Does Mental Distress Predict Cardiac Surgical Outcome?

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Thorac Cardiovasc Surg

Abstract

Background Mental distress is suspected to influence the morbidity of cardiac patients. Evaluating mental distress in cardiac patients is rare and the impact on surgical outcome is still not certified.

Methods In 94 cardiac surgical patients, mental distress was assessed by the Patient Health Questionnaire-4 (PHQ-4). We defined length of stay in hospital and on intensive care unit as well as time of mechanical ventilation as outcomes on surgery. Age, physical activity, diabetes, overweight, PHQ-4, and an inflammation marker were tested for their predictive value on outcomes.

Results Reportedly prevalence of generalized anxiety was 16.0% and depression rate was 13.8%. Length of stay in hospital was 13 ± 8 days, time of mechanical ventilation was 10 (0–1,207) hours, and length of stay on intensive care unit was 3 ± 6 days. Length of stay in hospital was significantly predicted by age ($p = 0.048$), low physical activity ($p = 0.029$), and high C-reactive protein (CRP; $p = 0.031$). Furthermore, CRP was the only significant predictor of time of mechanical ventilation and length of stay on intensive care unit.

Conclusion Outcome was not predicted by mental distress. However, inflammation marker CRP was predictive for outcome, potentially caused by higher cardiovascular risk profile. Additionally, depression was referred to be associated with inflammation. Probably, the small sample and the timing of assessment were responsible for the missing relation between mental distress and outcome. We presume a relation with low physical activity and depression. Nevertheless, further randomized studies are needed to pay more attention on patients' distress to intervene preoperatively to improve postoperative outcome.

Keywords
- outcomes (include mortality
- morbidity)
- inflammation
- systemic
- neurocognitive deficits

received
June 23, 2022
accepted after revision
August 22, 2022

DOI https://doi.org/10.1055/s-0042-1758824.
ISSN 0171-6425.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Introduction

To examine the predictive value of mental distress on surgical morbidity outcome in cardiac patients, there was primarily the need to define surgical outcome. Postoperative surgical morbidity outcome in cardiac patients is definable by common quality indicators. Those are (among others) length of stay (LOS) on intensive care unit (ICU),[1] LOS in hospital,[2] and time of mechanical ventilation.[3] These quality indicators are measurable and comparable in expressing cardiac surgical outcome.

There are already various risk factors known to estimate cardiac surgical risk. As independent variables, they influence postoperative outcome and have found their way into surgical risk scores for preoperative surgical mortality risk estimation. To exemplify, the EuroSCORE I includes age as an independent risk factor for postoperative mortality and the EuroSCORE II was supplemented by clinical symptoms (New York Heart Association [NYHA] and Canadian Cardiovascular Society [CCS]) as well as the diagnosis of diabetes mellitus.[1] Few years ago, the impact of body mass index and inflammation markers (C-reactive protein [CRP], interleukin 6) on cardiac surgical morbidity outcome was shown.[4]

Mental distress is suspected to also exert a predictive effect on cardiac patients' morbidity outcome (e.g., higher rate of major cardiac event in patients with coronary heart disease).[5–7] Anxiety has an adverse impact on surgical outcome in general induced by missing preoperative information to clarify fears and doubts related to surgical procedure.[8] Therefore, patients who have in their preoperative medication a higher rate of anxiolytic drugs such as benzodiazepines and more need of anesthetic drugs such as sedatives/hypnotics and analgesics during surgical procedure (caused by sympathetic activation with hypertension and higher heart rate) may consecutively prolong mechanical ventilation time and patients' recovery.[9]

Also, in former studies worse cardiac surgical outcome with prolonged LOS in hospital[10] was proven in depressive patients undergoing cardiac surgery as coronary artery bypass grafting (CABG).[11,12]

Before the coronavirus disease 2019 (COVID-19) pandemic, the prevalence of generalized anxiety disorders (GADs) was up to 5% in Germany[13] and the prevalence of subclinical depressive symptoms measured 25 to 30%.[14] Results from the Gutenberg Health Study suggested an association of metabolic syndrome (arterial hypertension, dyslipidemia, hyperglycemia, and abdominal obesity) with depression.[15] Tully and Baker made a comprehensive overview of recent literature about anxiety and depression and cardiac morbidity outcomes in CABG patients and recommended to screen cardiac surgical patients for anxiety and depression to improve surgeons' recognition of those still only presumed and not proven surgical risk factors.[16] However, preoperative screening of mental distress is still rare in cardiac surgery, and the impact of anxiety and depression on surgical outcome still remains unclear.

