Li *et al. Virology Journal* (2025) 22:89
https://doi.org/10.1186/s12985-025-02696-9

Virology Journal

RESEARCH Open Access

Identification of aberrant interferon-stimulated gene associated host responses potentially linked to poor prognosis in COVID-19 during the Omicron wave

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Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron has demonstrated decreased pathogenicity, yet a few individuals suffer severe pneumonia from coronavirus disease 2019 (COVID-19) infection; the underlying mechanisms are unknown.

Methods The present work investigated the role of Interferon-stimulated genes (ISGs) in the occurrence and progression of severe Omicron infection. The expression and dynamic changes of ISGs were assessed using quantitative real-time polymerase chain reaction (qRT-PCR), and the anti-ISG15 autoantibody in infected patients was detected by ELISA. Moreover, we evaluated the correlation of ISGs with disease severity and outcomes by comparing expression of ISGs among each group.

Results Decreased expression of several ISGs such as IFI6 are potentially linked to increased severity or poor outcomes of Omicron infection. Longitudinal data also demonstrates that the dynamic variation of IFI6 in the Omicron infection phase may be linked to the prognosis of the disease. The increase of anti-ISG15 autoantibody potentially links to the disease progression and poor outcome of patients with high level of ISG15 expression.

Conclusions These findings define aberrant Interferon-stimulated gene associated host responses and reveal potential mechanisms and therapeutic targets for Omicron or other viral infection.

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Importance

The current investigation reveals aberrant Interferon-stimulated gene associated host responses in patients infected with Omicron variant. These findings provide insights for revealing potential mechanisms and therapeutic targets for Omicron or other viral infections.

Keywords Antiviral restriction factors, COVID-19, Interferons, ISG, SARS-CoV-2 Omicron variant

Introduction

The high transmissibility and immune evasion ability of Omicron sparked global alarm during the coronavirus disease 2019 (COVID-19) pandemic since it was associated with a relatively lower risk of hospital admission than delta cases worldwide [1–5]. Major therapies for COVID-19 infection are based on anti-viral and anti-inflammatory approaches [6]. Anti-viral drugs such as paxlovid, azvudine, remdesivir, and molnupiravir primarily work best within 5 ~ 7 days of COVID-19 infection, and exhibit a strong protective efficacy against hospitalization and severity. Noticeably, Omicron has been linked to a significant increase in mortality, even in a highly vaccinated and increasingly immune population [7]. Therefore, research into immune responses to Omicron infection is critical to establish mechanisms and provide insights for future viral waves and therapeutic strategies.

Interferon (IFN) is crucial in protecting the host against virus infection. It is produced via the Cyclic-GMP-AMP synthase-Stimulator-of-interferon genes defense pathway and functions through proteins encoded by Interferon-stimulated genes (ISG) [8, 9]. ISG is a critical effector of the host defending virus through the entire process, from viral entry and import through mRNA and protein synthesis, replication, and assembly [10]. ISG is prospective therapeutic target for anti-viral strategies and drugs based on ISG for viral infections such as HBV and HCV are under preclinical phases [11]. Many studies have focused on innate immune characteristics and the differences in host antiviral capacity among patients with varying severity of COVID-19 [12–14]. ISGs, including IFI6, GBP5, IFI44L, MX1, IFITM3, IFIT2, OAS1, IFIT1, RSAD2, ISG15, IFITM1, and SIGLEC1 have been reported mostly in COVID-19 [12, 14–22]. Previous research on ISG, viral load, and interferon response in patients with diverse severity and variants of COVID-19 infection have demonstrated significant inconsistency and focused less on the distinct expressions of ISGs [12, 13, 23–25]. More importantly, though available investigations have assessed the functions of autoantibodies against type I IFNs in COVID-19 infection, research on autoantibodies in ISG associated host responses is scarce [26]. As a result, the present study examined ISG expression at transcriptional levels in COVID-19 patients infected with the Omicron variant and autoantibody responses to ISG encoded proteins in their plasma.

Methods

Subjects and samples

We enrolled 18 patients with severe Omicron infection, 8 patients with critically severe Omicron infection, 10 non-severe individuals (including mild and moderate patients with Omicron infection), 6 who succumbed to Omicron infection, and 17 healthy controls at Peking Union Medical College Hospital during the Omicron outbreak in China from January, 2023 to March, 2023 in this investigation. Twelve severe and critically severe patients were tracked from admission to the hospital until they were discharged or died. Laboratory findings including lymphocytes, hsCRP, D-Dimer, and ferritin were retrieved from medical records. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), was approved by the Institutional Review Committee of Peking Union Medical College Hospital (approval number: I-23PJ292). Written informed consent was obtained from all participants. All whole blood and plasma samples taken from patients and controls were immediately frozen at – 20 °C.

RT-PCR

Total RNA was isolated from whole blood samples using Ex-DNA Whole Blood Genome (3.0) following the manufacturer's instructions (Tianlong Technology, Co., Ltd) on NP968 Nucleic Acid Extraction System (Tianlong Technology, Co., Ltd). The RNA samples were preprocessed with gDNA plus remover mix to eliminate genomic DNA contamination and then reverse transcribed to cDNA using M5 RT Super plus Mix. HiPerSYBR Premix Estaq (Mei5 Biotechnology, Co., Ltd) was used to perform real-time PCR on an Applied Biosystems 7500 Real-Time PCR System, and the relative expression of the genes was evaluated using the $2-\Delta\Delta Ct$ method after normalization with endogenous GAPDH mRNA expression. Three replicate wells were set for each sample. Table 1 outlines the primer sequences for the 12 ISGs.

