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Research Article

Immunological Profiling of Toll-Like Receptor 3, Interferon-Alpha, and Antimicrobial Peptide LL-37 in Response to COVID-19 Infection and Vaccination in Iraqi Patients

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A B S T R A C T

Introduction: The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has prompted extensive research into the immune response mechanisms triggered by infection and vaccination. This study investigates the immunological profiling of Toll-like receptor 3 (*TLR3*), Interferon-alpha (IFN-α), and antimicrobial peptide LL-37 in Iraqi patients, comparing responses among unvaccinated, Pfizer-vaccinated, Sinopharm-vaccinated, and COVID-19 infected groups.

Materials and Method: A total of 120 participants were categorised into four subgroups: 30 unvaccinated and uninfected, 30 Pfizer-vaccinated, 30 Sinopharm-vaccinated after the second dose, and 30 COVID-19-infected but unvaccinated individuals. The study monitored *TLR3* gene expression, IFN-α, and LL-37 levels over three months using real-time PCR and ELISA techniques, respectively.

Results: The study revealed significant variations in *TLR3* gene expression across groups. The Pfizer group showed dynamic fluctuations, peaking at three months, indicating an active immune response. The Sinopharm group exhibited a steady increase in *TLR3* expression, suggesting sustained immune activation. The infected group had a high initial response, tapering to baseline, reflecting immune resolution. Serum IFN-α levels were significantly higher in both the infected and vaccinated groups compared to controls. The Sinopharm group also showed elevated LL-37 levels, indicating robust mucosal immunity

Conclusion: This study underscores the critical roles of *TLR3*, IFN-α and LL-37 in the immune response to COVID-19 infection and vaccination. The differential expression of these markers provides insights into the dynamics of the immune response, highlighting the importance of sustained immune surveillance and the potential of these markers for diagnostic and prognostic purposes. Further research is needed to explore the long-term implications and optimise vaccination strategies for better immune protection.

Keywords: COVID-19, SARS-CoV-2, *TLR3*, IFN-α, LL-37, Immune Response, Vaccination, Pfizer, Sinopharm, Iraq

Introduction

COVID-19, a novel illness caused by SARS-CoV-2, was first identified in Wuhan, China, with severity ranging from mild rhinorrhoea to life-threatening Adverse Drug Reaction (ADR) and non-respiratory manifestations.[1] The spike (S) protein of SARS-CoV-2 plays a critical role in infection. It acts like a key, binding to the ACE-2 receptor on host cells and enabling the virus to fuse and enter. Because of this crucial function, the spike protein is the target for all COVID-19 vaccines, despite their varied mechanisms of action.[2] These vaccines utilise various technologies, including mRNA, replication-incompetent vector, recombinant protein, and inactivated approaches.[3] Booster dosages are necessary to trigger a T cell response as well as a B cell response that results in the production of neutralising and binding antibodies.[4] Iraq's national vaccination program uses three primary COVID-19 vaccines: Pfizer, Oxford AstraZeneca, and Sinopharm. Pfizer uses engineered messenger RNA to trigger an immune response, AstraZeneca uses a modified chimpanzee adenovirus vector, and Sinopharm uses an inactivated virus to train the immune system.[5] The effectiveness of vaccines in preventing infections, particularly COVID-19, is assessed using serological and immunological indicators. Challenges include equitable global access and controlling outbreaks. The human immune system triggers innate and adaptive responses.[6] TLRs, located on different chromosomes, detect ligands, produce IFN, and trigger innate immune responses. They involve specialised T lymphocytes and B cells, producing antibodies and memory immunity.[7,8] TLRs have three domains: transmembrane, TIR, and extracellular. They initiate downstream signalling, identify PAMPs, and form dimers with coreceptors or assistance molecules.[9] TLRs, expressed by both innate and non-immune cells, contribute to the body's innate immunity. They can be divided into surface and intracellular TLRs, with TLRs dispersed on intracellular endosomes and on the cell surface. TLRs recognise various PAMPs, including lipids, lipoproteins, and nucleic acids, primarily for identifying bacteria.[10] *TLR3* recognises double-stranded RNA produced by RNA viruses.[11] *TLR3* stimulates NF-κB and IRF, producing IFN and pro-inflammatory cytokines. They indirectly activate the adaptive immune system by inducing costimulatory molecules. SARS-CoV-2 upregulates pro-inflammatory genes in lung epithelial cells, potentially triggering the innate immune system, leading to viral death and removal.[12] TLRs are linked to SARS-CoV and MERS pathogenesis, potentially playing a role in SARS-CoV-2. COVID-19 severity is correlated with IL-6 levels, and activation of TLRs triggers the inflammasome and IL-1 production. TLRs may also cause STAT.[13] IFN-α is a vital component of the antiviral immune response, with significant implications for both the treatment and prevention of COVID-19. Its ability to inhibit viral replication, modulate immune responses, and enhance vaccine efficacy underscores its potential as a therapeutic and prophylactic agent. Further research is needed to fully understand the optimal use of IFN-α in the context of COVID-19 and to develop effective strategies for its clinical application.[14] LL-37, an antimicrobial peptide, is a key part of the innate immune system, providing broad-spectrum antimicrobial activities and being produced by various cell types. LL-37, a protein, has shown potential in combating SARS-CoV-2, the virus responsible for COVID-19. It can bind to the ACE-2 receptor's binding domain, preventing infection. LL-37 also disrupts the viral membrane, similar to its activity against other viruses. It also exerts immunomodulatory effects, regulating neutrophil NETosis, which can help reduce inflammation and tissue damage in COVID-19 patients. LL-37's potential therapeutic applications include adjunctive therapy, reducing the severity of COVID-19-related complications, and regulating NETosis and inflammation.[15]

