General Hospital Psychiatry 74 (2022) 58–64

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

Prospective association between pro-inflammatory state on admission and posttraumatic stress following acute coronary syndrome

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ARTICLE INFO

Keywords:
Cardiovascular disease
Cytokines
Inflammation
Longitudinal study
Psychological stress
Trauma

ABSTRACT

Objective: The traumatic experience of acute coronary syndrome (ACS) may induce symptoms of posttraumatic stress disorder (PTSD). We examined whether the ACS-triggered acute inflammatory response predicts the development of PTSD symptoms.

Method: Study participants were 70 patients (all Caucasian, 80% male, mean age 59 years) with myocardial infarction (MI) during the acute treatment phase. Interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, IL-4, IL-10, and transforming growth factor (TGF)-1β were determined in plasma collected within 48 h of hospital admission. Participants self-assessed the severity of ACS-induced PTSD symptoms with the 17-item Posttraumatic Diagnostic Scale at 12 months.

Results: There was a significant positive association of the pro-inflammatory index (added standardized z-scores of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α) with total PTSD symptom severity ($\Delta R^2 = 0.050$, $p = .029$) and re-experiencing symptoms ($\Delta R^2 = 0.088$, $p = .008$), but not avoidance/numbing and hyperarousal symptoms. Analyses were adjusted for the anti-inflammatory index (added standardized z-scores of IL-4, IL-10, and TGF-β1), trauma-focused counseling, sex, age, time since pain onset, troponin, body mass index, and distress during MI. Results were robust when the anti-inflammatory index was removed from the model. Additional analyses showed significant associations of both the net-inflammatory index (i.e., pro-inflammatory index minus anti-inflammatory index) and IL-1β with total PTSD symptom severity, re-experiencing, and hyperarousal symptoms (ΔR^2 between 0.042 and 0.090) and of IL-1β with avoidance/numbing symptoms ($\Delta R^2 = 0.050$).

Conclusions: The findings suggest an association between the pro-inflammatory state launched during ACS and the development of PTSD symptoms. Increased IL-1β may play a particular role in the pathophysiology of ACS-induced PTSD symptoms.

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating mental health condition, which can be triggered by life-threatening diseases like acute coronary syndromes (ACS) [1]. The prevalence of clinically significant ACS-induced PTSD symptoms, including reliving aspects of ACS in

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https://doi.org/10.1016/j.genhosppsych.2021.12.003
Received 3 November 2021; Received in revised form 3 December 2021; Accepted 6 December 2021
Available online 10 December 2021

thoughts or dreams, avoidance of ACS-related cues, and hyperarousal with, for example, increased alertness and irritability, is 12% [2]. ACS-induced PTSD symptoms are associated with poor quality of life and an increased risk of adverse outcomes, including recurrent cardiac events and premature mortality [2].

Evidence is accumulating about demographic and biobehavioral predictors of ACS-induced PTSD symptoms such as younger age, female sex, distress during ACS [1], and low plasma cortisol levels [4]. Modifiable risk factors hold the potential for early behavioral and/or pharmacological interventions to prevent the development of cardiac disease/event-induced PTSD symptoms [3]. To illustrate this, stress doses of hydrocortisone before induction of anesthesia and on three postoperative days in patients undergoing cardiac surgery resulted in less 6-month total PTSD symptoms than placebo [5]. In another placebo-controlled study in cardiac surgery patients, a single dose of dexamethasone administered after induction of anesthesia was associated with a lower risk of severe PTSD symptomatology after a median follow-up of 33 months in women but not in men [6].

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction with lower cortisol levels and altered glucocorticoid sensitivity may partly explain increased pro-inflammatory cytokines (PICs) interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α in PTSD induced by various traumatizing events [7,8]. Variations in levels of the anti-inflammatory cytokines (AICs) such as IL-4 and IL-10 are less conclusive [7]. However, rather than from individual cytokines, the inflammatory state results from an interaction between PICs and AICs, both of which orchestrate the immune and inflammatory response relevant to mental and physical health, including atherosclerosis [9]. A pro-inflammatory state may be one mechanism to explain the poor prognosis of patients with ACS-induced PTSD symptoms because inflammation, and particularly PICs like IL-6 and TNF-α, are crucial for the development and clinical manifestation of cardiovascular disease [10].