ELISA

Anti-ISG15 antibody levels in plasma were examined using ELISA. The 96-well immunoplate (Corning) was coated with 25 ng/well of ISG15 (Cusabio) overnight, and then the protocol was followed as previously described [27]. Briefly, coated plates were blocked with 2% BSA at 37℃ for 2 h. After washing, plasma diluted in 2% BSA

Table 1 Primer sequences for real-time PCR

Gene	Forward primer	Reverse primer
IFI6	TGCTACCTGCTGCTCTTCAC	CGAGCTCTCCGAGCACTTTT
GBP5	TCTGGCCTCCGCTGCATACAA	CCCCACTGCTGATGGCATTGA
IFI44L	TTGTGTGACACTATGGGGCTA	GAATGCTCAGGTGTAATTG-GTTT
MX1	CACAAAGCCTGGCAGCTCTCTA	GGCTGTTTACCAGACTC-CGACA
IFITM3	CTGTCCAAACCTTCTTCTCTCC	GTAGGCGAATGCTATGAAGCC
IFIT2	GGAGAGCAATCTGCGACAG	GCTGCCTCATTTAGACCTCTG
OAS1	CATCCGCCTAGTCAAGCACTG	CCACCACCCAAGTTTCCT-GTAG
IFIT1	AGAAGCAGGCAATCACAGAAAA	CTGAAACCGACCATAGTG-GAAAT
RSAD2	ACATTCCTCTTTGGGGAAAG	AAAGCCCAAGGACACTGTTT
ISG15	TCTCAGAGGAGCCTGGCTAA	AGCATCTTCACCGTCAGGTC
IFITM1	CAGCAGTTTATACCCACACACC	GCACGTGCACTTTATTGAAT
SIGLEC1	CTAGTAGTCAGTTGGGAGT	AGCCAGAACAGCCTTTACT
GAPDH	CCTCAAGATCATCAGCAAT	CCATCCACAGTCTTCTGGGT

(1:200) was added and incubated at 37℃ for 2 h. The plate was then washed and incubated with horseradish peroxidase-conjugated anti-human IgG antibody (1:10 000) (ZSGB-BIO) at 37℃ for 1 h; Tetramethylbenzidine (TMB) was added after washes. ISG15 blocking experiment was performed to verify the specificity; Plasma was preincubated with ISG15 at different concentrations (1 ng/μL and 5ng/μL) overnight, and then detected by ELISA. Two replicate wells were set for each sample.

Statistical analysis

Data were analyzed by using GraphPad Prism 9.5 software (San Diego, CA, USA) and the online BioLadder tool (bioladder.cn) [28]. Independent sample t- test and one-way ANOVA was used to compare differences between two groups or among three or more groups with normal distribution. For data with non- normal distribution, non- parametric tests were applied. $P<0.05$ denoted statistical significance.

Results

Study design and baseline characteristics

Figure 1 depicts the study design. Table 2 outlines the demographics and clinical characteristics of the participants in our study. We examined 36 participants, including 10 mild and moderated patients, 18 severe patients, and 8 critically severe patients. Five severe patients and 1 critically severe patient succumbed to Omicron infection. The mean age of patients was 71.47 years. Males comprised 26 of 36 cases. Thirty patients had underlying diseases, including but not limited to hypertension and diabetes mellitus. Seven patients were immunocompromised. Twenty-one patients had complications. Ten patients with known vaccination histories were unvaccinated. Sixteen patients underwent the intensive care unit (ICU) during hospitalization.