We screened our elective cardiac patients preoperatively for mental distress using the Patient Health Questionnaire-4 (PHQ-4), which is a very short, self-administered questionnaire. The PHQ-4 was earlier described as a feasible screening method for anxiety and depression in CABG patients.[16]

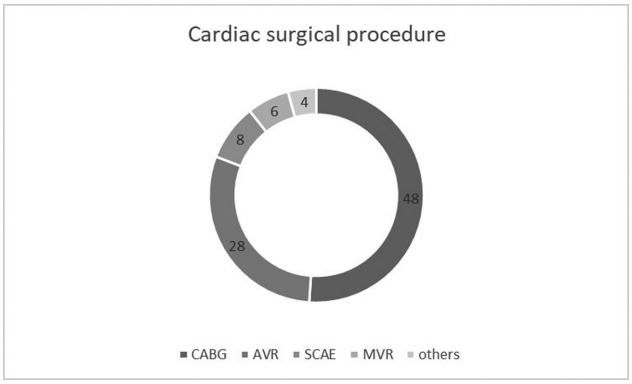

Fig. 1 Categories of cardiac operations ($n = 94$) our patients underwent. AVR, aortic valve replacement; CABG, coronary artery bypass grafting; MVR, mitral valve repair (/replacement); SCAE, supracoronary (aorta) ascendens replacement.

The aim of the study was to assess mental distress (self-administered by the PHQ-4) as a predictor for unfavorable postoperative outcome after elective cardiac surgery.

Patients and Methods

Patients and Assessment

A total of 94 consecutive and unselected patients scheduled for elective cardiac surgery were included in this prospective study during the admission interview by the nursing staff.

The self-administered questionnaire (see **Supplementary Material 1**, available in the online version only) was infilled by each patient and preoperatively submitted back to the nursing staff.

Cardiac Surgical Procedure

►**Fig. 1** shows the distribution of the different kinds of cardiac surgical procedures. Ninety patients underwent cardiac surgery via sternotomy under extracorporeal circulation. More than a half underwent CABG, a quarter got aortic valve replacement, and four patients even did not have to pass ICU.

Outcomes (Dependent Variables)

The surgical outcome was defined by three parameters:

- LOS in hospital.
- Time of mechanical ventilation.
- LOS on ICU.

Outcome variables were collected retrospectively after discharge of the patients.

Potential Predictors (Independent Variables)

- Age.
- Physical activity (minimal three to four times a month; see ►**Supplementary Material 1**, available in the online version only).

- Diabetes (anamnestic, see ►**Supplementary Material 1**, available in the online version only).
- Overweight (anamnestic).
- *Inflammation/CRP* (mg/L) (routinely determined with standardized preoperative blood tests).
- Mental distress (self-administered PHQ-4, see ►**Supplementary Material 1**, available in the online version only).

Measurement of Mental Distress

Mental distress was measured by the *PHQ-4* that screens for general distress. Wicke et al[17] have recently published data on validity of the German version of the *PHQ-4*. The *PHQ-4* consists of four questions; depression (*PHQ-2*) as well as anxiety (*Generalized Anxiety Disorder 2-item* [*GAD-2*]) is included with two items each. The *PHQ-2* captures the two Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) main criteria of major depression (depressed mood, loss of interest/joylessness). The four-step response format includes the answer options not at all (0), on individual days (1), on more than half of the days (2), and almost every day (3). Sum scores of the *PHQ-2* range from 0 to 6 points. A cutoff of $\geq$3 detects the diagnosis of major depression with sensitivity of 87% and a specificity of 78%.[18] Sensitivity to detect any depressive disorders is 79%, whereas specificity is 56%.[18] The *GAD-2* also includes two DSM-5 main criteria of GAD (excessive fear and worry, difficulty controlling worries). Sensitivity to detect GADs is 86%, whereas specificity is 83%.[19]

For statistical analysis, the PHQ-4 score indicating mental distress was used as an independent variable.

