ScienceDirect

Cytokine

Volume 186, February 2025, 156839

Circulating inflammatory markers predict depressive symptomatology in COVID-19 survivors

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https://doi.org/10.1016/j.cyto.2024.156839

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Highlights

- Post-COVID-19 depression mainly relates to unresolved low-grade inflammation.
- One-month post-discharge cytokines' levels predict post-COVID-19 depression.
- Dynamic changes of cytokines between follow-ups predict post-COVID-19 depression.

Abstract

Growing evidence suggests the neurobiological mechanism upholding post-COVID-19 depression mainly relates to immune response and subsequent unresolved low-grade

inflammation. Herein we exploit a broad panel of cytokines serum levels measured in COVID-19 survivors at one- and three-month since infection to predict post-COVID-19 depression.

87 COVID survivors were screened for depressive symptomatology at one- and three-month after discharge through the Beck Depression Inventory (BDI-13) and the Zung Self-Rating Depression Scale (ZSDS) at San Raffaele Hospital. Blood samples were collected at both timepoints and analyzed through Luminex. We entered one-month 42 inflammatory compounds into two separate penalized logistic regression models to evaluate their reliability in identifying COVID-19 survivors suffering from clinical depression at the two timepoints, applied within a machine learning routine. Delta values of analytes lowering between timepoints were entered in a third model predicting presence long-term depression. 5000 bootstraps were computed to determine significance of predictors.

The cross-sectional model reached a balance accuracy (BA) of 76% and a sensitivity of 70%. Post-COVID-19 depression was predicted by high levels of CCL17, CCL22. On the other hand, CXCL10, CCL2, CCL3, CCL8, CXCL5, CCL15, CCL23, CXCL13, and GM-CSF showed protective effects. The longitudinal model obtained good performance as well (BA=74% and sensitivity=68%), revealing CXCL16 and CCL25 as additional drivers of clinical depression. Moreover, dynamic changes of analytes over time accurately predicted long-term depression (BA=76% and sensitivity=75%).

Our findings unveil a putative immune profile upholding post-COVID-19 depression, thus reinforcing the need to deepen molecular mechanisms to appropriately target depression.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) caused a broad spectrum of clinical manifestations ranging from asymptomatic infection to severe life-threatening multi-organ disease [1]. After the acute Coronavirus Disease 2019 (COVID-19), persistent physical and psychological sequelae have been observed months following infection [2,3]. This phenomenon has been termed Post-Acute Sequelae of COVID-19 (PASC) which refers to long-lasting symptoms following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. PASC is now recognized by the National Institute for Health and Care Excellence (NICE) [4], and the World Health Organization (WHO) [5]. In the context of PASC symptoms, lung dysfunctions, psychopathological complaints, and cognitive impairments have been reported to linger over months after acute COVID-19 [[6], [7], [8]], largely affecting the quality of life of survivors [9].

During the first wave of the pandemic in Italy, in the spring 2020, we performed a systematic study of neuropsychiatric sequelae of COVID-19 pneumonia, by prospectively following up survivors at one and three months after hospital discharge and clearance of the virus. We showed that 31% developed clinically significant anxiety and depressive symptoms and cognitive impairment, a finding later confirmed in independent samples, with meta-analytic evidence affirming depressive symptoms, anxiety, and cognitive impairment as the most prevalent long-term neuropsychiatric sequelae [10]. Depressive psychopathology was confirmed in approximately 30–40% of COVID-19 survivors [11], with a 3:1 F:M sex ratio as observed in Major Depressive Disorder, and it was found to be strictly related with post-COVID-19 fatigue, cognitive impairment and reduced quality of life [7,8].

The psychopathological mechanisms underlying post-COVID-19 depression seems to be mainly related to the immune inflammatory response to the viral infection and subsequent unresolved low-grade inflammation, possibly fuelled by signals perpetually released by unhealed tissues, as in a vicious cycle [12,13]. Notably, COVID-19 induces a robust immune response characterized by a hyperinflammatory state with high levels of IL-1β, IL-4, IL-6, IL-10, TNF-α CXCL10, and CCL2 [[14], [15], [16]]. Higher immune/inflammatory set points with higher circulating inflammatory biomarkers are observed in mood disorders in the absence of known triggering factors and are currently investigated as underpinning pathogenic mechanisms for depressive psychopathology [[17], [18], [19]]. When directly looking at post-COVID depression, evidence from the literature suggested that routine markers of inflammatory response such as C-Reactive Protein (CRP), neutrophil/lymphocyte ratio (NLR) and Systemic Immune Inflammatory Index (SII) were associated with post-COVID-19 depressive symptoms [20]. To date, apart from easily available biomarkers of innate response, only sparse studies have investigated the role of cytokines and chemokines as a potential biomarker of post-COVID-19 depression and were mainly focused on IL-6, IL-10, and TNF-α [[21], [22], [23]]. Despite promising, these studies did not explore a wide range of cytokines being not able to get a broader picture of immune function in patients. Indeed, current pathophysiological perspectives point in the direction of viral-induced abnormal monocyte-endothelial interaction to account for fatigue-depressive phenotype among the long-haulers [24], hence prompting the need to expand focus to chemokine- and endothelial molecules-expressing profiles beyond canonical pro-inflammatory cytokines as facilitators for post-COVID-19 depression.