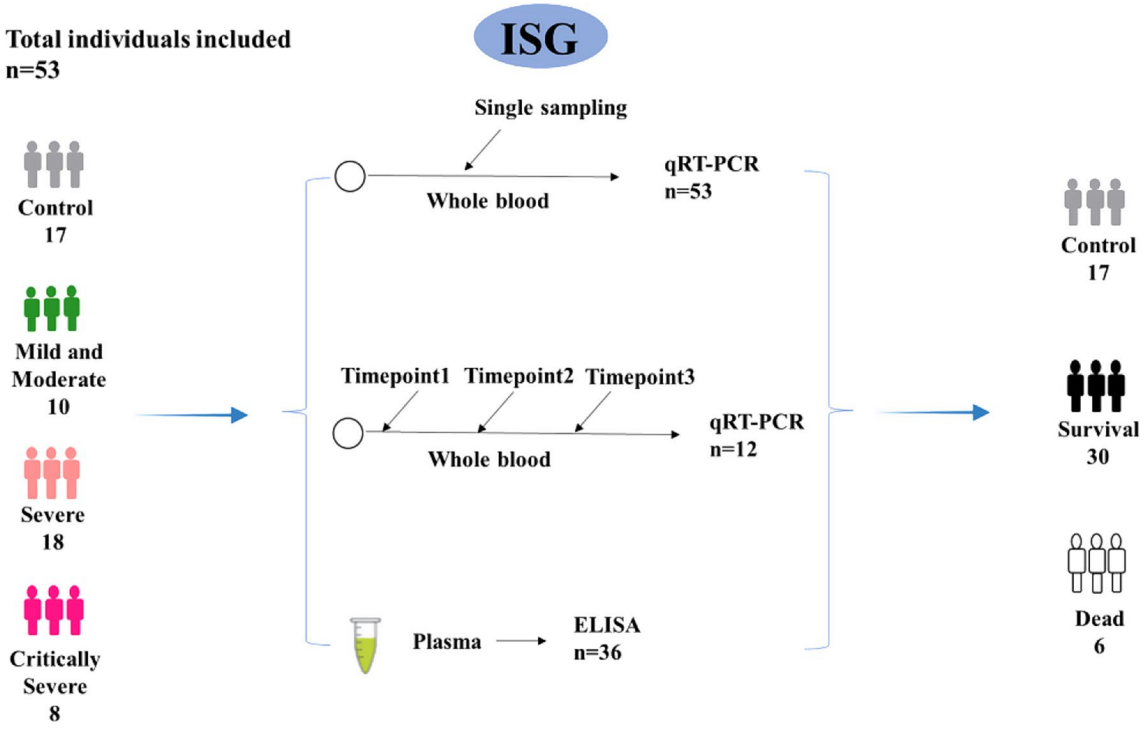

Fig. 1 Study design

Table 2 Demographics and clinical characteristics of COVID-19 patients and controls in the current study

Characteristics	Healthy Control	COVID-19			
		Mild and Moderate	Severe	Critically Severe	Total
Number	17	10	18	8	36
Age (median, range)	62.29 (52,76)	68.00 (14,88)	75.83 (54,95)	66.00 (51,77)	71.47 (14,95)
Gender (male, %)	47.06%	70%	66.67%	87.5%	72.22%
With underlying diseases	0	7/10	15/18	8/8	30/36
Immunosuppression status	0	2/10	1/18	4/8	7/36
Complications	0	2/10	13/18	6/8	21/36
Vaccination (Unvaccinated/known vaccination)	---	1/3	5/11	4/7	10/21
Steroids	0	6/10	17/18	8/8	31/36
Mechanical ventilation	0	3/10	17/18	8/8	28/36
ICU	0	0	8/18	8/8	16/26
Death	0	0	5/18	1/8	6/26

Abbreviations: *ICU* Intensive Care Unit

Clinical characteristics in patients infected with Omicron variant

Patients with COVID-19 frequently have overreactive inflammatory responses; thus, we investigated several clinical parameters to reflect their basic immune status (Fig. 2A-H). Our assessment revealed that peripheral lymphocytes were significantly lower in severe and critically severe patients compared with mild and moderate patients, indicating that fewer lymphocytes correlate with increased severity of Omicron infection ($p < 0.05$, Fig. 2A), which also reflected the reliability of our data. Furthermore, the more severe group exhibited an increasing tendency of inflammation parameters, including hsCRP, D-Dimer, and ferritin ($p > 0.05$, Fig. 2B-D). Patients with poor prognosis had decreased lymphocytes and a higher inflammation state ($p > 0.05$, Fig. 2E-H).

Expression of ISGs in whole blood of patients with different severity of Omicron infection

While previous research focused on consistent ISG expression to evaluate host resistance to SARS-CoV-2, different ISGs may work on viral infection by mediating different pathways. In this view, we focused on 12 ISGs (including IFI6, GBP5, IFI44L, MX1, IFITM3, IFIT2,