Besides the PHQ-4, we also assessed the PHQ-stress module with 10 items (each item 0–3 points; see ►**Supplementary Material 1**, available in the online version only); 0 to 4 points show minimally stressed, 5 to 9 points mild stress, 10 to 14 points moderate stress, and 15 to 20 strong stress. The PHQ-stress module was significantly related with the PHQ-4 in our study group. Thus, and with regard to the limited number of possible predictors for our regression models, we decided to omit the PHQ-stress module from further regression analyses.

Statistical Analysis

For statistical analysis, IBM SPSS Statistics 25 (IBM, Chicago, Illinois, United States) was used. For normally distributed outcome parameters, the mean was used, and for nonnormally distributed outcome parameters, the median was used.

Univariate correlations between all assessed patient characteristics (see ►**Supplementary Material 1**, available in the online version only) and dependent outcome data (LOS in hospital, time of mechanical ventilation, LOS on ICU) were determined using Spearman's rho correlations.

To analyze the relation between outcome variables and the potential predictors, the linear regression was used. For this statistical analysis, only $n = 73$ data were complete in all dependent and independent variables. We assumed a potential predictor as significant if $p < 0.05$.

Table 1 Sample patient characteristics ($n = 79$ of 94 totally completed the questionnaire)

	Mean (SD)/percent
Demographic data	
Age, y	69.4 (11.79)
Sex, female	27.2%
Education, at least high school certificate	11.4%
Partnership	76.9%
Risk factors	
Physically active	31.6%
Diabetes	27.2%
Overweight	18.5%
Currently smoking	10.0%
Inflammation	
CRP, mg/L	6.2 (16.70)
Mental distress	
Anxiety (GAD-2)	1.4 (1.57)
Depression (PHQ-2)	1.2 (1.34)
Distress (PHQ-4)	2.5 (2.51)

Abbreviations: GAD-2, Generalized Anxiety Disorder 2-item; PHQ-2, Patient Health Questionnaire-2; PHQ-4, Patient Health Questionnaire-4; SD, standard deviation.

Results

Patient Characteristics

Cardiac surgical patients had a mean age of 69.4 ($\pm$11.8) years and were predominantly male. The EuroSCORE II was 2.82 ± 3.63. ►**Table 1** shows the sample of patient characteristics. For better readability, potential predictors were organized in groups of different categories. Demographic data, risk factors, and mental distress are self-administered independent variables.

By the cutoff value of $\geq$3 in GAD-2 in 16.0% of patients ($n = 15$), anxiety was preoperatively detected and by the cutoff value of $\geq$3 in PHQ-2 in 13.8% of patients ($n = 13$) depressive symptoms were found preoperatively. Mean PHQ-stress level was even minimal with 3.84 ± 2.75.

Both PHQ-4 (GAD-2 and PHQ-2) and PHQ-stress module were not significantly related to the EuroSCORE II ($p > 0.05$).

Outcomes

- LOS in hospital was on average 13 ± 8 days. In-hospital mortality was 0%. There were three cases of postoperative cerebral stroke. Transient delirium was seen in 47 cases, but only two patients needed neuroleptic drugs.
- Median time of mechanical ventilation was 10 (0–1,207) hours. Thirty-one patients showed renal insufficiency postoperatively, and 13 patients needed hemofiltration on their way to extubation. One pulmonary infection was proven.
- Mean LOS on ICU was 3 ± 6 days.

Table 2 Correlations between patient characteristics and outcome (LOS in hospital, time of mechanical ventilation, LOS on ICU, $n = 79–94$ totally completed the questionnaire)

			Lengths of stay ($n = 79–94$)[a]	Ventilation time ($n = 79–94$)[a]	Intensive care ($n = 79–94$)[a]
1	Demographic data	Age	−0.304	0.155	0.313
		Sex, female	0.234	0.115	0.213
		Education, at least high school certificate	−0.115	−0.070	−0.210
		Partnership	−0.187	0.109	−0.023
2	Risk factors	Physically active	**−0.390***	−0.100	−0.120
		Diabetes	0.119	0.095	−0.046
		Overweight	−0.008	−0.105	−0.019
		Currently smoking	0.048	0.060	−0.061
3	Inflammation	CRP	0.203	0.029	0.141
4	Mental distress	Anxiety (GAD-2)	−0.068	0.047	−0.045
		Depression (PHQ-2)	0.015	−0.030	−0.011
		Distress (PHQ-4)	−0.083	−0.026	−0.053