As the bulk of studies on the pro-inflammatory state in PTSD is cross-sectional, with a scarcity of longitudinal data, there is limited information on whether a pro-inflammatory state precedes or follows PTSD symptom onset [7]. In war-zone deployed marines, higher baseline C-reactive protein levels were predictive of PTSD symptom severity 3 months after deployment [11]. In patients with traumatic orthopedic injuries, the PIC IL-8 and the AIC transforming growth factor (TGF)-β, assessed between 1 and 5 days of hospitalization, were associated with total PTSD symptoms independent of each other [12]. In contrast, in women in the longitudinal National Health Survey II, several pre-PTSD onset pro-inflammatory marker levels did not predict the onset of more severe PTSD [13].

Acute cardiomyocyte necrosis has been shown to trigger a systemic inflammatory response, including a cytokine cascade with increases in IL-1β, IL-6, and TNF-α and decreases in IL-10 and TGF-β1 [14]. However, it is unknown whether inflammation predicts ACS-induced PTSD symptoms. Given this lack of research, we tested the hypothesis that an ACS-triggered pro-inflammatory state is associated with more severe ACS-induced PTSD symptoms 12 months later. We selected this time interval for the follow-up investigation, because research shows that ACS-induced PTSD symptoms tend to decrease in the first year post-ACS but show remarkable persistence thereafter [15]. The primary analysis focused on an association between a pro-inflammatory index (sum of IL-1β, IL-6, and TNF-α), assessed within 48 h of ACS, adjusted for an anti-inflammatory index (sum of IL-4, IL-10, and TGF-β1) and additional covariates. Additional analyses examined the associations of a) the pro-inflammatory index without adjustment for the anti-inflammatory index, b) the net-inflammatory index (pro-inflammatory index minus anti-inflammatory index), and c) individual cytokines with 12-month PTSD symptoms.

2. Methods

2.1. Study design

For the current study, we analyzed data of a subsample of consecutive patients of the Myocardial Infarction-Stress Prevention Intervention (MI-SPRINT) randomized controlled trial (ClinicalTrials.gov NCT01781247) [16]. The trial enrolled a total of 190 patients of whom 106 completed the 12-month follow-up. Of the latter, 70 had complete data on cytokine measurements at hospital admission and self-rated PTSD symptoms at 12 months, both of which were required for the present study. The recruitment procedure and reasons for dropouts have been detailed elsewhere [17]. All patients underwent acute coronary intervention due to an ACS. The trial had been conducted between 2/2013 and 9/2015 at the cardiology department of a university hospital in Switzerland. The primary aim of the MI-SPRINT trial was to investigate the hypothesis that the development of ACS-induced PTSD symptoms could be prevented by a one-session intervention of trauma-focused counseling delivered to patients within 48 h of hospital admission, which could not be confirmed [17,18]. Nonetheless, the intervention group (trauma-focused counseling versus stress-focused counseling as the active control intervention) was included as a covariate in the current study. The study protocol was approved by the ethics committee of the State of Bern, Switzerland. All participants provided written informed consent.

2.2. Participants

To be included in the study, participants had to be at least 18 years old of age and have a verified ST-elevation MI (STEMI) or non-STEMI, stable circulation, and high distress during ACS based on the intensity (numerical rating scales ranging from 0 to 10) of perceived pain, fear of dying and/or helplessness during ACS. Scores of 5+ for pain and 5+ for fear of dying and/or feeling helpless defined high levels of distress. Exclusion criteria were emergency coronary bypass surgery, diseases leading to death within 1 year, cognitive impairment, limited orientation, current major depression per the cardiologist's clinical judgment (because we assumed that cognitive and motivational difficulties might be a barrier to focused participation in a counseling session), suicidal ideation in the last 2 weeks, and inadequate knowledge of German.

2.3. Measures

2.3.1. Posttraumatic stress

To assess the outcome variable - 12-month severity of PTSD symptoms - we used the validated German version [19] of the 17-item Posttraumatic Diagnostic Scale (PDS) according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV) [20]. Patients were invited to self-rate the frequency of each PTSD symptom in the past month on a 4-point scale (0 = not at all or only one time; 3 = five or more times a week/almost always). Total frequency/severity scores between 1 and 10, 11–20, 21–35, and 36–51 indicate mild, moderate, moderate-to-severe, and severe PTSD symptoms, respectively [21]. The minimal clinically important difference was defined as half a standard deviation (SD) of the sample's mean total PDS frequency score [22]. Agreement of a PTSD diagnosis with the PDS is 82% compared to a structured clinical interview [20]. Cronbach's α was 0.81 for the total symptom severity score, and 0.77, 0.77, and 0.80, respectively, for the PTSD symptom cluster scores of re-experiencing (5 items), avoidance/numbing (7 items), and hyperarousal (5 items), indicating good internal consistency for all scales.