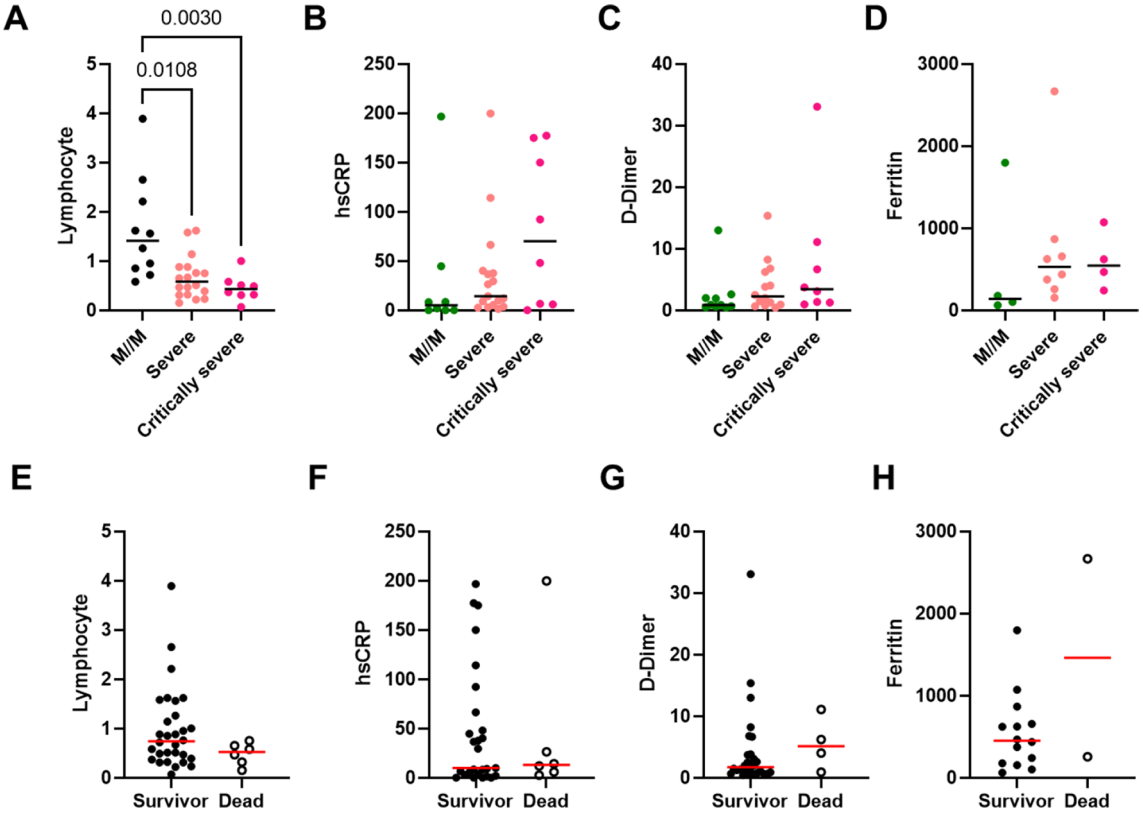

Fig. 2 The comparison of lymphocytes, hsCRP, D-Dimer, and ferritin in the peripheral blood among cases with different severity of Omicron infection (mild and moderate, severe, and critically severe patients, **A**-**D**) and between the survival group and mortality group (**E**-**H**). P-values were determined by Kruskal-Wallis test (**A**-**D**) and Mann-Whitney test (**E**-**H**). All comparisons unreported had p-values greater than 0.05. M/M: mild and moderate

OAS1, IFIT1, RSAD2, ISG15, IFITM1, and SIGLEC1) and examined their expressions in whole blood from 36 patients infected with Omicron variants and 17 healthy controls (Fig. 3A-L).

Our findings revealed that 7 of 12 ISGs were significantly differentially expressed in patients, with 4 ISGs (IFI6, IFI44L, IFITM1, MX1) downregulated ($p < 0.05$, Fig. 3A-D) and 2 ISGs (SIGLEC1, and IFIT2) upregulated ($p < 0.05$, Fig. 3G, H) in severe and critically severe groups compared with healthy controls. ISG15 expression was significantly higher in mild, moderate, and severe groups than in healthy controls ($p < 0.05$, Fig. 3F).

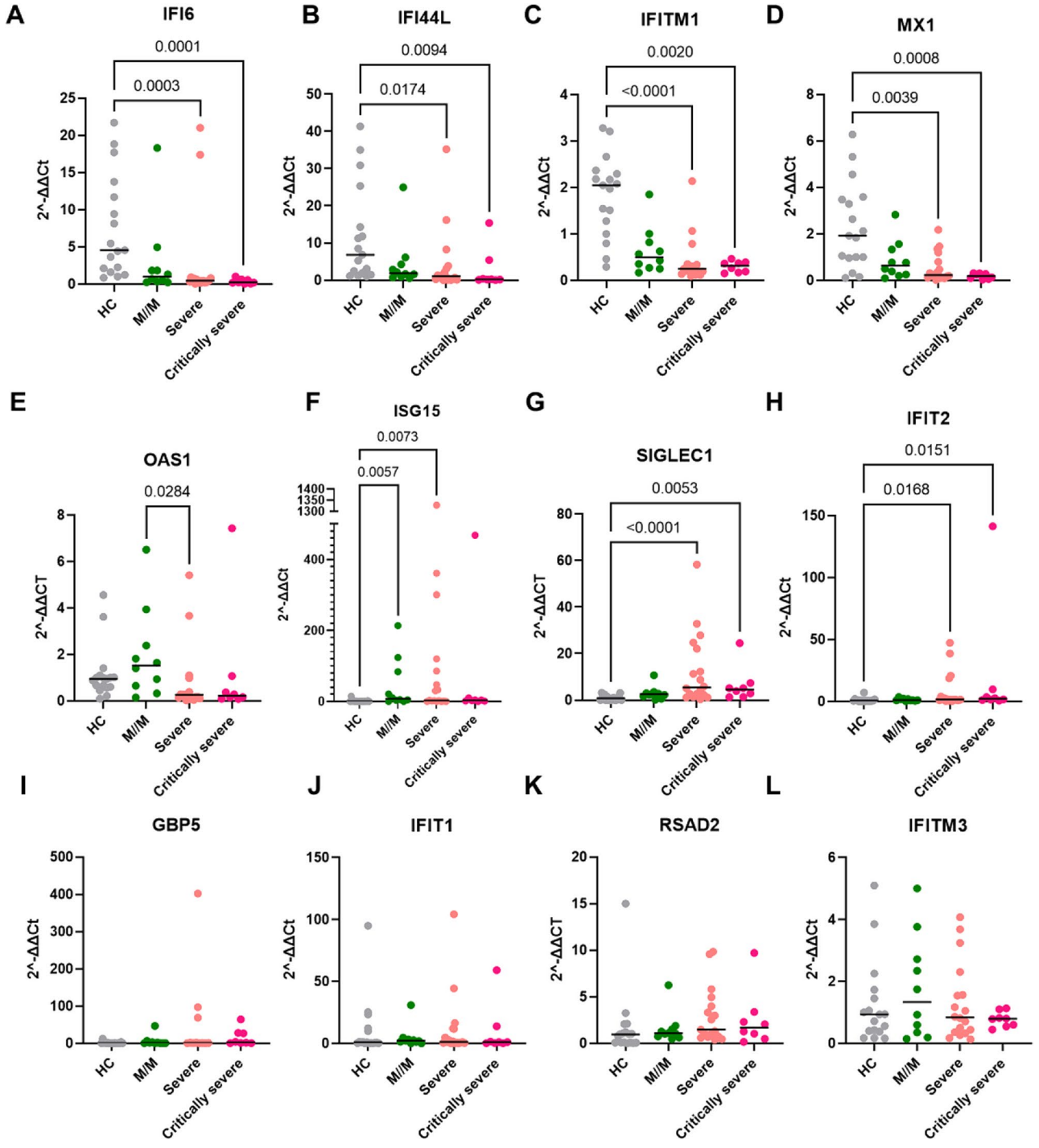

Fig. 3 The comparison of ISG mRNA expression in the peripheral blood among cases with different severity of Omicron infection (mild and moderate, severe, and critically severe patients) and healthy controls. P-values were determined by Kruskal-Wallis test. All comparisons unreported had p-values greater than 0.05. HC: healthy control

