


## LETTER TO EDITOR

# A unique dysregulation pattern of lipid metabolism and immune responses in patients with omicron SARS-CoV-2 recurrence

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The occurrence of re-positive Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in discharged patients infected with Omicron is common. But, the potential nature of host response in these patients remains unknown. Here, we report a unique host response pattern through mass spectrometry-based proteomics from patients with Omicron SARS-CoV-2 recurred positive (Omi-Rec) after discharge.

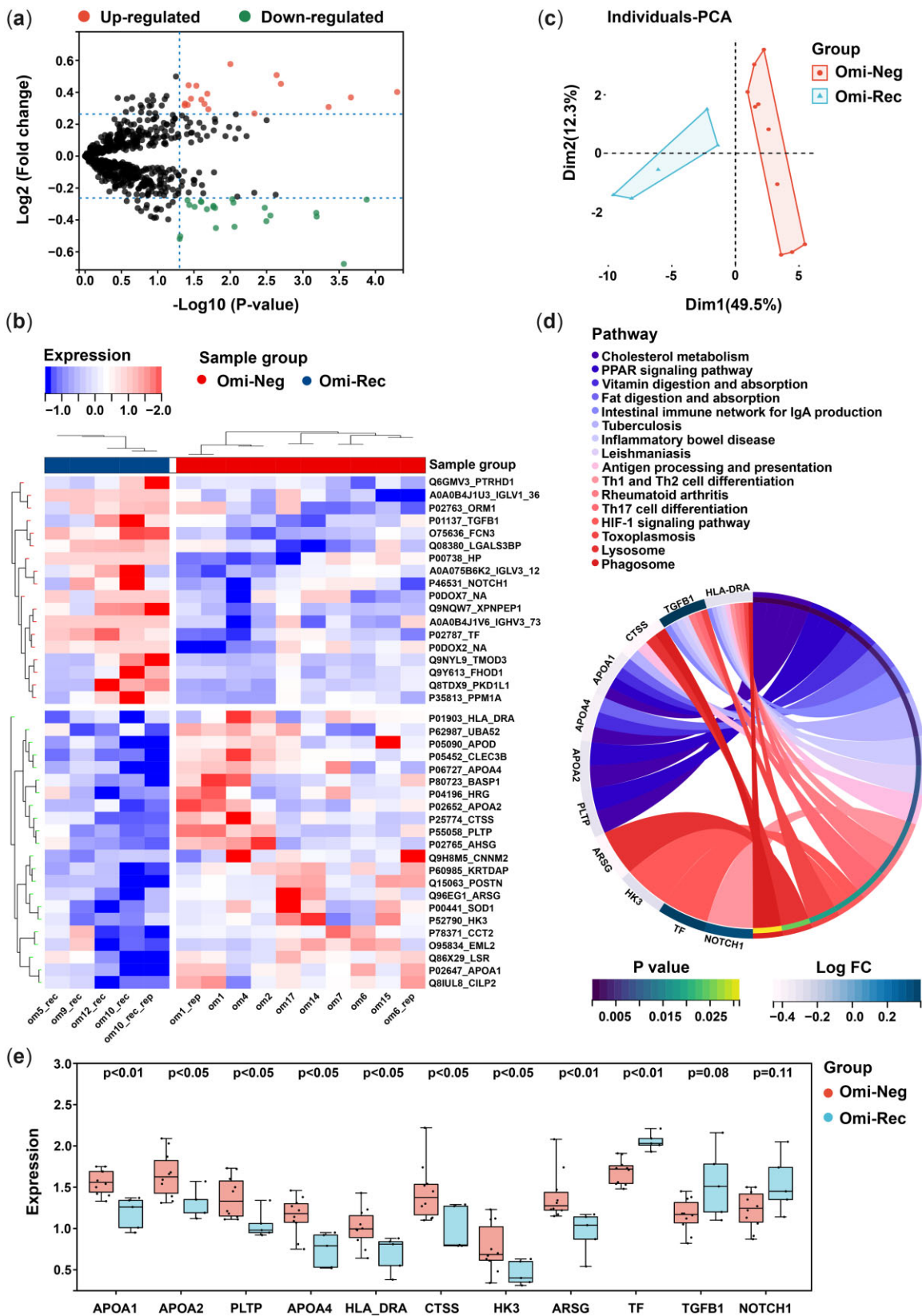
In this study, proteomic experiments were conducted at the Key Laboratory of Structural Biology of Zhejiang Province, School of Life Sciences, Westlake University (Zhejiang, Southeast China). The experimental details are described in the [Supplementary materials](#). This study was approved by the Institutional Review Board of Xixi Hospital. Informed consent was waived because of the retrospective nature of this study.