2.3.2. Cytokines

To assess cytokine concentrations as predictors of PTSD symptoms, fasting morning blood samples were collected into EDTA tubes within 48 h of admission, centrifuged for 10 min at 2000*g*, and obtained plasma

samples stored at −80 °C until analysis. Concentrations were determined using Luminex technology with magnetic bead-based immunoassays (Bio-Rad Laboratories Inc., Hercules, CA, USA) by the Institute of Immunology, Bern University Hospital, Inselspital. Intra- and inter-assay coefficients of variation were <10% for all cytokines. Detection limits and levels of lowest quantification (LLOQ) were 0.02 and 0.24 pg/mL for IL-1β, 0.67 and 1.65 pg/mL for IL-6, 0.07 and 0.57 pg/mL for TNF-α, 0.52 and 1.33 pg/mL for IL-4, 0.30 and 1.99 pg/mL for IL-10 and 3.9 and 4.18 pg/mL for TGF-β1.

We used fluorescence intensity results to distinguish undetectable from unquantifiable values. This distinction is used to express that a plasma sample with an unquantifiable amount of a cytokine has a higher concentration of that cytokine than a sample with an undetectable amount. IL-1β was quantifiable, unquantifiable (but detectable), and undetectable in 8, 58, and 4 participants, respectively. IL-6 was quantifiable in 66 participants and unquantifiable in 4. Both IL-4 and IL-10 were quantifiable, unquantifiable, and undetectable in 7, 55, and 8 participants, respectively. Concentrations of TNF-α and TGF-β1 were quantifiable in all participants. For analysis, we substituted undetectable values (i.e., below the sensitivity threshold) with half the limit of detection and unquantifiable values (i.e., between the sensitivity threshold and the LLOQ) with half the LLOQ.

2.3.3. Covariates

We selected covariates a priori based on known risk factors for ACS-induced PTSD symptoms [1] and associations with the ACS-triggered acute phase reaction [23,24]. The number of covariates was limited to guard against overfitting of multivariable models given the sample size. Information on age, sex, and peak cardiac troponin T level (high sensitive) from serial measurements during hospitalization was taken from medical records. For the calculation of the body mass index (BMI), participants provided self-reported height and weight. Distress during ACS was quantified using numerical rating scale scores for fear of dying and helplessness required for inclusion (see above). Pain intensity during ACS was not considered to obtain an undiluted measure of distress. For the analysis, the scores for fear of dying and helplessness were added and divided by two. The time between onset of pain and arrival at the hospital was asked by study personnel and noted (<24 h versus longer time intervals). Additional variables were assessed to characterize the sample and/or for additional analyses of exploratory interest. These were index MI (STEMI or non-STEMI), previous MI (yes/no), use of antidepressants (yes/no), and events between hospital discharge and 12-month follow-up: chest tightness or pain (frequent/occasionally or never), hospitalizations (cardiac-related, non-cardiac-related, none), and the number of emergency department visits. The data for patient characteristics and covariates were complete in all 70 participants.

2.4. Data analysis

Data were analyzed using SPSS 27.0 for Windows (SPSS Inc., Chicago, IL) with two-tailed significance level of $p < .05$. Due to non-normal distribution, PDS scores were square-root transformed, and IL-6, TNF-α and troponin levels were base 10 log-transformed. Because of the many undetectable and nonquantifiable plasma concentrations, measures for IL-1β, IL-4, and IL-10 were categorically transformed: 0 = undetectable, 1 = nonquantifiable, and 2 = quantifiable levels (irrespective of the absolute concentration). Standardized z-scores of IL-1β (categorical values), IL-6 (log values), and TNF-α (log values) were added and divided by three to form a pro-inflammatory index. Likewise, to form an anti-inflammatory index, standardized z-scores of IL-4 (categorical values), IL-10 (categorical values), and TGF-1β (original values) were added and divided by three. *Z*-scores of cytokine measures were used in all analyses.