Additionally, we discovered that several ISGs varied in relation to the severity of patients. Lower levels of IFI6, IFI44L, and IFITM1, and MX1 were linked to increased severity ($p < 0.05$, Fig. 3A-D). OAS1 was significantly lower in severe patients compared with mild and moderate patients ($p < 0.05$, Fig. 3E).

Expression of ISGs in whole blood of patients with different outcomes of Omicron infection

Based on the varied expression of ISGs observed in patients with different severity of Omicron infection, we hypothesized whether ISGs were associated with prognosis. As a result, we compared the expression of ISGs in patients with outcomes of survival or death (Fig. 4A-L). The results demonstrated varied expression of ISGs between patients who survived and those who succumbed to Omicron infection: higher levels of ISG15 and IFIT1 were linked to poor prognosis ($p < 0.05$, Fig. 4A, B).

Dynamic expressions of ISGs in whole blood from patients infected with Omicron variant

Because the expression of ISGs was associated with the severity and outcome of patients infected with Omicron variant, we investigated whether the ISGs variated during disease progression. We measured the levels of 4 ISGs with the highest significance of expression in the whole blood from our follow-up cohort. We followed up on 12 severe and critically ill patients infected with Omicron variant and evaluated their ISG expressions; 2 succumbed to Omicron infection (Fig. 5A-H). Three timepoints were selected for analysis to reflect their dynamic and consistent variation. Timepoint 1 was the first sample collection time 24 h following their admission. Timepoint 2 was an intermediate point in the disease process. Timepoint 3 was the final sample collection time before the patients were discharged or died. Table 3 outlines detailed time for the three timepoints. IFI6, IFITM1, and ISG15 were discovered to have significant dynamic variation during the entire phase of Omicron infection (Fig. 5). IFI6 levels continued to rise in surviving patients as symptoms improved until the patient was discharged from the hospital (Fig. 5A). IFITM1 and ISG15 levels decreased continually in disease remission patients (Fig. 5C, E). In addition, their variation was detected in 2 deceased patients following their admission to the hospital (Fig. 5B, D, F, H). Compared with surviving patients, IFI6 did not increase in decreased patients, suggesting that an unsuccessfully increasing of IFI6 potentially relates to the outcome of death (Fig. 5B).

Anti-ISG15 autoantibody detection

After observing that ISG15 levels were higher in patients with more severity and poor outcome, we hypothesized whether the existence of autoantibodies could neutralize the antiviral role of ISG15 against Omicron variant. In this view, we detected anti-ISG15 in plasma collected from 36 patients infected with Omicron variant. The results showed an increasing tendency of anti-ISG15 autoantibodies in the death group compared to the survival group (Fig. 6).

Discussion

Our study emphasizes the host antiviral signature mediated by ISGs in patients infected with Omicron variant during the Omicron wave, both cross-sectionally and longitudinally. Decreased lymphocyte levels and higher inflammation status were observed in patients with poor prognosis, consistent with previous findings [29–31]. The expression of several ISGs, including IFI6 and ISG15, was revealed to be potentially associated with the severity or outcome of Omicron infection. In addition, we discovered a dynamic variant of IFI6 that could be related to the prognosis of Omicron.

IFN alpha-inducible protein 6 (IFI6) is an IFN-stimulated gene that belongs to the FAM14 protein family and is localized in mitochondria, playing a crucial role in immune regulation, stabilizing mitochondrial function and blocking apoptosis [32]. Previous research found that knocking- down or knocking- out IFI6 increased the expression of IFN, ISG, and pro-inflammatory cytokines after SARS-CoV-2 infections and decreased the production of infectious SARS-CoV-2, highly likely owing to its roles in inhibiting inflammation and modulating antiviral responses [33]. Cytokine storm and a lack of IFN responses against SARS-CoV-2 early in infection have been supposed to be critical factors linked to the rapid death of COVID-19 patients [34]. Our findings demonstrated that IFI6 levels were significantly lower in severe and critically severe patients infected with Omicron variant; while IFI6 levels continued to rise in some subjects who eventually survived as the symptoms improved and they were discharged from the hospital. Similar observations were not true for 2 dead patients. The increasing tendency of inflammation and decreasing tendency of IFI6 were reported concurrently as disease severity increased, perhaps supporting the role of IFI6 in inhibiting inflammation. We hypothesize that subjects with lower IFI6 levels are more likely to develop into more severe patients after Omicron infection and have a poor prognosis due to their inability to suppress excessive immune responses induced by Omicron variant.

