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LETTER TO THE EDITOR

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Mast cell activation may contribute to adverse health transitions in COVID-19 patients with frailty

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ABSTRACT

A prominent aspect of the post-coronavirus disease-2019 (post-COVID-19) era is long-COVID. Therefore, precise patient classification and exploration of the corresponding factors affecting long-COVID are crucial for tailored treatment strategies. Frailty is a common age-related clinical syndrome characterized by deteriorated physiological functions of multiple organ systems, which increases susceptibility to stressors. Herein, we performed an inclusion and exclusion analysis (definite COVID-19 infection diagnosis, clear underlying disease information, ≥60 years old, and repeated sampling of clinical cases) of 10,613 blood samples and identified frailty cases for further investigation. RNA-Seq data were used for differential gene expression and functional and pathway analyses. The results revealed that patients with frailty were more prone to poor health conversions and more sequelae, and the blood transcriptome had obvious disturbances in pathways associated with immune regulation, metabolism, and stress response. These adverse health transitions were significantly associated with mast cell activation. Additionally, NCAPG, MCM10, and CDC25C were identified as hub genes in the peripheral blood differential gene cluster, which could be used as diagnostic markers of poor health conversion. Our results indicate that healthcare measures should be prioritized to mitigate adverse health outcomes in this vulnerable patient group, COVID-19 patients with frailty, in post-COVID era.

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KEYWORDS Long-COVID; mast cell; frailty; etiology; transitions

Dear Editor:

Long-COVID, also known as long-hauler syndrome, post-acute sequelae of COVID-19 (PASC), or post-COVID-19 condition, is a general term used to describe a complex array of multisystem symptoms that continue after an acute COVID-19 infection, regardless of whether the individual was symptomatic or asymptomatic during infection [1]. These sequela include but are not limited to fatigue, dyspnea, brain fog, body aches, and problems with smell and taste. Long-COVID can persist for years, as its related condition, severe acute respiratory syndrome (SARS), even has caused sequela that last 10 years [2]. COVID-19 has only been around for three years, so its long-term outcomes and corresponding driving factors remain unclear. The high number of COVID-19 cases and the unidentified risks of long-COVID place significant pressure on healthcare systems globally [3]. Long-COVID has no precise definition, but it is considered a highly heterogeneous condition. Therefore, classifying patients and exploring the corresponding factors causing healthy transitions is crucial for precise treatment; however, few studies have voiced this aspect [4].

Age is highly associated with long-COVID. Frailty is a core of geriatric medicine and is a common age-related clinical syndrome characterized by deteriorated physiological functions of multiple organ systems, which increases susceptibility to stressors. The frail population is not only a key risk group for COVID-19 deaths [5] but is also recommended as a crucial reference basis for elderly people infected with COVID-19 to obtain priority medical resources [6]. Additionally, approximately 40% of severe patients present poor health transitions 3–6 months after their discharge [7]. Epidemiological study has shown that the poor health transition process in older people accelerates during the COVID-19 pandemic [8]. However, no studies reported the effects of frailty on poor health transitions of patients with COVID-19 from cellular and molecular aspects. Hence, the current study aims to address these research gaps. An inclusion and exclusion analysis (definite COVID-19 infection diagnosis, clear

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underlying disease information, ≥ 60 years old, and repeated sampling of clinical cases) on 10,613 clinical samples from Mount Sinai COVID-19 Biobank (Project synID: syn35874390) [4] was performed (Figure 1A). Given that, there is a strong coupling between frailty and comorbidities, which can be seen directly from the Rockwood Frailty Index method used in clinical assessment of frailty. Here, we focused on frailty cases. The frailty index method was used to select frailty samples, with patients over 60 years old and a comorbidity count of ≥3 as the critical parameter for frailty characterization (Tables S1 and S2). The health transition results were classified as "worse," "same," and "better." RNA-Seq data for the corresponding patients were obtained (GSE215865, whole blood transcriptome at 0–2 days of onset), and an R-language package was used for standardized processing. Differential gene analysis (Deseq2, log2 ≥ 0.58, $P < 0.05$), GO analysis, KEGG analysis, and figure generation were conducted using SANGERBOX (http://vip.sangerbox.com/). The online tool STRING (https://cn.string-db.org/) was used for protein–protein interaction (PPI) analysis, while Cytoscape was used for PPI mapping and hub gene analysis. Finally, CIBERSORTx (https://cibersortx.stanford.edu/) was used for immune cell composition analysis, and GraphPad Prism 7.0 for conventional mapping.