We performed Pearson correlation analysis and multivariable linear regression analyses to determine associations between inflammatory measures and PTSD symptoms. The primary multivariable model tested the hypothesis of a direct association between the pro-inflammatory index and severity of ACS-induced PTSD symptoms at 12-months, adjusting for intervention group, sex, age, time since onset of pain, troponin, BMI, distress during ACS, and the anti-inflammatory index. These covariates were selected on the basis of a potential influence of demographic factors, MI size, severity of psychological trauma, and body fat as a source of cytokines on cytokine levels and the development of ACS-induced PTSD symptoms. To avoid overfitting of statistical models, we considered a maximum of 10 covariates in regression models. Two additional multivariable models were run to test the robustness of the association between the pro-inflammatory state and the development of PTSD symptoms. The first model tested the association of the pro-inflammatory index without adjustment for the anti-inflammatory index. The second model tested the net-inflammatory index (equal to pro-inflammatory index minus anti-inflammatory index) as the independent variable [25]. In case of a significant association with the PTSD symptom total score, post hoc analyses were run for each PTSD symptom cluster separately with family-wise adjustment to alpha for these three tests (i.e., alpha-adjusted = 0.05/3, yielding a *p*-value<.017 for significance). Complementary analyses were run for each cytokine and PTSD symptom cluster separately to better understand the potential mechanisms linking the ACS-triggered acute inflammatory response with the development of PTSD symptoms. Homoscedasticity of regression models was verified with the Koenker test, and the regression output revealed no concern for multicollinearity or influential outliers among predictor variables using Cook's distance. For exploratory reasons, further adjustment was made for patient characteristics and events during follow-up one-by-one, as such analyses could yield potential explanations for an association between inflammation at the time of ACS and the development of PTSD symptoms at 12 months.

Table 1
Participant characteristics at baseline and at 12 months ($n = 70$).

Sex, male, *n* (%)	56 (80.0)
Age (years), mean (SD)	59.0 (9.7)
Previous myocardial infarction, *n* (%)	3 (4.3)
ST-elevation myocardial infarction, *n* (%)	46 (65.7)
Peak troponin, μg/L, median (IQR)	2.4 (0.9, 6.4)
<24 h between onset of pain and hospital arrival, *n* (%)	56 (80)
Body mass index, kg/m2, mean (SD)	27.7 (4.9)
Distress, score, mean (SD)	5.6 (1.7)
Antidepressant use, *n* (%)	4 (5.7)
Trauma-focused counseling, *n* (%)	42 (60)
Interleukin-1β, pg/mL, median (IQR)	0.12 (0.12, 0.12)
Interleukin-6, pg/mL, median (IQR)	50.5 (20.9, 87.4)
Tumor necrosis factor-α, pg/mL, median (IQR)	7.3 (6.0, 8.7)
Interleukin-4, pg/mL, median (IQR)	0.67 (0.67, 0.67)
Interleukin-10, pg/mL, median (IQR)	1.0 (1.0, 1.0)
Transforming growth factor-β1, pg/mL, mean (SD)	31,499 (6513)
Pro-inflammatory index, z-score, mean (SD)	0 (0.61)
Anti-inflammatory index, z-score, mean (SD)	0 (0.69)
Net-inflammatory index, mean (SD)	0 (0.81)
Chest tightness/pain during follow-up, *n* (%)	42 (60)
Hospitalization during follow-up	
Cardiac-related, *n* (%)	27 (38.6)
Non-cardiac-related, *n* (%)	16 (22.8)
None, *n* (%)	27 (38.6)
Number of emergency department visits, mean (SD)	0.51 (0.88)
PDS total severity score, median (IQR)	4.5 (1.0–7.3)
PDS re-experiencing score, median (IQR)	1.0 (0–2.0)
PDS avoidance/numbing score, median (IQR)	1.0 (0–2.0)
PDS hyperarousal score, median (IQR)	2.0 (0–3.0)

IQR, interquartile range; SD, standard deviation; PDS, Posttraumatic Diagnostic Scale.

3. Results

3.1. Participant characteristics

Table 1 shows baseline characteristics, events that occurred during follow-up, and PDS scores at 12 months of participants (all Caucasian). The sample was on average 59 years old, predominately male, and had a mean BMI in the overweight range. Ten (14.3%) participants had a PDS total severity score between 11 and 27, indicating either moderate (n = 6) or moderate to severe (n = 4) PTSD symptoms at 12 months. Based on a mean (SD) PDS total severity score of 5.6 (6.4), the minimal clinically significant difference was 3.2 score points, equivalent to half a SD. During the 12-month follow-up, approximately three in five patients each suffered frequent or occasional chest tightness/pain, were hospitalized for cardiac or non-cardiac reasons, and had at least one emergency department visit.

3.2. Associations between inflammatory measures and posttraumatic stress

There were significant zero-order correlations (Table 2) between the pro-inflammatory index and total PTSD symptom severity (r = 0.26, p = .033) and re-experiencing symptoms (r = 0.31, p = .008). These associations were particularly driven by IL-1β, which showed positive correlations with total PTSD symptom severity (r = 0.33, p = .006), re-experiencing (r = 0.29, p = .015), avoidance/numbing (r = 0.27, p = .024), and hyperarousal (r = 0.26, p = .028) symptoms. Moreover, the net-inflammatory index was correlated with total PTSD symptom severity (r = 0.26, p = .028), re-experiencing (r = 0.25, p = .040), and hyperarousal (r = 0.25, p = .041) symptoms. Peak troponin levels were not significantly related to any inflammatory index or individual cytokines (all p-values >.16).