IFN-stimulated gene 15 (ISG15) encodes a ubiquitin-like protein, mediates ISGylation of various proteins, competes with ubiquitin for ubiquitin-binding sites, and regulates protein degradation [35]. ISG15 is thought to play crucial antiviral roles during infection for a broad range of viruses, potentially via ISGylation of viral and host protein, and functions extracellularly

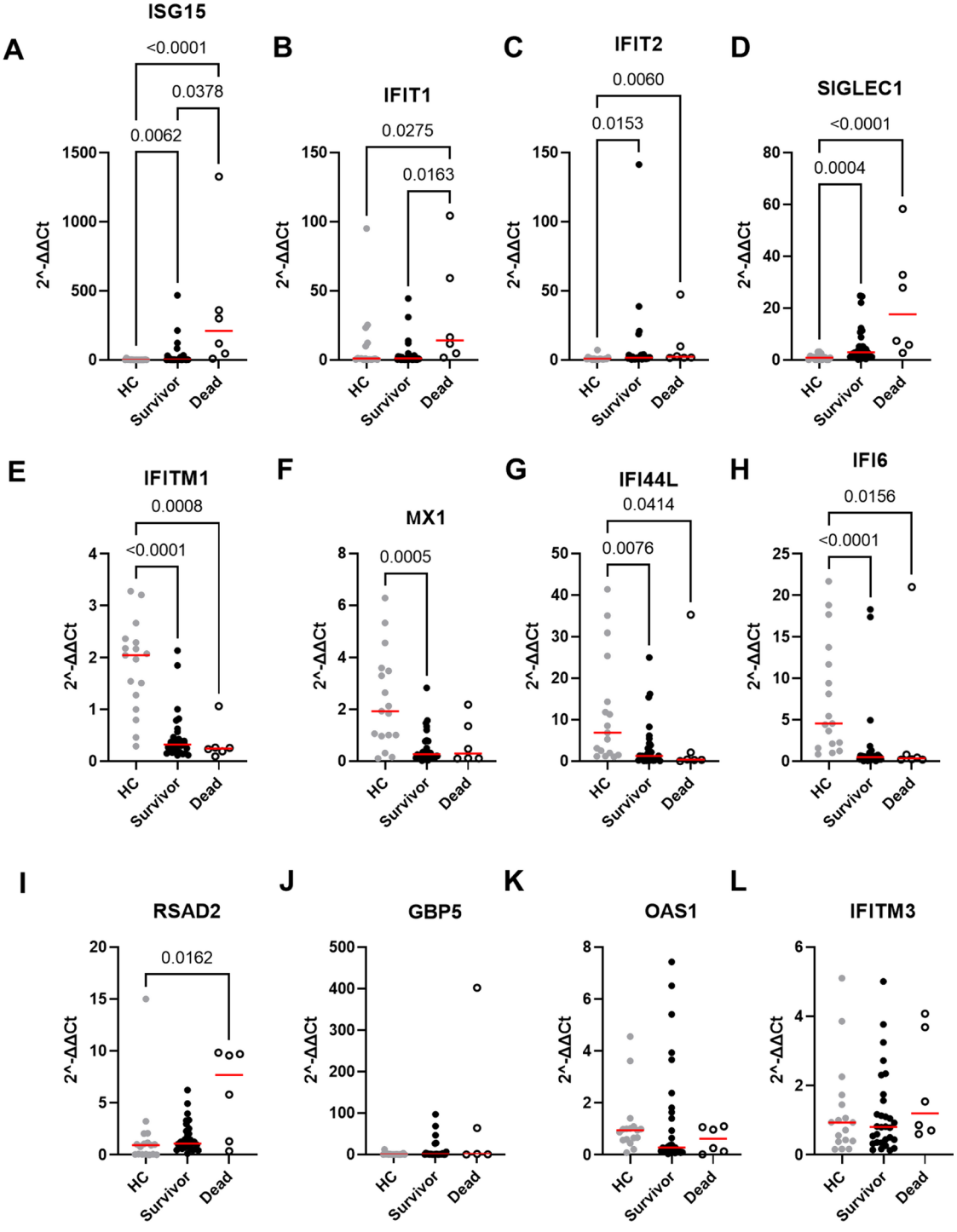

Fig. 4 The comparison of ISG mRNA expression in the peripheral blood among cases with different outcomes of Omicron infection (survival and dead patients) and healthy controls. P-values were determined by Kruskal-Wallis test. All comparisons unreported had p-values greater than 0.05

and intracellularly, diversely and pathogen-dependently, as one of the most strongly and rapidly induced ISGs during pathogen invasion [35]. In addition, ISG15 may dysregulate IFN-α/β immunity by inhibiting the ubiquitination and degradation of USP18, a negative regulator, and boosting its stability and function [36]. In our study, ISG15 was significantly higher in mild, moderate, and severe patients infected with Omicron variant and in patients with poor prognosis compared with survivors. Patients with increased ISG15 mRNA have more severity or poor prognosis probably because ISG15 protein cannot adequately exert anti-inflammation effects