We obtained 113 unique patients over the age of 60 years from the Mount Sinai COVID-19 Biobank (MSCB) database, consisting of 75 non-frail and 38 frail individuals. We obtained a total of 82 ideal target samples for gene function and signalling pathway analysis after filtering RNA-seq data (Figure 1A). We observed that almost 45% of individuals in frailty group demonstrated an unfavourable health status "worse" one month after infection, while approximately 39% of those in non-frailty group exhibited such a status (Figure 1B). No significant difference in comorbidities was found between the two subgroups (Figure S1), which just rules out the possible effects of pre-infection comorbidity on COVID sequelae. The "worse" subgroup had a significantly higher number of long-COVID sequela than the "same" subgroup in both the frailty and non-frailty groups, with the frailty group having a significantly higher number (Figure 1C). Only the data from the frailty group was used for further analysis (Figure 1D-K), which revealed a significantly higher proportion of individuals in the "worse" subgroup than that in the "same" subgroup for multiple phenotypes of long-COVID (Figure 1D). Additionally, 477 differentially expressed genes (DEG) were found in the transcriptome of whole blood in the "worse" subgroup compared to the "same" subgroup, with 294 genes up-regulated and 183 genes down-regulated (Figure 1E).

KEGG analysis of DEGs revealed several inflammatory pathways, including the AGE–RAGE signalling pathway, Rap1 signalling pathway, cytokine–cytokine receptor interaction, and rheumatoid arthritis (Figure 1F). Notably, the AGE–RAGE interaction induced histamine production in mast cells, in addition to its well-known involvement in diabetic complications. All of the top 20 terms, except for cell proliferation and protein processing-related terms, were significantly related to inflammation/immunity based on GO analysis of DEGs (Figure 1G). Notably, "metabolic pathway" ranks first among KEGG terms, while "response to stress" holds the top position among GO terms (Figure 1 F and G). PPI and hub gene analysis of DEGs identified NCAPG, MCM10, and CDC25C as key hub genes involved in regulating cell division (Figure 1H and I). These genes were further evaluated as potential diagnostic biomarkers for adverse outcomes of long-COVID, with active combination level showing superior performance with an area under the curve of 0.808 (Figure 1J). Immune cell proportion analysis by CIBERSORTx based on the gene expression matrix indicated a significant discrepancy for "mast cell activated" when comparing "worse" versus "same" (Figure 1K). Mast cell activation syndrome (MCAS) and long-COVID share many signs and symptoms, such as fatigue, anxiety, and depression (Figure 1L).

Our study findings indicate that mast cell activation may contribute to adverse health transitions in COVID-19 patients with frailty. Specifically, the involvement of hub genes in cell division, which may reflect mast cell proliferation during inflammatory conditions, may be associated with sustained cellular inflammation and thus contribute to adverse health outcomes in this population. This implies that the etiology of long-COVID may not be limited to non-proliferative simple mast cell activation, as previously thought, but also involves both proliferative and non-proliferative cellular processes. Hub genes can be a diagnostic tool for identifying vulnerable patients requiring protection against severe long-COVID and should be evaluated further. Given the conflicting results from previous studies on the complex relationship between mast cells and COVID-19 in mixed populations [9–14], our identification of a specific vulnerable population has significant clinical implications for precise long-COVID treatment and prevention, supporting the positive relationship of mast cell activation and long-COVID. The mechanism of famotidine in alleviating long-COVID symptoms involving antihistamine action confirms the role of mast cells and the clinical value of classifying COVID populations [15]. Further, the terms "metabolic pathway" and "response to stress" rank highest in functional and pathway enrichments. This indicates that the virus greatly disrupts cell metabolism, causing significant stress that hinders the body's ability to restore normal function, potentially causing a frailty phenotype. These findings warrant further evaluation before