The regression of the pro-inflammatory index on PTSD symptoms, adjusted for intervention group, sex, age, time between pain onset and arrival at the hospital, peak troponin, BMI, distress, and the anti-inflammatory index, is summarized in Table 3. The pro-inflammatory index was significantly associated with total PTSD symptom severity (p = .029) and re-experiencing symptoms (p = .008), explaining 5.0% and 8.8% of the total variance, respectively. For a one-unit increase in the pro-inflammatory index (range − 1.46 to 2.17), there was a 3.04-unit increase in the PDS total severity score (original unit), suggesting clinical significance. Fig. 1A illustrates the linear association across tertiles of the pro-inflammatory index with total PTSD symptom severity. In both alternative models, similar results emerged for a significant association between the pro-inflammatory state and more severe PTSD symptoms, with the net-inflammatory index also showing a significant association with hyperarousal symptoms.

Additional adjustment of the primary multivariable model for events during follow-up, i.e., chest tightness/pain, hospitalizations and emergency department visits one-by-one, did not change the significance of the positive association of the pro-inflammatory index with total PTSD symptom severity (p-values ≤.033) and re-experiencing symptoms (p-values ≤.014) at 12 months. In these models, chest tightness/pain (B = 0.622, s.e. = 0.300; p = .042), but not hospitalizations (p = .96) and emergency departments visits during follow-up (p = .41), was independently associated with total PTSD symptom severity. Table 4 shows the fully adjusted multivariable associations between the concentration of individual cytokines at hospital admission and PTSD symptoms at 12 months. IL-1β was significantly associated with total PTSD symptom severity (ΔR^2 = 0.090, p = .003; Fig. 1B), re-experiencing (ΔR^2 = 0.067, p = .019), avoidance/numbing (ΔR^2 = 0.050, p = .039) and hyperarousal (ΔR^2 = 0.064, p = .011) symptoms. The difference in mean PDS total severity scores in patients with quantifiable versus nonquantifiable IL-1β was 6.0, and between the latter and those with nondetectable IL-1β it was 2.7 (Fig. 1B). This indicates clinical significance across these categories of Il-1β plasma concentrations for the prediction of ACS-induced PTSD symptoms. IL-6, TNF-α, IL-4, IL-10 and TNF-β1 were not significantly associated with PTSD symptoms.

Table 2
Zero-order correlations between inflammatory measures at admission and PTSD symptoms at 12 months.

Cytokine in model	Total severity	*Re-*experiencing	Avoidance/ numbing	Hyperarousal
PI	0.255*	0.312**	0.202	0.174
Interleukin-1β	0.328**	0.290*	0.269*	0.263*
Interleukin-6	0.216	0.195	0.196	0.188
Tumor necrosis factor-α	−0.079	0.084	−0.097	−0.134
AI	−0.085	−0.015	−0.076	−0.136
Interleukin-4	−0.200	−0.114	−0.091	−0.283*
Interleukin-10	−0.013	−0.053	0.011	−0.054
Transforming growth factor-β1	0.038	0.127	−0.078	0.056
NI	0.262*	0.245*	0.215	0.245*

AI, anti-inflammatory index; NI, net-inflammatory index (PI minus AI); PI, pro-inflammatory index; PTSD, posttraumatic stress disorder (square root transformed Posttraumatic Diagnostic Scale scores). Significance level for Pearson correlation coefficients: *p < .050, **p < .010.

Table 3
Multivariable linear associations between inflammatory measures at admission and PTSD symptoms at 12 months (n = 70).

Variables entered (one block)	Total severity	Re-experiencing	Avoidance/ numbing	Hyperarousal
Trauma-focused counseling	−0.201 (0.305)	−0.230 (0.203)	−0.130 (0.230)	−0.022 (0.212)
Female sex	0.608 (0.365)	0.262 (0.243)	0.025 (0.275)	0.639 (0.254)
Age	0.070 (0.075)	−0.008 (0.050)	0.093 (0.056)	0.026 (0.052)
<24 h since pain onset	−0.388 (0.369)	−0.078 (0.246)	0.087 (0.278)	−0.506 (0.257)
Peak troponin	0.868 (0.438)	0.306 (0.292)	0.808 (0.330)*	0.572 (0.305)
BMI	−0.043 (0.029)	−0.046 (0.019)*	−0.014 (0.022)	−0.018 (0.020)
Distress	0.327 (0.090) ***	0.154 (0.060)*	0.158 (0.068)*	0.231 (0.063) ***
AI	−0.256 (0.224)	−0.107 (0.149)	−0.139 (0.169)	−0.244 (0.156)
PI	0.553 (0.247)*	0.455 (0.165)**	0.253 (0.186)	0.292 (0.172)
Model statistics				
Total R2	0.397***	0.312**	0.292**	0.417***
Change in R2 after adding PI	0.050*	0.088**	0.022	0.028
Alternative Model 1: without AI				
Change in R2 after adding PI	0.041*	0.082**	0.017	0.018
Alternative Model 2: without AI and PI				
Change in R2 after adding NI	0.044*	0.051*	0.022	0.042*