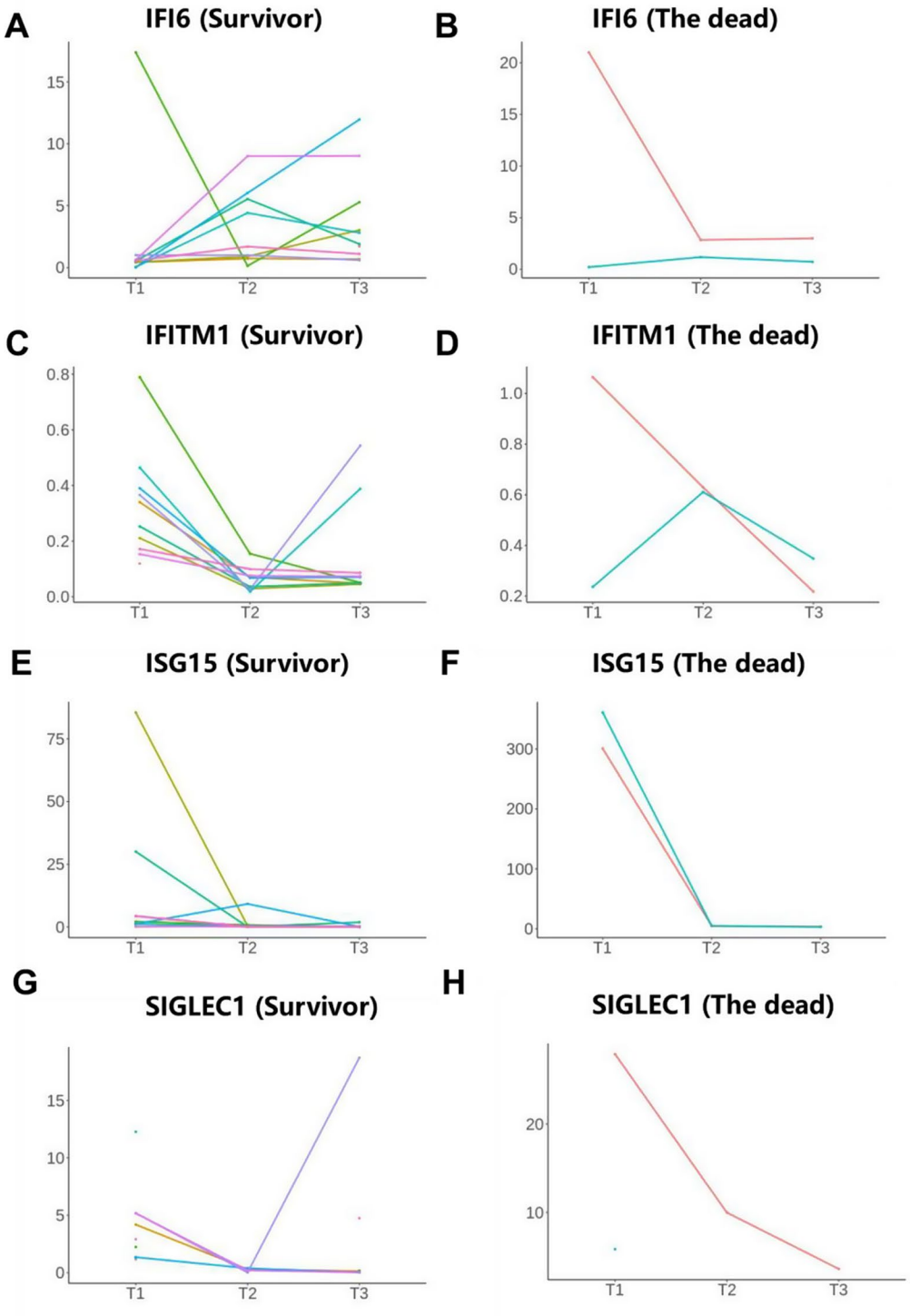

Fig. 5 Dynamic variation of IFI6, IFITM1, ISG15, and SIGLEC1 mRNA expression across three sampling timepoints in patients who survived or died during the entire phase of Omicron infection. The x-axis shows the three timepoints. The y-axis represents 2^-△△Ct. T, timepoint

due to immune-evasion strategies or autoimmune status. SARS-CoV-2 may evade host antiviral immune response by releasing SARS-CoV-2 papain-like cysteine protease (PLpro) to combine ISG15 and inhibit its antiviral and anti-inflammatory functions; a preclinical drug, GRL0617, can block the binding of ISG15 C-terminus to PLpro and act as a hot spot for antiviral drug [37, 38]. There is no current research on autoantibodies

Table 3 Median (range) time (day) of three times of sampling since hospitalization from cases with different outcomes of Omicron infection

Patients	Timepoint1	Timepoint2	Timepoint3	Outcome
Survival ($N=10$)	1 (1, 2)	20 (5, 56)	33 (4, 120)	37 (6, 130)
Dead ($N=2$)	0 (0, 0)	17 (15, 19)	37 (31, 42)	39 (31, 46)

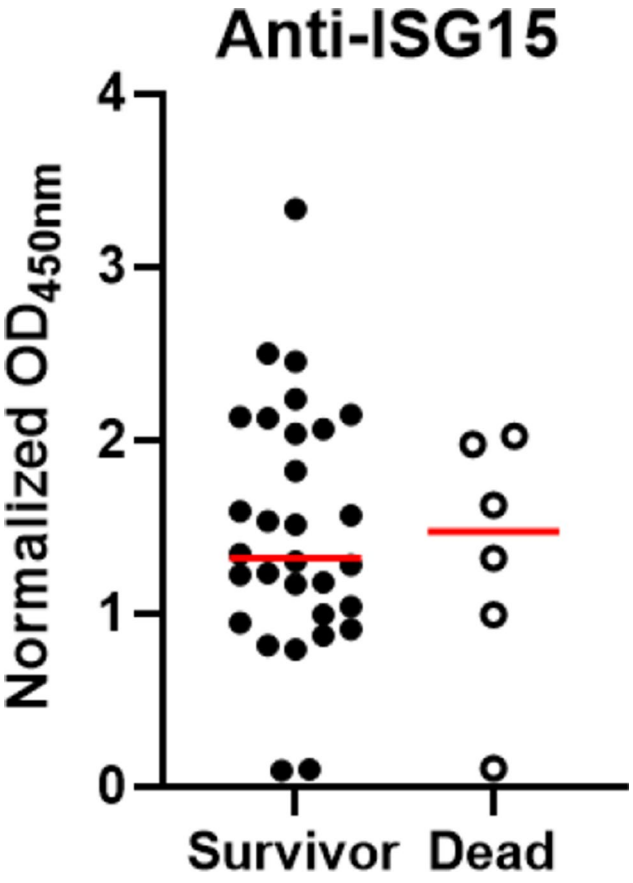

Fig. 6 The comparison of anti-ISG15 autoantibody in the plasma in cases with different outcome of Omicron infection. P-value was determined by Kruskal-Wallis test ($p > 0.05$)