Abbreviations: CRP, C-reactive protein; GAD-2, Generalized Anxiety Disorder 2-item; PHQ-2, Patient Health Questionnaire-2; PHQ-4, Patient Health Questionnaire-4.
[a]Spearman's rho correlations.
*$p < 0.00139$ (after Bonferroni adjustment).

Patient Characteristics and Outcomes

►**Table 2** shows the univariate correlation between patient characteristics and outcomes. *Physical activity* was negatively correlated with *LOS in hospital*.

Furthermore, there was no significant correlation of *currently smoking* and time of mechanical ventilation.

Outcomes and Potential Predictors

- LOS in hospital: ►**Table 3** shows that *age* and the inflammation marker *CRP* were positively correlated with LOS in hospital. *Physical activity* was negatively predictive for LOS in hospital.
- Time of mechanical ventilation (►**Table 4**).
- LOS on ICU: ►**Table 4** and ►**Table 5** show that only the inflammation marker *CRP* was positively correlated with the outcome variables *time of mechanical ventilation* and *LOS on ICU*.

In conclusion, the inflammation marker CRP was the only independent variable that had a predictive value for all three outcomes. Mental distress was neither significantly predictive for any designated surgical outcome parameter nor for any complicated cases (e.g., cerebral stroke).

Discussion

In our prospective study, we tested the hypothesis that mental distress has a predictive impact on cardiac surgical morbidity outcome defined as time of mechanical ventilation and LOS in hospital and on ICU. Concluding our results, our hypothesis had to be rejected.

The definition of surgical outcome by the time of mechanical ventilation and LOS on ICU and in hospital is a common method to have fast clinical outcome parameters in every cardiac surgical patient who needs to be ventilated and pass ICU postoperatively.[20,21]

Table 3 Potential predictors of LOS in hospital ($n = 73$).

Predictor variables	β	$P(\beta)$	R^2	Adj. R^2	F	$p(F)$
Age	0.218	0.**048**	0.256	0.189	3.84	0.002
Physically active	−0.243	**0.029**				
Diabetes	0.171	0.118				
Overweight	−0.050	0.639				
CRP	0.237	**0.031**				
Distress (PHQ-4)	−0.060	0.581				

Abbreviations: CRP, C-reactive protein; PHQ-4, Patient Health Questionnaire-4.

Table 4 Potential predictors of time of mechanical ventilation ($n = 73$)

Predictor variables	β	$p(\beta)$	R^2	Adj. R^2	F	$p(F)$
Age	0.073	0.442	0.428	0.377	8.53	<0.001
Physically active	0.030	0.757				
Diabetes	0.172	0.074				
Overweight	−0.072	0.443				
CRP	0.605	**0.000**				
Distress (PHQ-4)	−0.016	0.868				

Abbreviations: CRP, C-reactive protein; PHQ-4, Patient Health Questionnaire-4.

Table 5 Potential predictors of LOS on ICU ($n = 73$)

Predictor variables	β	$p(\beta)$	R^2	Adj. R^2	F	$p(F)$
Age	0.184	0.083	0.306	0.244	4.92	<0.001
Physically active	0.014	0.894				
Diabetes	0.106	0.321				
Overweight	−0.043	0.681				
CRP	0.496	**0.000**				
Distress (PHQ-4)	0.021	0.839				

Abbreviations: CRP, C-reactive protein; PHQ-4, Patient Health Questionnaire-4.

