the remaining predictors.

3. Results

3.1. Descriptive statistics

Table 1 represents the descriptive statistics of all measures. Internal consistencies (as assessed by Cronbach´s α and presented in the 2.2. *Measures*) were excellent to very good with the exception of CAQ-Attention. The lower internal consistencies of this scale (.70) are in line with other findings and show a similar pattern (Eifert et al., 2000a).

By analysing the frequency of responses in which patients express how often they have been bothered by anxiety, depression or feelings of uncertainty, the results showed that 37.2% of patients experienced moderate or severe anxiety, 55.4% of patients experienced moderate or severe depression, and 18.4% experienced high level of IUC (16.2% of HF patients). In the sample, 21.6% of patients show an increased overall score on HFA (32.4% on the subsample of HF patients).

Clinical, psychological and treatment characteristics for the two subsamples of patients are shown in Table 3. HF patients with lower health status and more comorbidities (e.g., diabetes mellitus, anaemia or renal disease), who were treated with diuretics and anticoagulants, were more often anxious and depressed.

Table 3. Characteristics of the participants enrolled in the study

Variable	Hospital (HF) patients N=74	Out-patients N=74	*p* value
Comorbidities			
Diabetes Mellitus	27 (36.5%)	8 (11.3%)	**<.001**
Hypertension	48 (64.9%)	42 (59.2%)	.48
Chronic Obstructive Pulmonary Disease	10 (13.5%)	3 (4.2%)	**.05**
Anaemia	24 (32.4%)	2 (2.8%)	**<.001**
Renal Disease	44 (59.5%)	1 (1.4%)	**<.001**
Medical Treatment			
Beta blockers	55 (74.3%)	50 (69.4%)	.51
Statins	30 (40.5%)	33 (45.8%)	.52
ACE inhibitors	36 (48.6%)	26 (36.1%)	.13
Diuretics	48 (64.9%)	20 (27.8%)	**<.001**
Antiaggregation therapy	26 (35.1%)	19 (26.4%)	.25
Anticoagulants	23 (31.1%)	11 (15.3%)	**.02**
Psychological Characteristics			
Anxiety	34 (45.9%)	21 (28.4%)	**.03**
Depression	55 (74.3%)	27 (36.5%)	**<.001**

Note. Anxiety: total score of > 5 on General Anxiety Disorder Questionnaire (GAD-7); Depression: total score of > 5 on Patient Health Questionnaire (PHQ-9)

3.2. Correlations between CAQ scores and predictors

First, we computed the partial correlations between predictor and criterion variables (Table 4) using the groups hospitalized vs. out-patients as a covariate.

A lower level of haemoglobin is related to overall cardiac anxiety, avoidance of physical activity and heart-focus attention. A lower level of erythrocytes is related to higher avoidance, and anaemia as comorbidity is related to higher level of HFA. Correlation between anxiety, depression, intolerance of uncertainty, and different aspects of cardiac anxiety are all moderately but positively related. Correlations show that women have higher scores on overall level of cardiac anxiety and on fear of chest and heart sensations.

Table 4. Coefficients of partial correlations between predictor variables and CAQ scales (total, fear, attention, avoidance) with the control of group affiliation

Variable	CAQ-Total	CAQ-Fear	CAQ-Avoidance	CAQ-Attention
Laboratory/ Medical				
hs_CRP	-.03	-.09	.19	-.20
cTnT	-.02	.09	-.04	-.16
NT_proBNP	-.01	-.06	.04	.03
eGFR	.12	.16	-.03	.16
Urea	-.09	-.12	.03	-.13
Creatinine	-.10	-.13	-.02	-.12
Haemoglobin	**-.24***	-.14	**-.22***	**-.24***
Erythrocytes	-.19	-.06	**-.25***	-.18
Hypertension	-.06	-.08	.01	-.06
Diabetes	.03	.02	.05	-.01
Anaemia	.16	.10	.11	**.22****
Chronic kidney disease	.08	.10	-.01	.10
Psychological				
Anxiety	**.52****	**.52****	**.26****	**.50****
Depression	**.59****	**.56****	**.43****	**.47****
IUC	**.53****	**.52****	**.37****	**.43****
Demographic/ Lifestyle				
Gender	**-.17***	-.13	-.14	**-.18***
Age	.06	.06	.12	-.03
BMI	.11	.04	.15	.12
Smoking	.11	.11	.14	.01