Study Design, Materials and Methods

Subjects

This investigation comprised 120 Iraqi participants. The participants were categorised into four subgroups: 30 unvaccinated and uninfected individuals (aged 24–38 years), 30 individuals vaccinated with the Pfizer vaccine, 30 individuals vaccinated with the Sinopharm vaccine (after the second dose), and 30 individuals infected with COVID-19 but unvaccinated. The ages of the vaccinated and infected groups, which ranged from 25 to 365 years, were monitored for the first three months following vaccination or infection. The duration of vaccination or infection was used to further divide each of these subgroups into three categories: one month, two months, and three months. Each subgroup consisted of 10 individuals. Healthcare providers supervised the collection of infected samples from Baghdad Teaching Hospital and Ibn Al-Kateeb Hospital in Baghdad, Iraq, between October 2023 and January 2024. Clinical features and positive PCR test results for active COVID-19 were used to diagnose hospitalised patients under the supervision of a specialist.

Inclusion Criteria

Those who were infected but not vaccinated, as well as those who had received the Sinopharm and Pfizer vaccines, were the subjects of follow-up cases after the initial three months of immunisation. Moreover, health precautions (those who are not infected and not vaccinated).

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Exclusion Criteria

Those who have a history of other infections, diabetes, hypertension, cancer, and autoimmune disorders, or who receive additional vaccinations.

Ethical Approval Statement

Ethical approval was obtained from the Ethics Committee of the College of Biotechnology, Al-Nahrain University. Informed consent was obtained from all individual participants included in the study. The participants were informed about the study's purpose, procedures, potential risks, and benefits, and their rights to refuse or withdraw from the study at any time without any consequences. All data collected was kept confidential and used solely for the purpose of this research.

Gene Expression of *TLR3*

The expression of *TLR3* involved the use of a SaCycler-48 Real-Time PCR system from Sacace (Italy) and a Luna Universal qPCR Master Mix from Biolab (England). Chemicals such as chloroform and ethanol were sourced from Ocon Chemicals (Ireland), and TRIzol reagent was obtained from Transgene (China).

Sampling and RNA Extraction

Peripheral blood samples (10 mL) were collected from subjects. For RNA extraction, 300 µL of blood was mixed with 600 µL of TRIzol reagent and 250 µL of chloroform in a micro-centrifuge tube. After homogenisation and incubation at room temperature, the samples were centrifuged, and the supernatant was treated with ethanol and processed through ReliaPrep columns (Promega, USA). RNA was eluted with DNase/ RNase-free water.

RNA Quantification

The concentration and purity of RNA were determined using the Quantus Fluorometer (Promega, USA). Samples were prepared by mixing RNA with QuantiFluor dye in TE buffer. The fluorescence was measured to quantify RNA concentration.

cDNA Synthesis

RNA was converted to cDNA using the LunaScript Reverse Transcriptase kit (Biolab, England). The reaction mixture included LunaScript RT SuperMix, random primers, and RNA. The mixture was incubated for primer annealing, cDNA synthesis, and heat inactivation steps.