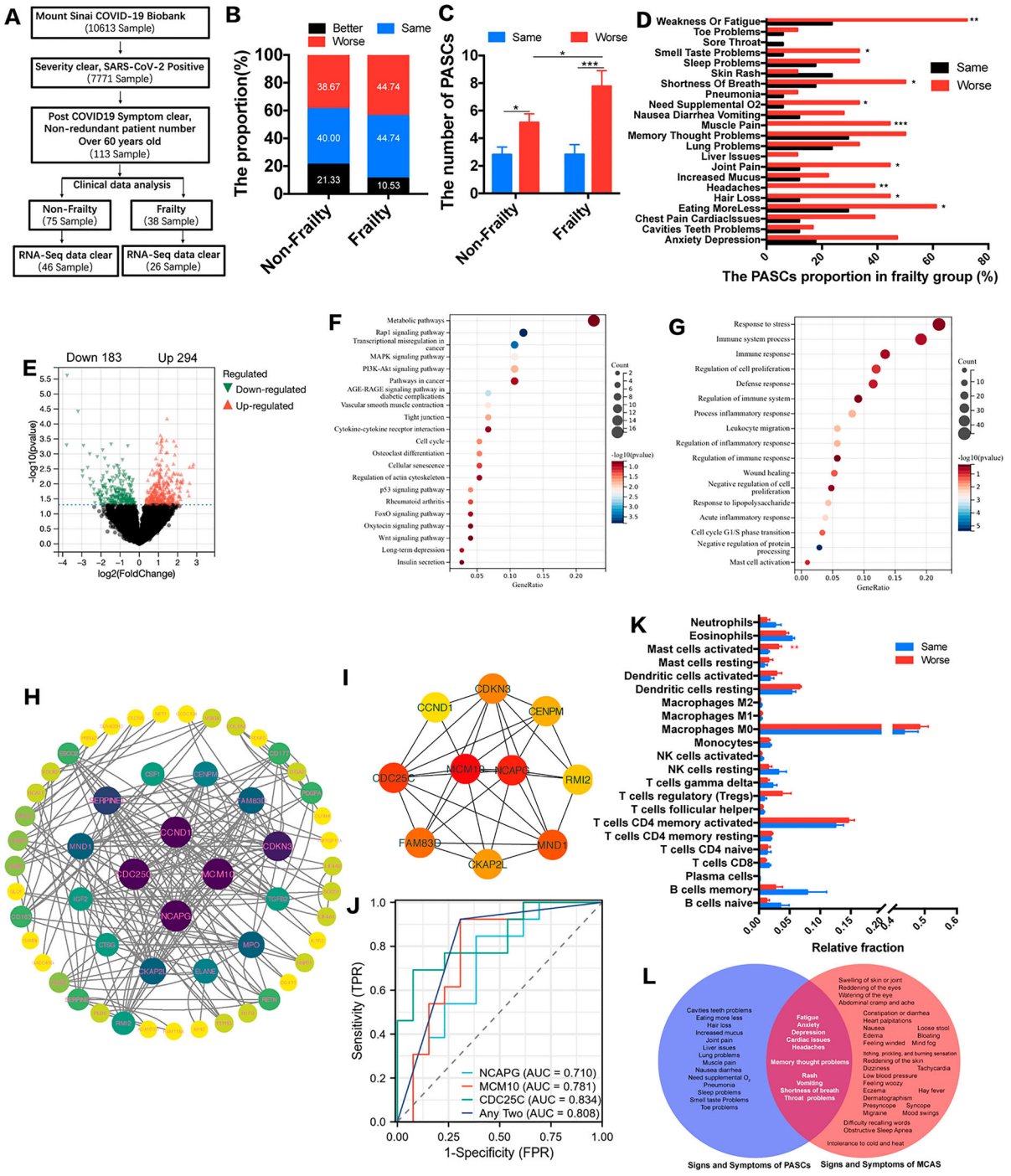

Figure 1. Mast cell activation is associated with adverse health transitions in the COVID-19 population with frailty. A. Flowchart depicting clinical sampling procedures. B. Proportions of poor health transition in frailty and non-frailty populations. C. Number of Post-Acute Sequelaes of SARS-CoV-2 infection (PASC) in frailty and non-frailty group. D. Proportions of different PASC categories using "worse" versus "same" in the frailty group. E. Differentially expressed genes in peripheral blood using "worse" versus "same" in the frailty group. F. KEGG analysis of differentially expressed genes using "worse" versus "same" in the frailty group. G. GO analysis of differentially expressed genes using "worse" versus "same" in the frailty group. H. Protein–protein interaction analysis of differentially expressed genes using "worse" versus "same" in the frailty group. I. Identification of hub genes from differentially expressed genes using "worse" versus "same" in the frailty group. J. ROC curves for NCAPG, MCM10, CDC25C, and their combinations using"worse" versus "same" in the frailty group. K. Analysis of immune cell compositions for gene expression matrix using "worse" versus "same" in the frailty group. L. Mast Cell Activation Syndrome (MCAS) and long-COVID exhibit significant symptom overlap. Note: Patients subjectively assessed their health status before and after COVID-19 infection, which was divided into three categories: "worse," "same," and "better."