Note. Group Affiliation: hospitalized vs. out-patient group, hs_CRP: high-sensitivity C-Reactive Protein, cTnT: Cardiac Troponin T antibodies, NT-proBNP: N-Terminal pro-Brain Natriuretic Peptide in pg/ml, eGFR: estimated Glomerular Filtration Rate in ml/min per 1.73 m2, CAQ: Cardiac Anxiety Questionnaire, IUC: Intolerance of Uncertainty, BMI: Body Mass Index
* $p < .05$; ** $p < .01$.

3.2. Regression analysis for the CAQ total score and CAQ subscales

Correlational analyses (Table 4) showed that there are no correlations between the same laboratory and medical characteristics of patients (e.g., hs_CRP, cTnT, NT-proBNP), different comorbid diagnoses (e.g., hypertension, diabetes), and criterion variables. In the regression analyses, we included only those variables that had significant correlations with the criterion

variables: haemoglobin, erythrocytes, anaemia, gender, and age due to the large age range. When the previously named variables were introduced in the regression analyses, some of them did not produce statistically significant results and the percentage of explained variance remained invariant. Consequently, we decided to introduce the final three sets of regression analyses: gender, age, group (hospitalized/ HF vs. out-patient/ CVD group), haemoglobin, anaemia, and psychological characteristics (anxiety, depression, intolerance of uncertainty).

In order to explore the contribution of the psychological characteristics of patients (anxiety, depression, IUC) in the development of cardiac anxiety beyond and above socio-demographic variables (age, gender) and laboratory/medical values related to HF, three sets of hierarchical regression analyses were performed. In the first set of regression analyses, sociodemographic variables (Table 5) were entered in the first step, while psychological characteristics were entered in the second step. In the second set of hierarchical regression analyses, group and laboratory characteristics of patients (Table 6) were entered in the first step, while psychological characteristics were entered in the second step. Finally, in the third set of analyses, group and medical characteristics (Table 7) were entered in the first step, while the same set of three psychological variables were entered in the second step. In Tables 5 to 7 we only present the results of analyses for which at least one of the laboratory or medical characteristics was a significant predictor.

Table 5. Results of hierarchical regression analysis with sociodemographic variables and psychological characteristics as predictors of cardiac anxiety

Predictor variables		Criterion variables			
		CAQ-Total (β)	CAQ-Fear (β)	CAQ-Avoidance (β)	CAQ-Attention(β)
Step 1	Gender	-.07	-.05	-.02	-.12
	Age	.19*	.15	.25**	.05
	R	.19	.16	.25**	.13
	R^2	.04	.02	.06	.02
	$F_{(df)}$	2.94 $_{(2,144)}$	1.90 $_{(2,144)}$	4.93 $_{(2,144)}$ **	1.23 $_{(2,144)}$
Step 2	Gender	.06	.07	.08	-.03
	Age	.07	.04	.16*	-.03
	Anxiety	.10	.17	-.18	.28*
	Depression	.44**	.36**	.52**	.23*
	IUC	.19*	.21*	.13	.13
	R	.66**	.64**	.53**	.56**
	R^2	.44	.41	.28	.32
	ΔR^2	.40**	.39**	.22**	.30**
	$F_{(df)}$	22.09 $_{(5,141)}$ **	19.70 $_{(5,141)}$ **	11.07 $_{(5,141)}$ **	13.10 $_{(5,141)}$ **

Note. IUC: Intolerance of uncertainty

* $p < .05$, ** $p < .01$.