Primers used in this Study

Macrogene, a South Korean company, synthesised high-quality genetic materials using the NCBI Primer-BLAST tool for precise and efficient amplification of target sequences. The primer sequences used for *TLR3* were carefully selected to ensure optimal binding and amplification. The forward primer for *TLR3* had the sequence 5'-TGCACGGGCTTTTCAATGTG-3', while the reverse primer was 5'-CAGGGTTTGCGTGTTTCCAG-3'. For the reference gene GAPDH, which is commonly used as a normalisation control in gene expression studies, the forward primer sequence was 5'-TTTTGCGTCGCCAGCC-3', and the reverse primer sequence was 5'-ATGGAATTTGCCATGGGTGGA-3'.

RT-PCR

Gene expression was analysed using the Luna Universal qPCR Master Mix in a real-time PCR system. The reaction components included forward and reverse primers, nuclease-free water, and cDNA. The cycling conditions involved initial denaturation, denaturation, annealing/ extension, and a melting curve analysis.

Immunological Assays

The levels of IFN-α and LL-37 were measured using sandwich ELISA kits (Sunglong Biotech, China).

Statistical Analysis

Data were analysed using SPSS version 23 and GraphPad Prism 9. Statistical tests included mean, standard deviation, standard error, independent samples T-test, ANOVA, and Receiver Operating Characteristic (ROC) curves. Gene expression was evaluated using the 2^(-ΔΔCT) method, with GAPDH as the endogenous control. Samples were categorised as upregulated or downregulated based on their fold change relative to the control.

Results

Gene Expression of *TLR3*

The study revealed significant variations in *TLR3* gene expression across different groups over time. The control group maintained a constant fold change of 1.0, indicating stable *TLR3* expression. In contrast, the Pfizer vaccinated group showed marked fluctuations, with a notable increase at one month (4.354), a decrease at two months (0.623), and a dramatic spike at three months (14.312), suggesting a dynamic immune response. The Sinopharm vaccinated group exhibited a consistent increase in *TLR3* expression, with fold changes of 1.913, 2.532, and 2.221 at one, two, and three months, respectively, indicating a sustained immune activation. The infected group demonstrated a high initial response (5.11) at one month, followed by a gradual return to baseline levels at two (1.34) and three months (1.01), reflecting an effective resolution of the immune response. These findings highlight the variable nature of

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TLR3 activation in response to vaccination and infection, providing insights into the immune dynamics and potential implications for clinical outcomes as shown in Figure 1.

Evaluation of IFN-α and LL-37 in the Infected and Vaccinated Group

The study found significant increases in serum IFN-α in infected and vaccinated groups compared to controls. In the Sinopharm group, IFN-α levels rose to 18.068 ± 2 pg/mL after one month but showed no significant differences in the second (12.394 ± 1 pg/mL) and third months (8.469 ± 2 pg/mL). The Pfizer group showed a significant increase in the second month (16.359 ± 1 pg/mL), with no significant differences in the first (9.612 ± 3 pg/mL) and third months (9.368 ± 2 pg/mL). The results displayed a significant elevation ($p < 0.05$) in serum IFN-α in the infected group during three months (12.6 ± 1.4, 11.2 ± 2.4 and 10.5 ± 2.1 pg/mL) respectively, compared to controls (5.4 ± 1.1 pg/mL). Serum LL-37 levels were significantly elevated in the Sinopharm group at three months (337.277 ± 8.9, 221.564 ± 12.1 and 402.207 ± 8.73 µg/mL) compared to controls (71.8 ± 8.7 µg/mL) and Pfizer recipients (185.662 ± 6.12 µg/mL). The findings highlight the role of IFN-α and LL-37 in the immune response and the variability in vaccine-induced immunity as illustrated in Figure 2.