large-scale application. As such, healthcare measures, specifically focusing on mast cell function, should be prioritized for this vulnerable patient group to minimize the healthcare burden of subsequent waves.

Collectively, through clinical characters and bioinformatics analysis, we reveal that mast cell activation may contribute to adverse health transitions in COVID-19 patients with frailty. Our study provides

an obvious clue for revealing the underlying mechanisms of poor health transition at the molecular level of immune cells in frail populations with COVID-19, laying a theoretical foundation for continuing to prevent COVID infection in the frail population in the post-COVID era.

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Author contributions

Conception and design: Xiangqi Li and Chaobao Zhang; Administrative support: Zhijun Bao; Provision of study materials: Chaobao Zhang; Collection and assembly of data: Chaobao Zhang; Data analysis and interpretation: All authors; Manuscript writing: Xiangqi Li and Chaobao Zhang; Final approval of manuscript: All authors.

Data availability statement

All data is contained in the article, besides repository data in databases.

References

[1] Batiha GE, Al-Kuraishy HM, Al-Gareeb AI, et al. Pathophysiology of Post-COVID syndromes: a new perspective. Virol J. 2022;19(1):158.
[2] Jingna Hua XS, Wu Q, Li L, et al. Analysis of the quality of life in patients with severe acute respiratory syndrome for 10 years. Tianjin Med J. 2016;44(10):1247–1250.
[3] Nurek M, Rayner C, Freyer A, et al. Delphi p: recommendations for the recognition, diagnosis, and management of long COVID: A Delphi study. Br J Gen Pract. 2021;71(712):e815–e825.
[4] Thompson RC, Simons NW, Wilkins L, et al. Molecular states during acute COVID-19 reveal distinct etiologies of long-term sequelae. Nat Med. 2023;29(1):236–246.
[5] Chaobao Z, Hongzhi W, Zilu W, et al. Collective and individual assessment of the risk of death from COVID-19 for the elderly, 2020–2022. China CDC Weekly. 2023;5(18):407–412.
[6] Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health. 2020;5(8):e444–e451.
[7] Taniguchi LU, Aliberti MJR, Dias MB, et al. Twelve months and counting: following clinical outcomes in critical COVID-19 survivors. Ann Am Thorac Soc. 2023;20(2):289–295.
[8] Shinohara T, Saida K, Tanaka S, et al. Factors for the change in frailty status during the COVID-19 pandemic: a prospective cohort study over six- and 12-month periods in Japan. Geriatr Nurs. 2022;48:111–117.
[9] Gebremeskel S, Schanin J, Coyle KM, et al. Mast cell and eosinophil activation Are associated With COVID-19 and TLR-mediated viral inflammation: implications for an Anti-Siglec-8 antibody. Front Immunol. 2021;12:650331.
[10] Giannetti MP, Weller E, Alvarez-Twose I, et al. COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms. J Allergy Clin Immunol Pract. 2021;9(5):2083–2086.
[11] Arun S, Storan A, Myers B. Mast cell activation syndrome and the link with long COVID. Br J Hosp Med (Lond). 2022;83(7):1–10.
[12] Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis. 2020;100:327–332.
[13] Weinstock LB, Brook JB, Walters AS, et al. Mast cell activation symptoms are prevalent in Long-COVID. Int J Infect Dis. 2021;112:217–226.
[14] Wechsler JB, Butuci M, Wong A, et al. Youngblood BA: mast cell activation is associated with post-acute COVID-19 syndrome. Allergy. 2022;77(4):1288–1291.
[15] Malone RW, Tisdall P, Fremont-Smith P, et al. COVID-19: famotidine, histamine, mast cells, and mechanisms. Front Pharmacol. 2021;12:633680.