A total of 12 patients who recovered from Omicron infection were enrolled for subsequent analysis, 8 patients maintained negative SARS-CoV-2 RNA after discharge (Omi-Neg group) and 4 were SARS-CoV-2 RNA re-positive patients after discharge from the hospital (Omi-Rec group). As shown in [Supplementary Table S1](#), there were no significant differences in all baseline characteristics between Omi-Rec cases and Omi-Neg controls on admission. But, significant differences were observed in 40 circulating proteins between the two groups (fold-change >1.2 and P-values <0.05; [Figure 1a and b](#)). Principal component analysis (PCA) showed that dysregulated proteomes of each group clustered tightly apart from each other ([Figure 1c](#)), consolidating that these 40 proteins well resolved Omi-Rec and Omi-Neg types.

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**Figure 1.** Proteomic analysis in Coronavirus disease 2019 (COVID-19) patients with or without Omicron SARS-CoV-2 recurrence. (a) Volcano plots compare pairs of patient groups as indicated in the plot. Proteins with fold-change >1.2 and P-value <0.05 were considered as significantly differential expressions; (b) Heatmap plot of 40 differentially expressed proteins (fold-change >1.2 and P-value <0.05) between Omi-Rec patients and Omi-Neg controls; (c) PCA of 40 circulating proteomes; (d) Top 16 pathways dysregulated in Omi-Rec patients. Pathway analysis was performed based on 40 differentially expressed proteins using the R package (ClusterProfiler 3.14.3). P-value <0.05 was considered statistically significant; (e) Differential expression of APOA1, APOA2, PLTP, APOA4, HLA-DRA, CTSS, HK3, ARSG and TF across the Omi-Rec and Omi-Neg groups. Omi-Rec, Omicron SARS-CoV-2 recurred positive after discharge; Omi-Neg, Omicron SARS-CoV-2 maintained negative after discharge; Om, Omicron; \_rec, \_recurrence; \_rec\_rep, \_recurrence\_replication.

Of note, the Omi-Rec showed enriched lipid metabolism and immune-related pathways, including Cholesterol metabolism, Peroxisome proliferators-activatedreceptor (PPAR) signaling pathway, Vitamin digestion and absorption, Fat digestion and absorption, Intestinal immune network for IgA production, Tuberculosis, Inflammatory bowel disease, Leishmaniasis, Antigen processing and presentation, Th1 and Th2 cell differentiation, Rheumatoid arthritis, Th17 cell differentiation, HIF-1 signaling pathway, Toxoplasmosis, Lysosome and Phagosome (Figure 1d). This indicates lipid metabolism disturbance and immune dysregulation in Omi-Rec patients.

The Omi-Rec patients showed four significantly downregulated proteins related to metabolism pathways, including Apolipoprotein A-I (APOA1), Apolipoprotein A-II (APOA2), Phospholipid transfer protein (PLTP) and Apolipoprotein A-IV (APOA4) compared to Omi-Neg patients (Figure 1e). Some recent studies have reported that patients with diverse infections, such as Epstein-Barr virus, cytomegalovirus and tuberculosis, had lower levels of lipoproteins in comparison with non-infected individuals.<sup>1-3</sup> In the research by Vignesh *et al.*,<sup>4</sup> lower lipid was also observed in COVID-19 patients compared to uninfected controls. Consistent with these reports, our research revealed the reduced lipoprotein pattern in Omi-Rec patients and highlights the important role of lipid metabolism in SARS-CoV-2 shedding.