ROC Test Analysis

The comparison of immune responses between Pfizer and Sinopharm vaccines revealed distinct patterns for each marker. The Pfizer vaccine showed a robust early immune response with IFN-α sensitivity of 91%, specificity of 93%, and an Area Under Curve (AUC) of 0.96, particularly evident in the second month post-vaccination. In contrast, the Sinopharm vaccine demonstrated 100% sensitivity and specificity for IFN-α with an AUC of 0.93, notable in the first month post-vaccination but aligning with infection levels in later months. For LL-37, both vaccines exhibited high sensitivity and specificity (100% for Pfizer, 99% for Sinopharm), with Pfizer inducing significant elevations indicating a strong innate response (AUC 0.99), while Sinopharm showed pronounced mucosal immunity with elevated levels in the lungs and saliva (AUC 0.97). *TLR3* responses were higher and sustained in the Pfizer group (sensitivity 82%, specificity 84%, AUC 0.71), indicating potential memory cell establishment, whereas the Sinopharm vaccine also increased *TLR3* expression (sensitivity 83%, specificity 81%, AUC 0.77), reflecting ongoing immune surveillance. Overall, both vaccines effectively stimulated the immune system, with Pfizer showing sustained IFN-α and *TLR3* responses and Sinopharm enhancing mucosal immunity with higher LL-37 levels as shown in Figure 3.

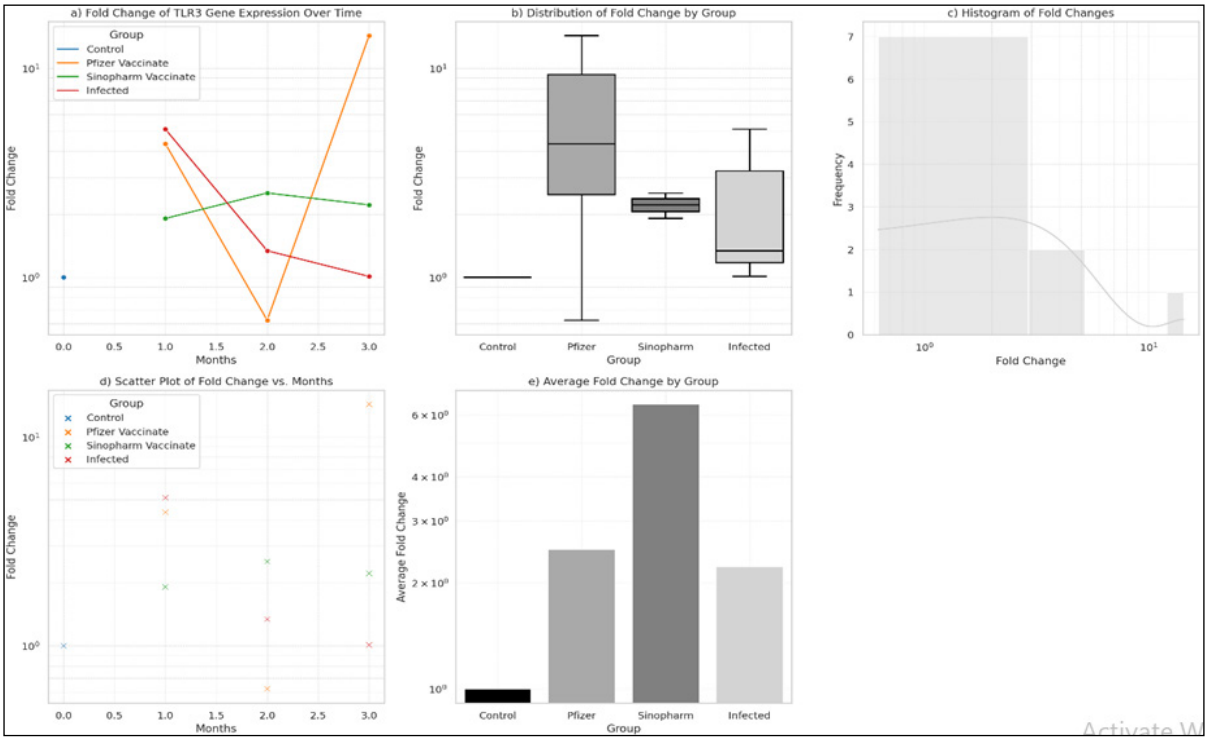

Figure 1(a).Fold Change Over Time. This line plot shows the variation in *TLR3* gene expression over three months for each group. (b).Distribution of Fold Change by Group, distinguishing each group: Control, Pfizer, Sinopharm, and Infected. (c).Histogram of Fold Changes. (d).Scatter Plot of Fold Change vs. Months. This scatter plot shows individual data points for fold changes at different time points for each group. (e).Average Fold Change by Group