against ISG encoded proteins such as anti-ISG15 in COVID-19. In this study, we found an increasing tendency of anti-ISG15 autoantibody levels in death group compared to survival group, necessitating further research to validate the potentially neutralizing role of anti-ISG15 against the anti-viral role of ISG15.

Sialic acid-binding immunoglobulin-like lectin 1 (SIGLEC1) encodes CD169, a surface adhesion molecule on human myeloid cells with fundamental implications for innate and adaptive immunity [39]. SIGLEC1 has been identified as an attachment receptor by increasing angiotensin-converting enzyme 2-mediated infection and regulating the neutralizing activity of different spike-specific antibodies [40]. It is also a central molecule in SARS-CoV-2 uptake via sialic acid recognition, and its presence on APCs harboring SARS-CoV-2 mediates trans-infection in vivo [41]. Therefore, the increased expression of SIGLEC1 in severe and critically severe groups in our study may reflect their involvement in Omicron variant invasion and the active status of infection.

Moreover, we noted the differences in the expression of other ISGs between groups. 2'-5'-oligoadenylate synthetase 1 (OAS1) is thought to activate RNase L to block SARS-CoV-2 replication, with a protective function for OAS1 in COVID-19 adverse outcomes [15, 42, 43]. OAS1 was significantly lower in severe patients than in mild and moderate patients, consistent with previous findings [15, 42, 43]. IFN-induced protein 44-like (IFI44L) is a negative feedback regulator of IFN responses induced following infection with different viruses [44]. IFN-induced transmembrane protein 1 (IFITM1) is an active member of the IFITM family, consisting of restriction factors that block the entry of several viruses and inhibit S-mediated fusion and SARS-CoV-2 infections [45, 46]. MX1 encodes a guanosine triphosphate metabolizing protein involved in the cellular antiviral response and has been shown to play a crucial role in defining less severe types [47, 48]. In the present investigation, we found significantly decreased expressions of IFI44L, IFITM1, and MX1 in severe and critically severe patients, which might be associated with disease severity. These results suggest that a poor ability to fight inflammation and virus in the host could contribute to increased severity of Omicron infection.

Our study has some limitations. First, our findings might be impacted by several factors, including age, gender, underlying diseases, immunosuppression status, and therapies, which are unavoidable in severe and critically severe infected patients. Then, the study population was relatively small because of the limited availability of patients with severe and fatal Omicron infection and that few mild and moderate patients admitted to the hospital during the omicron wave. Further validation based on ISG encoded proteins were crucial to identify our findings.

Conclusions

Decreased expression of several ISGs such as IFI6 are potentially linked to increased severity or poor outcomes of Omicron infection. Longitudinal data also demonstrates that the dynamic variation of IFI6 in the Omicron infection phase may be linked to the prognosis of the disease. The increase of anti-ISG15 autoantibody potentially links to the disease progression and poor outcome of patients with high level of ISG15 expression. Our findings filled the research gaps in anti-ISG15 autoantibodies in patients infected with Omicron variant. These data shed light on a proposed mechanism for viral infection such as COVID-19 and prospective diagnostic and disease activity evaluating biomarkers and viable therapeutic targets.

Further research on ISGs in COVID-19 or other viral infections is necessary.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Coronavirus disease 2019
ISGs	Interferon-stimulated genes
qRT-PCR	Quantitative real-time polymerase chain reaction
IFN	Interferon
IRBs	Institutional Review Boards
ICU	Intensive care unit
IFI6	IFN alpha-inducible protein 6
ISG15	IFN-stimulated gene 15
PLpro	Papain-like cysteine protease
SIGLEC1	Sialic acid-binding immunoglobulin-like lectin 1
OAS1	2′-5′-oligoadenylate synthetase 1
IFI44L	IFN-induced protein 44-like
IFITM1	IFN-induced transmembrane protein 1

Acknowledgements
Not applicable.

Author contributions
ZL, LLC, and YZL conceived the original ideas and designed the project. ZL extracted data, performed software analyses, and visualized graphs and tables. ZL wrote the manuscript. ZL and LLC performed the experiments. ZRW provided professional consultant to the experiments. ZL, XXF, and SYW collected the clinical samples. ZL, ZYW, FTF, XXF, and SYW collected the data of participants. ZL, MP, LLC, YG, and YZL revised and examined the manuscript. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Funding
This research was supported by grants from Beijing Natural Science Foundation (M23008) and the National High Level Hospital Clinical Research Funding (2022-PUMCH-B-124) to YL. This research was also supported by grants from the National Natural Science Foundation of China (82402181) and the China Postdoctoral Science Foundation (2023T160060) to LLC.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), was approved by the Institutional Review Committee of Peking Union Medical College Hospital (approval number: I-23PJ292). Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 18 December 2024 / Accepted: 6 March 2025
Published online: 28 March 2025

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