As can be seen from Table 5, psychological characteristics significantly improved the prediction of all indicators of cardiac anxiety beyond and above sociodemographic variables. Depression significantly positively predicted fear and worry about chest and heart sensations (Fear), avoidance of activities believed to elicit cardiac symptoms (Avoidance), heart-focused attention and monitoring of cardiac activity (Attention), and the overall level of cardiac anxiety. Intolerance of uncertainty was a significant positive predictor of fear of heart related sensations and the overall level of cardiac anxiety, while anxiety predicted only heart-focused attention. Regarding sociodemographic variables, older age predicted more avoidance of physical activity and higher overall level of cardiac anxiety only in the first step.

Table 6. Results of hierarchical regression analysis with group and laboratory analysis (haemoglobin) and psychological characteristics as predictors of cardiac anxiety

Predictor variables		Criterion variables			
		CAQ-Total (β)	CAQ-Fear (β)	CAQ-Avoidance (β)	CAQ-Attention (β)
	Group	.19	.11	.24*	.12
	Haemoglobin	-.25*	-.16	-.22*	-.26*
Step 1	*R*	.33**	.21	.34**	.30*
	R^2	.11	.04	.12	.09
	$F_{(df)}$	5.36 $_{(2,89)}$**	1.98 $_{(2,89)}$	5.84 $_{(2,89)}$ **	4.38 $_{(2,89)}$ *
	Group	.08	.01	.16	.05
	Haemoglobin	-.16	-.07	-.16	-.20*
	Anxiety	.16	.21	-.11	.32**
	Depression	.31**	.28*	.32*	.14
Step 2	IUC	.24*	.26*	.16	.15
	R	.66**	.62**	.48**	.58**
	R^2	.43	.38	.24	.34
	ΔR^2	.32**	.34**	.12**	.25**
	$F_{(df)}$	13.07 $_{(5,86)}$ **	10.85 $_{(5,86)}$ **	5.42 $_{(5,86)}$ **	8.65 $_{(5,86)}$ **

Note. IUC: Intolerance of uncertainty

* $p < .05$, ** $p < .01$.

Table 6 shows that psychological characteristics as a group significantly improved the prediction of all indicators of cardiac anxiety beyond and above group and laboratory variables. Depression significantly positively predicted fear and worry about chest and heart sensations (Fear), the avoidance of activities believed to elicit cardiac symptoms (Avoidance), and the overall level of cardiac anxiety. Intolerance of uncertainty was a significant positive predictor of fear of heart related sensations and overall level of cardiac anxiety, while anxiety predicted heart-focused attention. Heart failure predicted more avoidance of physical activity but only in the first step of analysis. When the psychological variables enter in the second step, the HF is no more significant. Lower levels of haemoglobin predicted higher avoidance, attention and overall level

of cardiac anxiety in the first step of analysis, but in the second step, haemoglobin remains negatively significant only for heart-focus attention.

Table 7. Results of hierarchical regression analysis with group and medical characteristics (anaemia comorbidity) and psychological characteristics as predictors of cardiac anxiety

Predictor variables		Criterion variables			
		CAQ-Total (β)	CAQ-Fear (β)	CAQ-Avoidance (β)	CAQ-Attention(β)
Step 1	Group	.26**	.21*	.31**	.13
	Anaemia	.16	.11	.12	.23**
	R	.36**	.27**	.37**	.31**
	R^2	.13	.07	.13	.09
	$F_{(df)}$	10.37 $_{(2,141)}$**	5.62 $_{(2,141)}$ **	11.20 $_{(2,141)}$ **	7.29 $_{(2,141)}$ **
Step 2	Group	.16*	.12	.22**	.07
	Anaemia	.11	.05	.07	.19*
	Anxiety	.12	.18	-.16	.30**
	Depression	.34**	.30**	.41**	.13
	IUC	.24**	.23**	.19*	.17
	R	.69**	.66**	.56**	.60**
	R^2	.48	.43	.31	.35
	ΔR^2	.35**	.36**	.18**	.26**
	$F_{(df)}$	25.44 $_{(5,138)}$ **	20.91 $_{(5,138)}$ **	12.61 $_{(5,138)}$ **	15.24 $_{(5,138)}$ **

Note. IUC: Intolerance of uncertainty

* $p < .05$, ** $p < .01$.