BMI, body mass index; AI, anti-inflammatory index; NI, net-inflammatory index (PI minus AI); PI, pro-inflammatory index; PTSD, posttraumatic stress disorder (square root transformed Posttraumatic Diagnostic Scale scores); Age was entered in 5-year intervals. Alternative Models 1 and 2 are adjusted for intervention group, sex, age, time since pain onset, peak troponin, BMI, and distress. Values are unstandardized coefficients B (s.e.) with significance level: *p < .050, **p < .010, ***p < .001.

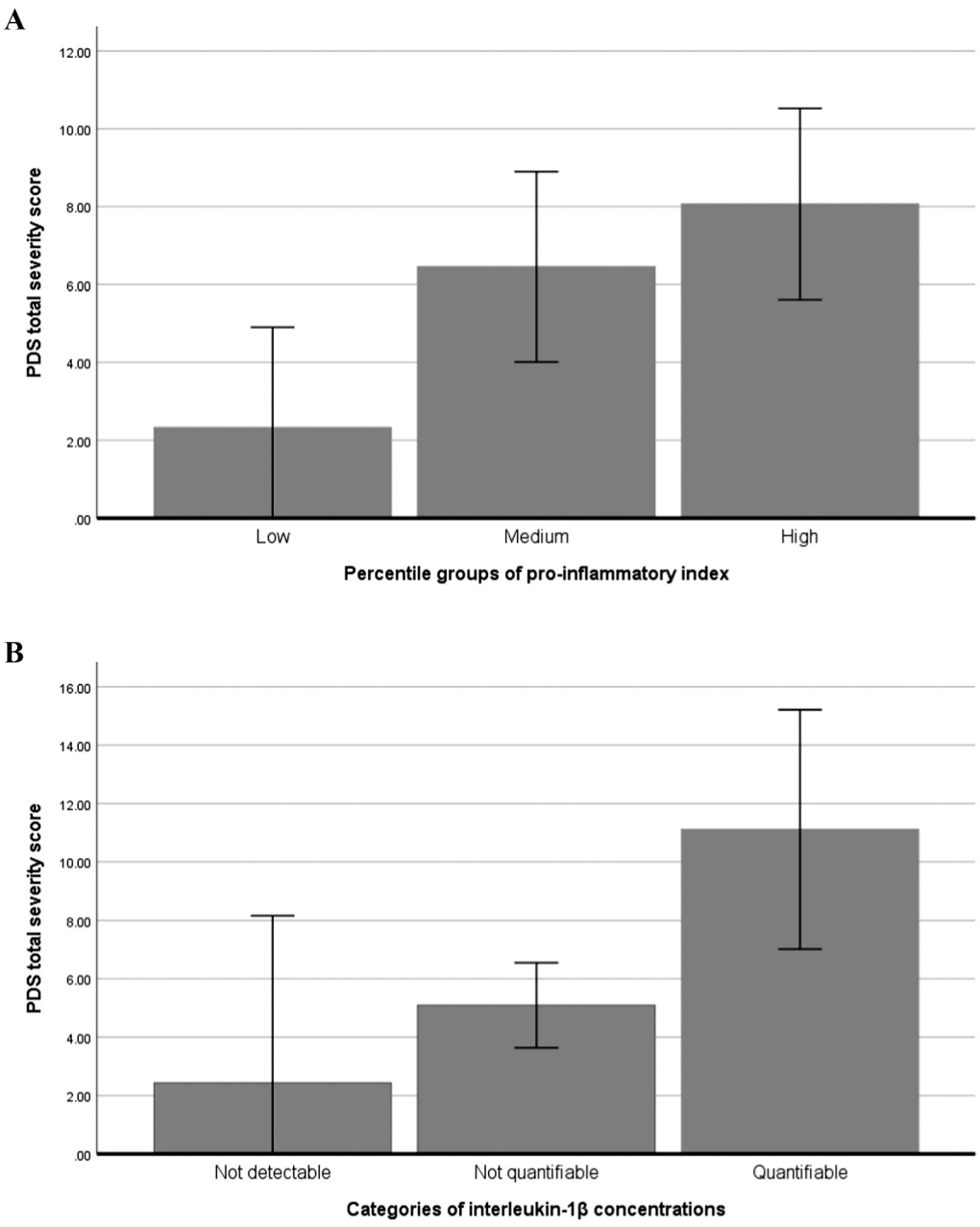

Fig. 1. Association between pro-inflammatory cytokines and post-traumatic stress.
The figure displays the significant association of tertiles of the pro-inflammatory index (A) and categories of interleukin (IL)-1β concentrations (B) on admission with posttraumatic stress at 12-month follow-up (i.e., mean of the Posttraumatic Diagnostic Scale (PDS) total severity score with 95% confidence interval in original units). Tertiles of low, medium and high pro-inflammatory index were calculated on added standardized z-scores of IL-1β, IL-6 and tumor necrosis factor-α. The concentration of IL-1β was not detectable in 4 participants, not quantifiable (although detectable) in 58 participants, and quantifiable in 8 participants (range 1.35–188.43 pg/mL). Adjustments were made for intervention group, sex, age, time since pain onset, peak troponin, body mass index, and distress for both the pro-inflammatory index and IL-1β categories, and, additionally, for the anti-inflammatory index (added standardized z-scores of IL-4, IL-10 and transforming growth factor-1β) in part figure A.

4. Discussion

This study showed that a pro-inflammatory state resulting from the ACS-triggered systemic inflammatory response within 48 h of hospitalization is associated with ACS-induced total severity of PTSD symptoms 12 months later. Specifically, the relationship between total PTSD symptom severity and a pro-inflammatory index formed from concentrations of circulating IL-β, IL-6, and TNF-α was independent of an anti-inflammatory index, formed from concentrations of circulating IL-4, IL-6, and TGF-β1, and other covariates. Results remained the same when the anti-inflammatory index was not adjusted for. In addition, a net-inflammatory index, reflecting pro-inflammatory index minus anti-inflammatory index, was also associated with total PTSD symptom severity, independent of covariates. Based on these results, a potential influence of ACS-triggered pro-inflammatory changes on the increased risk of developing PTSD symptoms seems a robust finding that is not substantially reduced by anti-inflammatory changes.