Undoubtedly, mortality is the worst surgical outcome. Cardiac surgical risk scores such as the *EuroSCORE II* calculate the risk for a worse surgical outcome: to die. In our study group of cardiac surgical patients perioperative mortality risk was low with an averaged EuroSCORE II 2.8 % (<4%) Lit.[22] Interestingly, mental distress screened by the PHQ-4 was independent from the EuroSCORE II. We presume that the stress before surgery is proportionally raised the more diseased the patient is (Median EuroScore II was 0.5 - 24.5%). Nevertheless, no patient of our study group did die during first 30 days after cardiac surgery. Thus, we had to define other outcome parameters. There are studies that also used the variables of the EuroSCORE II (e.g., age or diagnosis of diabetes mellitus) as potential predictors of cardiac surgical morbidity outcome defined by time of mechanical ventilation or LOS on ICU.[1] Confirming that former study[1] our study had similar results with a significant influence of *age* on LOS in hospital explained by prolonged mobilization and more need of rehabilitation before returning home after cardiac surgery in older patients.

The negative relation of physical activity with LOS in hospital probably demasks a hypoactive depressive syndrome resulting in prolonged LOS in hospital.[23] Nevertheless, we did not find a relation of mental distress and LOS in hospital.

Regarding measured preoperative prevalence of 16% of GAD in elective cardiac surgical patients, more than threefold higher compared with average population.[13] References describe anxiety prevalence up to 80% before big surgery (e.g., cardiac surgery).[24]

We presume that at the time of admission and while completing the questionnaire, the patient is not yet properly educated by the surgeon concerning his procedure, which could lead to a lack of information and therefore trigger fear as well as doubts at this moment.[8] We assume that after the surgeon provided patient education and answered all questions the patient had about the surgical procedure, a reassessment of the GAD-2 could be quite lowered. Unfortunately, the reassessment of the PHQ-4 was not part of our study plan. To maintain our hypothesis, we refer again the study group around Moosdorf and coworkers. Patients got more benefit of long-term life quality by preoperative brief psychological presurgery intervention to optimize outcome expectations instead of psychological control intervention focusing on emotional support and general advice.[25,26]

Preoperative measured depression (by the cutoff value $\geq$ 3 in GAD-2) had a prevalence of 13.8% similar to other references.[16] Furthermore, preoperative depression scores were shown to be best predictors of depressive mood after CABG.[27] This context emphasizes the importance of depression assessment prior to surgery. Nevertheless, there are studies that found an increase of depression postoperatively.[11,28] Unfortunately, we did not re-evaluate depression postoperatively.

Considering retrospectively, the timing of mental distress assessment was unfavorable in our study. Reminding the role of inflammation in our former studies predicting raised cardiovascular risk profile (e.g., worse left ventricular ejection fraction or severe coronary sclerosis) in CABG patients,[4] we retrospectively analyzed a predictive value of standardized preoperatively determined inflammation marker *CRP* on surgical outcome. As expected, the inflammation marker CRP was significantly predictive for all three surgical outcome parameters. There are references that elevated

inflammation markers were correlated with depressive symptoms.[11,12,29] Recently, Salzmann et al could show a moderating effect of inflammation markers (e.g., CRP) on the success of psychological intervention before CABG surgery.[30] Nevertheless, it remains unclear whether an undetected pathophysiological pathway of depression provoked by inflammation could be responsible for worse surgical outcome predicted by the CRP. More than this, we could imagine that the CRP is a predictive marker for prolonged time of mechanical ventilation and LOS on ICU and in hospital by undetected elevated cardiovascular risk profile in these patients with raised inflammation marker as we did prove in a former study.[4] The higher the cardiovascular risk profile, the worse the surgical outcome was.

Limitations and Perspectives

Our methods (e.g., timing of measurements, sample size) seem to be of high importance to detect effects of distress (anxiety and depression) validly.

There is a need of prospective trials with larger sample sizes in single CABG surgery with measurement of mental distress (anxiety and depression) preoperatively before and after patient education as well as postoperatively before discharge. Depending on patients' distress, the following interventions/offers should be made:

- Repeated preoperative patient education by the surgeon with the chance to clarify all fears and doubts in context with the surgical procedure.
- Psychological intervention to clarify patients' outcome expectations.
- Postoperative physical mobilization therapy, if depressive symptoms were detected, because this is predictive for postoperative depressive symptoms with hypoactivity and may be with consecutively prolonged LOS in hospital.

However, the effects of mental distress are complex; thus, collaborative care models including mental health care professionals are recommended.

Conflict of Interest
None declared.

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