Table 7 shows that psychological characteristics as a group significantly improved the prediction of all indicators of cardiac anxiety beyond and above group and medical variables. Depression significantly positively predicted fear and worry about chest and heart sensations (Fear), the avoidance of activities which are believed to elicit cardiac symptoms (Avoidance), and the overall level of cardiac anxiety. Intolerance of Uncertainty was a significant positive predictor of fear of heart-related sensations, avoidance of activity and the overall level of cardiac anxiety. Anxiety predicted only heart-focused attention. HF predicted more avoidance of physical activity, overall cardiac anxiety, and fear of heart sensation, but only in the first step of the analysis. Anaemia as a comorbid condition predicted a higher level of heart-focused attention.

When predicting CAQ total score with the three psychological variables and two medical/ laboratory values mentioned above, the model including depression (β=.34), intolerance of uncertainty (β=.24), and group (β=.16), predicted the CAQ total score best (Table 7). Together they explained about 48% of the variance in the CAQ total score. Patients with HF with higher levels of depression and intolerance of uncertainty had higher overall levels of HFA.

When predicting CAQ-Fear score with the three psychological variables and two medical/ laboratory values mentioned above, a model including depression (β=.30) and intolerance of

uncertainty (β=.23) predicted the CAQ-Fear score best (Table 7). Together they explained about 43% of the variance in CAQ-Fear. Patients with higher levels of depression, and intolerance of uncertainty had higher levels of fear and worry about chest and heart sensations.

When predicting CAQ-Avoidance score with the three psychological variables and two above-mentioned medical/ laboratory values, a model including depression (β=.41), intolerance of uncertainty (β=.19), and group (β=.22) predicted the CAQ-Avoidance score best (Table 7), together explained about 31% of the variance. Patients with HF with higher levels of depression and IUC had higher levels of activity avoidance. A model including depression (β=.52) and age (β=.16) explained 28% of variance (Table 5). Older patients with higher levels of depression had higher levels of activity avoidance, especially activities believed to elicit cardiac symptoms.

Finally, when predicting CAQ-Attention score with three psychological variables and two medical/ laboratory values mentioned above, the two models explain 35% and 34% of the variance, respectively. The first model, which includes anxiety (β=.30) and anaemia as a comorbid condition (β=.19), predicted the CAQ-Attention score (Table 7). Cardiac patients with higher level of anxiety and with anaemia as comorbidity had higher levels of HFA and monitoring of cardiac activity. The second model including anxiety (β=.32) and lower levels of haemoglobin (β=-.20) predicted CAQ-Attention (Table 6). It is interesting to note that these are two different ways of measuring anaemia. The first is based on data from medical records and the second on laboratory findings.

4. Discussion

The aim of this study was to examine which variable groups best predict heart-focused anxiety and its components: fear, avoidance, and attention focused on cardiac symptoms. As predictor variables, we examined the psychological characteristics of HF and other CVD patients: anxiety, depression, and intolerance to uncertainty, some medical/ laboratory variables, as well as demographic variables. The results showed that all three psychological variables were significant predictors of HFA, while only two medical/ laboratory variables and one demographic variable had a significant predictive value for certain aspects of cardiac anxiety (see Table 5-7).

In line with our expectation, we found that HF patients had higher overall levels of HFA, and more than one-third of patients (32.4%) had an elevated score on the CAQ questionnaire. These results were obtained by other authors in studies on HF patients, e.g. Wedegartner et al. (Wedegärtner et al., 2020). Research demonstrated that up to 49% of them showed elevated levels of HFA and it seems that this specific form of anxiety in this population is significantly more common than general anxiety (Bunz et al., 2016). In our study, we did not find gender

differences, but older patients had higher levels of physical activity avoidance that could trigger cardiac symptoms, which are in line with the results obtained by Bunz et al. (Bunz et al., 2016).