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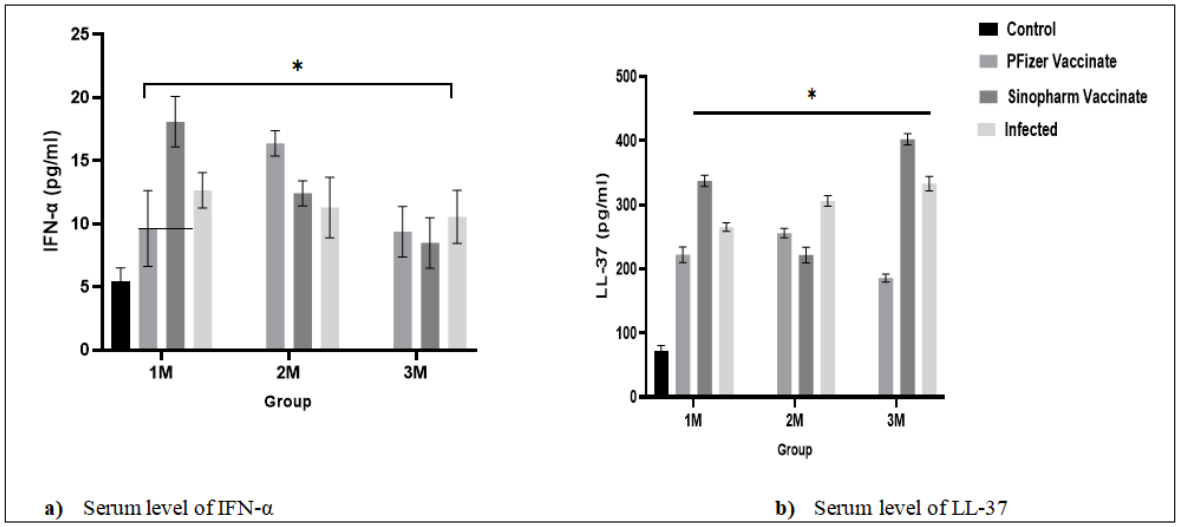

Figure 2(a).IFN-α and (b).LL-37 Serum Levels in the Infected and Vaccinated Groups