This interpretation is substantiated by the observation that elevated IL-1β, although not any other cytokine examined in our study, was significantly associated with more severe total PTSD symptoms at 12 months. Interestingly, one previous study in earthquake survivors found a cross-sectional relationship between total PTSD symptoms and IL-1β, but not other cytokines, including IL-6, TNF-α, IL-4, and IL-10 in the covariate-adjusted analysis, suggesting that IL-1β could play a particularly important role in the pathophysiology in PTSD [24]. In fact, in animal models of PTSD, IL-1β has been shown to be involved in stress-enhanced fear learning and to impair contextual memory, possibly contributing to reliving trauma-related aspects [26,27]. In agreement, regarding PTSD symptom clusters, we found that both pro-inflammatory state and categorized IL-1β levels were most consistently associated with re-experiencing symptoms. Significant associations were also found between categorized IL-1β levels and both avoidance/numbing and hyperarousal symptoms.

The effect sizes of the associations between pro-inflammatory measures and PTSD symptoms indicated the clinical significance of our major study findings. This warrants some speculation about possible

Table 4
Multivariable linear associations between cytokines at admission and PTSD symptoms at 12 months.

Cytokine in model	Total severity	Re-experiencing	Avoidance/ numbing	Hyperarousal
Interleukin-1β	0.427 (0.138)**	0.231 (0.096)*	0.222 (0.105)*	0.256 (0.097) *
Interleukin-6	0.112 (0.154)	0.124 (0.103)	0.068 (0.113)	0.035 (0.106)
Tumor necrosis factor-α	−0.013 (0.155)	0.120 (0.104)	−0.059 (0.113)	−0.048 (0.107)
Interleukin-4	−0.180 (0.157)	−0.055 (0.107)	−0.074 (0.116)	−0.197 (0.106)
Interleukin-10	−0.073 (0.149)	−0.093 (0.100)	−0.020 (0.109)	−0.083 (0.102)
Transforming growth factor-β1	0.055 (0.155)	0.138 (0.103)	−0.027 (0.114)	0.021 (0.107)

PTSD, posttraumatic stress disorder (square root transformed Posttraumatic Diagnostic Scale scores). Multivariable associations were calculated separately for each cytokine entering standardized z-score, adjusted for intervention group, sex, age, time since pain onset, peak troponin, body mass index, and distress. Values are unstandardized coefficients B (s.e.) with significance level: *$p < .050$, **$p < .010$.