Heart-focused attention and monitoring of cardiac activity is predicted by lower levels of haemoglobin and anaemia as a comorbid disease. Anaemia is defined as low haemoglobin levels (<12g/dL in women and <13 g/dL in men) (Mcdonagh et al., 2021; Shah & Agarwal, 2013). The incidence of anaemia, which is a very common comorbid condition in patients with HF, is between 30% and 50 %. In HF patients the most common reason is iron deficiency (Chopra & Anker, 2020; Von Haehling et al., 2012). Increased heart rate and stroke volume are compensatory mechanisms in healthy people with oxygen delivery at low haemoglobin levels. These mechanisms are impaired in patients with HF and anaemia, leading to more pronounced dyspnoea and fatigue, exercise intolerance and worsening quality of life than in healthy people (Ebner et al., 2016). Patients that have both anaemia and HF also have increased rates of major cardiovascular events, hospitalizations, and death compared with non-anaemic HF patients (Paolillo et al., 2020). Global well-being, general health, physical functioning, and limitation of physical activity were independently associated with anaemia in hospitalized HF patients. Heart related quality of life (HR-QoL) was particularly low in patients with severe-to-moderate anaemia. The authors found a remarkable association between HR-QoL and severe anaemia in HF patients (Kraai et al., 2012).

We found that depressive and anxiety symptoms, intolerance of uncertainty, and cardiac anxiety were moderately related to each other and that many patients suffered from these conditions. About 55% of the study participants and 74% of the HF patient group experienced moderate or severe levels of depressive symptoms, which is in line with research results from Rutledgea et al. (Rutledge et al., 2006) and higher than in some studies e.g. 26% (Mourad et al., 2016). Our results are consistent with previous studies of HF and other groups of CVD patients, which show that psychological characteristics such as anxiety, depression, and quality of life are significantly correlated or even predictive of cardiac anxiety. The results of our study showed that depression has predictive value for the overall level of cardiac anxiety, fear about heart sensation, and avoidance of activities believed to elicit cardiac symptoms. A similar finding was obtained by Hamang et al. (Hamang et al., 2011) which shows that fear and avoidance were symptoms of HFA significantly related to depression. In the research, patients who had higher levels of fear and avoidance were more likely to report higher levels of depression and general anxiety. In our study, depression was a predictor of fear and avoidance, while anxiety was a predictor of symptom-focused attention. Regarding patients undergoing cardiac surgery, HFA

has been shown to be significantly correlated with increased symptoms of depression and anxiety (Hoyer et al., 2008).

Fear of cardiac sensations may also increase levels of perceived pain, resulting in greater disability and avoidance behaviour (Aikens et al., 2001). If we look at symptoms of depression such as, loss of interest or pleasure in most or all normal activities, or tiredness and lack of energy, anxiety, and agitation, feelings of sadness, or hopelessness, we notice that there is an overlap with avoidant behaviour in heart patients or with fear and worry about chest and heart sensations. Avoidance of activities and passivation is behaviour that is often encountered in people with depressive symptoms as well as in cardiac patients. In the literature, cardio-protective avoidance has been described as one of the core symptoms of HFA (Eifert et al., 2000b; Eifert & Forsyth, 1996). The avoidance of certain physical activities is not only associated with depression, but it is also one of the recommendations for patients with cardiological problems (Hamang et al., 2011). Therefore, "cardio-protective avoidance" can be equated with good adherence of patients to appropriate medical recommendations (Hamang et al., 2011).