Our Milano COVID-BioB study involved blood sampling from the patients, aimed at exploring a wide range of inflammatory proteins to provide potential biological signature useful for diagnostic and prognostic medical purposes in emergency settings, and to tentatively identify new therapeutic targets [25,26]. Here, for the first time, we measured a broad panel of cytokine/chemokines and adhesion moleculs' serum levels in COVID-19

survivors at one and three months after infection and investigated whether these inflammatory analytes predicted post-COVID-19 depression.

Section snippets

Participants and data collection

We prospectively evaluated the immune-inflammatory profile of 87 COVID-19 survivors at one- and three-months after discharge, and screened them for depressive symptomatology at the same timepoints during an ongoing prospective study at IRCCS San Raffaele Hospital in Milan, providing biobanking for COVID-19 research [27]. The COVID-BioB study protocol conforms to the Declaration of Helsinki, was approved by the Hospital Ethics Committee (prot. 34/int/2020) and registered on ClinicalTrials.gov ↗ (NCT04318366 ↗ …

Results

Description of the sample is reported in Table 1. 10/87 (11.49%) patients at one- and 12/87 patients (13.79%) scored above the clinical threshold for depression at both ZSDS and BDI-13.

The cross-sectional elastic net model predicted clinical depression with a BA of 76%, an AUC of 80%, a sensitivity for post-COVID-19 depression of 70%, a specificity of 82% (Fig. 1, top). Despite proportion of survivors reporting relevant depressive symptoms was relatively small (n=10), this performance …

Discussion

The main finding of the current study is that levels of circulating cytokines and chemokines at one month after infection can predict depression at one and three-month follow-up after discharge in COVID-19 survivors. Moreover, dynamic changes of immune mediators from the first to the third month predicted post-COVID-19 depression at three months after discharge. These results strengthen the hypothesis of persistently altered immuno-inflammatory setpoints as biological underpinnings of …

Conclusions

Overall, the aforementioned weaknesses do not bias the main finding of a strict relationship between post-COVID-19 depression and immune-inflammatory setpoints in survivors. We proved that not only 'point-in-time' inflammatory milieu critically impact on depressive state, yet also dynamic changes of analytes concentration inform on the risk to develop post-COVID-19 clinical depression. …

Funding Source

MP salary: Italian Ministry of University, XXXVII PhD cycle, FSE REACT-EU 2021 PON projects, Action IV.5.

This work was supported by the Italian Ministry of Health (grant GR-2021-12374872-1 to MGM). …

CRediT authorship contribution statement

Mariagrazia Palladini: Writing – original draft, Methodology, Formal analysis, Data curation. **Mario Gennaro Mazza:** Writing – original draft, Data curation, Conceptualization. **Rebecca De Lorenzo:** Project administration, Investigation, Data curation. **Sara Spadini:** Project administration, Methodology, Data curation. **Veronica Aggio:** Project administration, Methodology, Data curation. **Margherita Bessi:** Writing – review & editing. **Federico Calesella:** Methodology, Formal analysis. **Beatrice Bravi:** …

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mario Gennaro Mazza reports financial support was provided by Italy Ministry of Health Directorate General of Health Prevention. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Acknowledgements

The COVID-19 BioB Outpatient Clinic Study group includes:

Caterina Conte, Sara Poletti, Benedetta Vai, Irene Bollettini, Elisa Maria Teresa Melloni, Elena Beatrice Mazza, Cristina Lorenzi, Roberto Furlan, Fabio Ciceri, Angelo Manfredi, Cristina Tresoldi, Nicola Farina, Valentina Sofia, Marta D'Amico, Paola Casanova, Giulia

Magni, Marica Ferrante, Elisabetta Falbo, Elena Cinel, Elena Brioni, Cristiano Magnaghi, Chiara Lanzani, Valentina Canti, Alessandro Patrizi, Marta Cilla, Sabina Martinenghi, …

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