In addition to the downregulation pattern of lipid metabolism, our proteomic analysis also exhibited significant dysregulation of immune-related proteins, including HLA class II histocompatibility antigen, DR alpha chain (HLA-DRA), Cathepsin S (CTSS), Hexokinase-3 (HK3), Arylsulfatase G (ARSG) and Transferrin (TF) in Omi-Rec cases. The proteins of HLA-DRA,<sup>5</sup> ARSG<sup>6</sup> and CTSS<sup>7</sup> guide antibody-mediated immune response, lysosome and macrophage activation, to ultimately eliminate the infectious agents. Interestingly, our data showed the reduction of the three proteins in the pathway of Antigen processing and presentation, Lysosome and Phagosome, suggesting that the primary immune responses were suppressed in Omi-Rec patients. Apart from these proteins, we also observed marked alterations of TF and HK3 in the HIF-1 signaling pathway. These observations are consistent with a recent proteo-transcriptomics study reporting a dysregulation of the HIF-1 signaling pathway in SARS-CoV-2 infected cells.<sup>8</sup>

Our study has limitations. The inherent shortcomings due to the small sample size make it difficult to reach a firm conclusion. Future analyses of larger cohorts are needed to systematically investigate the entire landscape of Omi-Rec host responses.

Currently, the re-positivity of Omicron SARS-CoV-2 tests is widely reported. However, the mechanism leading to these re-positive cases is still unclear.<sup>9</sup> From this current study, our proteomic analysis demonstrated a unique pattern of lipid metabolism and immune response in Omi-Rec patients, which might spur further interest in exploring the association of lipid levels with inflammation in Omi-Rec patients and identifying a possible molecular link between lipoprotein metabolism, immune regulation and SARS-CoV-2 re-positive. The significant dysregulation proteins presented in our study may be valuable potential targets for identifying or treating Omicron-infected patients' re-positive episodes.

## Supplementary material

Supplementary material is available at QJMED online.

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## Authors contributions

F.L. conceived, designed and organized the study, interpreted the results and drafted the manuscript. J.B. and J.H. helped supervise the research. R.S. assisted in experiments and proteomic analysis. The other authors contributed to collecting and managing the data on-site.

Conflict of interest: None declared.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

## References

1. Fleck-DeRderian S, McClellan W, Wojcicki JM. The association between cytomegalovirus infection, obesity, and metabolic syndrome in U.S. adult females. *Obesity (Silver Spring)* 2017; 25: 626-33.
2. Apostolou F, Gazi IF, Lagos K, Tellis CC, Tselepis AD, Liberopoulos EN, *et al.* Acute infection with Epstein-Barr virus is associated with atherogenic lipid changes. *Atherosclerosis* 2010; 212:607-13.
3. Sahin F, Yildiz P. Distinctive biochemical changes in pulmonary tuberculosis and pneumonia. *Arch Med Sci* 2013; 9:656-61.
4. Chidambaram V, Shanmugavel Geetha H, Kumar A, Majella MG, Sivakumar RK, Voruganti D, *et al.* Association of lipid levels with COVID-19 infection, disease severity and mortality: a systematic review and meta-analysis. *Front Cardiovasc Med* 2022; 9:862999.
5. Galperin M, Farenc C, Mukhopadhyay M, Jayasinghe D, Decroos A, Benati D, *et al.* CD4(+) T cell-mediated HLA class II cross-restriction in HIV controllers. *Sci Immunol* 2018; 3: eaat0687.
6. Frese MA, Schulz S, Dierks T. Arylsulfatase G, a novel lysosomal sulfatase. *J Biol Chem* 2008; 283:11388-95.
7. Baranov MV, Bianchi F, Schirmacher A, van Aart MAC, Maassen S, Muntjewerff EM, *et al.* The phosphoinositide kinase PIKfyve promotes cathepsin-S-mediated major histocompatibility complex class II antigen presentation. *iScience* 2019; 11:160-77.

8. Appelberg S, Gupta S, Svensson Akusjarvi S, Ambikan AT, Mikaeloff F, Saccon E, et al. Dysregulation in Akt/mTOR/HIF-1 signaling identified by proteo-transcriptomics of SARS-CoV-2 infected cells. *Emerg Microbes Infect* 2020; **9**:1748–60.
9. Zhao H, Zhang C, Chen XX, Zhu Q, Huang WX, Zeng YL, et al. The relationship between SARS-COV-2 RNA positive duration and the risk of recurrent positive. *Infect Dis Poverty* 2021; **10**:45.