Another important finding in our research is that around 37% of all patients and 46% of HF patients experienced moderate or severe anxiety. In other words, around a 40% of our patients are moderately to severely anxious, which certainly interferes with cardiac problems, especially if they suffer from HF. Anxious individuals are irritable, have muscle tension, and have difficulty in controlling feelings of worry. The research by Wedegärtner et al. (Wedegärtner et al., 2020) demonstrated that anxiety showed predictive value for fear and worry about chest and heart sensations. In our research anxiety predicted only heart-focused attention and monitoring of cardiac activity. In recent research conducted by Forte et al. (Forte et al., 2021) individuals with high anxiety showed a bias in elaborating threatening stimuli. The hypervigilance toward threatening stimuli (Wieser & Keil, 2020) can be considered as a component of the attentional bias, often described as an adaptive neurocognitive function useful for identifying and responding to an upcoming threat (Notebaert et al., 2017). It is possible that the attention of cardiological patients is preferentially directed toward changes in heartbeat or chest pain, which can be very disturbing if a person focuses on them for too long. Misinterpreting these symptoms as more dangerous than they really are, actually perpetuates anxiety. Attentional bias in anxious individuals is present both in contexts where the danger can be mitigated and in contexts where the danger cannot be mitigated, as noted by Notebaert et al. (Notebaert et al., 2017). Although our results are not surprising, they may be significant in understanding the aetiology and maintenance of anxiety specifically in cardiac patients. Several factors highlight the importance of identifying anxiety disorders in HF patients. First, anxiety has been associated with poor heart

health and higher rates of mortality in patients with coronary artery disease, which often co-occurs with HF (Celano et al., 2015; Roest et al., 2012). Second, in patients with HF and depressive symptoms, the presence of comorbid anxiety increases the risk of poor cardiac outcomes, leading to rehospitalisation and mortality (Reeves et al., 2015). Finally, in patients with major depression, the presence of anxiety may reduce antidepressant efficacy and lead to depression persistence (Celano et al., 2012, 2018).

The study conducted by Rigueira et al. (Rigueira et al., 2021) demonstrates that 14% of hospitalized HF patients had an abnormal level of depression, while 19% had an abnormal score on the anxiety questionnaire. Anxiety and depression worsened during hospitalization in 10% and 21% of HF patients, respectively. Advanced age, higher natriuretic peptide levels, and acute decompensation of chronic HF were associated with worsening anxiety, and longer hospitalization length was associated with worsening depression (Hamatani et al., 2022).

Although some advocate that negative emotions may be a risk factor for HF, others suggest that HF may activate anxiety or depression, or that perhaps there exists an interactional effect whereby negative emotions and HF affect one another in deleterious ways (Celano et al., 2018). Numerous studies have shown the association of type D personality with symptoms of depression, anxiety and chronic stress (Lambertus et al., 2018; Pedersen & Denollet, 2006), which indicates a propensity for maladaptive coping styles and increased risk of adverse prognosis (Borkoles et al., 2018), independently of medical risk factors and disease severity (Pedersen & Denollet, 2006). Type D personality combines two stable traits, i.e., the propensity to experience negative emotions (e.g., fear, sadness, irritability), and social inhibition in different situations (Denollet, 2005; Kupper & Denollet, 2018).

Two pathways have been proposed linking depression or anxiety and adverse outcomes in patients with HF: (1) physiological and (2) behavioural. Anxiety and depression, and the mental stress associated with them, are associated with excessive activation of the sympathetic nervous system, and catecholamine release, evidenced by decreased heart rate variability and increased plasma norepinephrine in both healthy persons and individuals with poor health (Carney et al., 2001; Stein et al., 2000). Another possible explanation for the link between depression or anxiety and increased risk of death or rehospitalisation is the effect of depression on patient adherence. No adherence to HF treatment plans is common (Michalsen et al., 1998; Monane et al., 1994), and unfortunately, poor adherence increases the risk of mortality and morbidity in patients with HF (McDermott et al., 1997). In 42–64% of HF readmissions, lack of adherence to prescribed medication or diet plans has been implicated as the proximate cause of readmission.

Consequently, such conditions not only worsen HF, but also the quality of family, professional and social functioning (Alemoush et al., 2021). In a study conducted by De Jong et al. (De Jong et al., 2011) the results showed that no adherence to medication links anxiety and event-free survival for patients with HF.