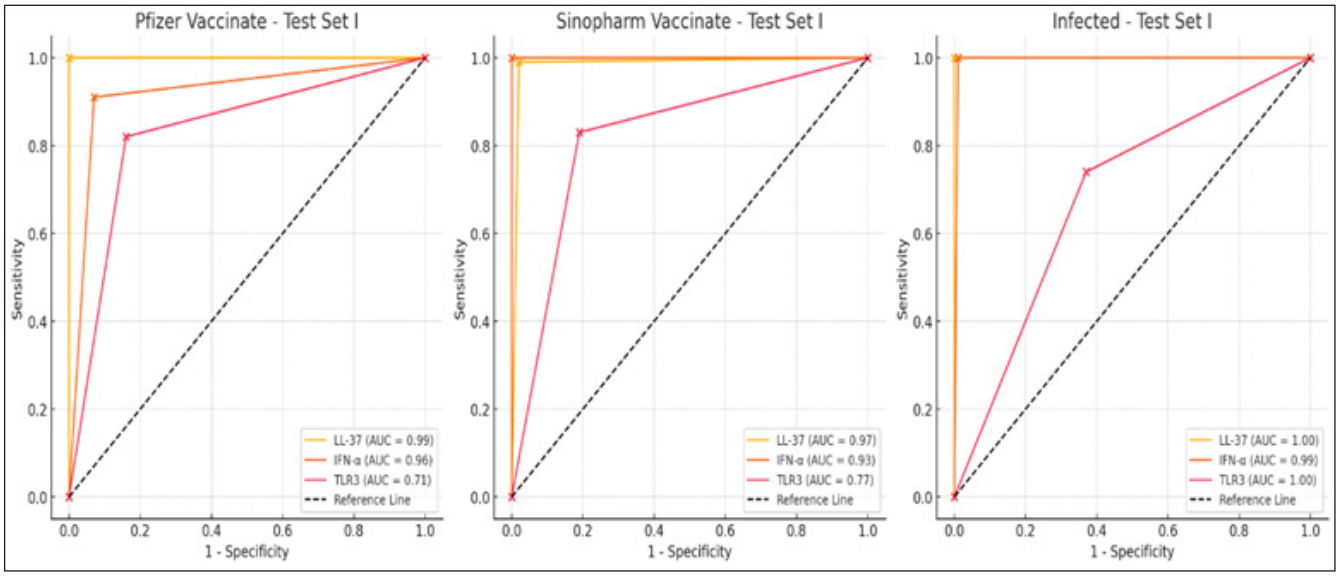

Figure 3.ROC Curve Analysis of Sensitivity and Specificity of Studied Biomarkers

Discussion

This study highlights the significant roles of *TLR3*, IFN-α and LL-37 in the immune response to COVID-19 infection and vaccination. Results showed that serum IFN-α levels were significantly increased in the infected group compared to controls. Notably, both the Sinopharm and Pfizer vaccinated groups exhibited significant differences in IFN-α levels compared to controls, particularly in the first month after vaccination. The analysis revealed a substantial increase in IFN-α in the Sinopharm vaccinated group after the first month compared to the first month after infection. However, no significant differences were observed between the Sinopharm vaccinated group in the second and third months compared to the infected group during the same period. Interestingly, the Pfizer vaccinated group showed significant increases in IFN-α in the second month post-vaccination compared to the infected group, indicating a robust early immune response to the Pfizer vaccine. These findings are supported by Nakhlband et al.[16] and Basolo et al.[17], who reported that dendritic cells produce significant quantities of IFN-α following vaccination. However, Altmann et al.[18] noted that while systemic immunity is boosted, current vaccines may not effectively prevent viral transmission, emphasising the need for enhanced mucosal immune memory in the respiratory system.

TLR3 expression was significantly elevated in the Pfizer vaccinated group compared to controls, with the highest expression observed three months post-vaccination. This upregulation of *TLR3* indicates a sustained immune response and the establishment of memory immune cells ready to respond to future viral challenges.[19] The Sinopharm vaccinated group also showed increased *TLR3* expression, albeit to a lesser extent than the Pfizer group. In contrast, the infected group exhibited a significant increase in *TLR3*

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expression in the first month post-infection, followed by a gradual decline. These variations in *TLR3* expression may be attributed to several factors, including immune tolerance and the early immune response focusing on different pathways before initiating *TLR3*-mediated responses. The gradual increase in *TLR3* expression over time reflects the maturation and strengthening of the immune system post-vaccination.[20] Additionally, *TLR3*'s role in recognising viral infections and initiating immune responses highlights its importance in antiviral defence mechanisms.[21]

The study also demonstrated that IFN-α levels were three times higher in individuals who received their second vaccine dose within a month compared to those who received it more than a month earlier. This suggests a gradual decline in T-cell activity over time, with the immune system undergoing a tolerance process to reduce pro-inflammatory cytokine production.[22] Additionally, excessive or uncontrolled IFN-α production, particularly in the late stages of COVID-19, can contribute to a "cytokine storm," leading to severe lung damage and adverse outcomes.[23] Regarding LL-37, significant elevations were observed in the Sinopharm vaccinated group compared to controls and infected groups. The Sinopharm vaccine appeared to stimulate mucosal immunity, leading to increased LL-37 production, particularly in the lungs, as noted by Bagheri-Hosseinabadi et al.[24] The Pfizer vaccinated group also showed significant increases in LL-37 levels, although to a lesser extent compared to the Sinopharm group. These findings suggest that both vaccines effectively enhance innate immune responses, with Sinopharm showing a more pronounced effect on mucosal immunity. The ROC analysis further demonstrated the diagnostic potential of IFN-α, LL-37, and *TLR3* as immune response markers.

Conclusion

Our findings underscore the critical roles of IFN-α, LL-37, and *TLR3* in the immune response to COVID-19. The differential expression of these markers in vaccinated and infected individuals provides insights into the dynamics of the immune response, highlighting the importance of sustained immune surveillance and the potential of these markers for diagnostic and prognostic purposes. Further studies are warranted to explore the long-term implications of these findings and to optimise vaccination strategies for better immune protection.

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Conflict of Interest: None

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