anti-inflammatory pharmacological treatments for the prevention of ACS-induced PTSD with, for example, glucocorticoids or direct cytokine inhibition. Previous studies showed that glucocorticoid administration in patients undergoing cardiac or orthopedic traumatic surgery, both associated with a systemic inflammatory response, reduced the risk of developing PTSD symptoms [5,6]. Thus, it would be of interest to investigate whether this effect can be explained by glucocorticoids curtailing PIC activity. In turn, in patients with ACS, dexamethasone-eluting stents mitigated systemic inflammatory response after percutaneous coronary intervention [28], and corticosteroid treatment came with a mortality benefit [29], but these earlier data have controversially been discussed more recently [30]. Nonetheless, it has not been examined whether the anti-inflammatory effects of corticosteroids translate to lower PTSD symptoms in patients with ACS. The IL-1β inhibitor canakinumab was shown to reduce the risk of recurrent cardiovascular events in patients with prior MI and low-grade systemic inflammation along with circulating levels of CRP and IL-6 [31]. It would be intriguing information to know whether patients who receive canakinumab will develop fewer PTSD symptoms in the aftermath of a recurrent cardiac event compared to patients who receive placebo.

Our study has a number of limitations, so the above results should be considered preliminary and will need to be confirmed in future investigations with larger samples. We analyzed data from a convenience sample of 70 patients who had complete data for the variables of interest and were enrolled into a behavioral intervention trial. Due to the trial's inclusion/exclusion criteria, the results of our study may not generalize to samples with a greater share of female patients, to patients with low distress levels during ACS and those with a current severe depressive episode. Also, the validity of the cardiologist's clinical assessment of the presence of severe depression can be considered low. However, only four patients were taking an antidepressant, indicating that our sample probably included few patients with major depression. Residual confounding is possible as the sample size precluded the inclusion of additional covariates in the multivariable models, such as health behaviors, medical comorbidities, medications prior to ACS and used for treatment of ACS and psychosocial factors. For instance, it is possible that symptoms of anxiety, depression, or PTSD due to prior traumatic experiences could be associated with pro-inflammatory measures at admission. Hence, associations between inflammatory measures in the aftermath of ACS and subsequent PTSD symptoms could partly reflect the association of symptoms of anxiety, depression and PTSD prior to ACS with PTSD symptoms at 12 months.

The inflammatory status before the onset of ACS was not known. As inflammation plays a central role in the development of atherosclerosis and the triggering of ACS, it is likely that at least some of the patients had elevated levels of pro-inflammatory markers before ACS. We measured acute-phase proteins only once within 48 h after ACS onset, but peak levels of each cytokine may have occurred at different time points between individuals, even when controlling for the time interval since onset of pain. The pro-inflammatory index as a predictor of PTSD symptoms may not only result from the ACS-triggered systemic inflammatory response, as research suggests that the inflammation-PTSD association may be explained bidirectionally [32]. For instance, one study showed that IL-1β and IL-6 levels rose over time among combat veterans with chronic PTSD [33]. Chronically elevated pro-inflammatory cytokines in the months after ACS could also have contributed to the development of PTSD symptoms. At least, we were able to account for events that occurred during the post-ACS period. Consistent with the persistent somatic threat model of PTSD induced by medical events [34], chest tightness/pain during follow-up was independently associated with PTSD symptoms at 12 months. The categorization of cytokine concentrations for the analyses due to low sensitivity of several cytokine assays, comes with a loss of statistical power. The use of more sensitive cytokine assays in the future, particularly to measure IL-1β, may allow researchers to examine a continuous relationship between IL-1β and PTSD symptoms, resulting in greater statistical power. PTSD symptoms were self-reported and not assessed using DSM-5 criteria because DSM-IV criteria were in effect at the time the study was designed. However, an interviewer-rated scale for hyperarousal symptoms showed unacceptable reliability in another analysis of data from the MI-SPRINT study [17].

Taken together, PICs may not only be related to PTSD cross-sectionally, as shown in numerous previous studies, but as part of the cytokine cascade launched during ACS, but they may also predict the development of ACS-induced PTSD symptoms. Replication of our findings in larger and more heterogeneous samples of patients with ACS and with assessment of the dynamics of cytokines and their interactions during ACS is needed. Future research should repeatedly examine inflammatory markers and ACS-induced PTSD symptoms to explore their temporal relationship over several months.

Financial support

This work was supported by the Swiss National Science Foundation [grant No. 140960]. Additional funding came from the Teaching and Research Directorate, Bern University Hospital, Switzerland.

Conflicts of interest

None.

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