The results of our study showed that between 16.2 - 18.4% of patients experienced a high level of intolerance of uncertainty, which predicts fear of heart related sensations and the overall level of cardiac anxiety. Difficulties tolerating uncertainty as a "dispositional characteristic result from negative beliefs about uncertainty and its implications" (Robichaud et al., 2019) when a possible negative event, is considered threatening, irrespective of the probability of its occurrence (Carleton et al., 2007). Negative beliefs about uncertainty interfere with the individual's ability to effectively deal with these situations, and consequently, they use worry as a dysfunctional strategy to cope with or prevent feared outcomes (Behar et al., 2009; Dugas et al., 1998). These results support the assumption that IUC will reduce the capacity of cardiac patients to use functional coping strategies and that they are more likely to use worry, which is an ineffective coping strategy. In an attempt to reduce their fear of the consequences of cardiac disease, it is very likely that the cardiac patients' fear will increase.

4.1 Limitation, strength and conclusion

The limitations of this study are the relatively small sample size, lack of follow-up, especially for HF patients, and data were collected at one measurement point. A longitudinal analysis of change in psychological factors and its effects on change in health behaviours would provide more comprehensive answers to the research questions and enable the identification of underlying mechanisms or the verification of bidirectional relationships. The use of self-assessment scales in the examination of psychological characteristics can be a problem due to social desirability, and in addition, due to a lack of understanding of some of the items, which can cause a random response, especially in elderly patients. There are fewer females in the sample than males who are commonly predominant in samples of patients with cardiac disorders. This disparity may also reduce the statistical strength of the gender effect, which has not been shown to be a significant predictor, although it correlates with overall HFA and attention.

There are several strengths in this study. First, the association of heart-focus anxiety with IUC has not been mentioned in other studies. Second, an interesting finding was that we observed a predictive significance of anaemia and low haemoglobin levels as predictors, especially the increased focus of attention on cardiac symptoms. This, however, should be further verified in

studies involving a larger number of patients. Involving a group of patients with heart disease but without HF is also a strong point because there is not much research using clinical control groups. Although our patients differ with respect to age and the number of comorbid disorders, we find that HF is a predictor of the overall level of HFA, which supports research findings that highlight the particular vulnerability of these patients.

This research has a practical implication because it shows the importance of recognizing HFA in patients with cardiac disease, especially in patients with HF. Recognizing this specific form of anxiety is a major challenge because there is an overlap of symptoms related to heart disorders and symptoms related to anxiety, e.g., rapid heartbeat, sweating, and rapid breathing. If cardiac patients with HFA are not recognized, they will not receive the necessary psychological help, which can have very serious consequences for their mental and physical health. Research with patients who have experienced myocardial infarction has shown that the existence of heart-focused anxiety is a predictor of severe cardiac events and accelerated rehospitalisation (Van Beek et al., 2016). In patients with HF, the presence of HFA significantly reduces the quality of life, leads to avoidant behaviours, and is associated with anxiety and depressive symptoms. Furthermore, these patients are more likely to seek medical help and specialist services, but the need for psychological help is very rarely recognized. The existence of psychological difficulties also has a strong effect on health outcomes, reducing the responsiveness of patients to treatment. Therefore, short, reliable psychological instruments are needed in clinical practice to enable the assessment of psychological symptoms in patients who are at high risk due to pre-existing anxiety and depressive disorders.

Our study suggests the importance of diagnosing psychological problems in the population of cardiac patients, especially those with HF. However, it also highlights the need to develop psychological interventions that would make it possible to break the vicious circle between fear of heart symptoms, avoidant behaviours, and depressive symptoms, which are thus perpetuated. The results of this research support the idea that excessive focus on cardiac symptoms is more present in more anxious individuals, which is certainly an important factor in maintaining the symptoms.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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DOI: 10.13129/2282-1619/mjcp-3415