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Interplay of upper respiratory tract microbiota, ımmune response, and molecular dynamics in SARS-CoV-2 infection

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Abstract

Understanding the interplay between upper respiratory tract microbiota, immune responses, and molecular changes is critical for improving the diagnosis and management of SARS-CoV-2 infections. In this study, we investigated the association between respiratory tract microbiota composition, immune markers, and molecular diagnostic parameters in 123 RT-PCR-confirmed COVID-19 patients. Co-infection rates with Gram-positive and Gram-negative bacteria were high, particularly in the nasopharynx (35.4% and 64.4%, respectively), highlighting the risk of secondary bacterial infections. Diagnostic evaluation showed that RT-PCR cycle threshold (Ct) values and serological markers (IgG, IgM) had high sensitivity and specificity for distinguishing infection status. Lower Ct values correlated with higher viral loads and acute infection, while antibody levels reflected immune response dynamics. Significant correlations were observed between bacterial presence and immune parameters such as ACE-2, FASL, and RBD. These findings underscore the importance of integrated diagnostic approaches that consider microbiota, molecular, and immunological markers for effective management of COVID-19 and its complications.

Keywords: SARS-CoV-2, Immune response, Co-infection, Secondary bacterial infections, Respiratory microbiota, Molecular diagnostics.

1. Introduction

SARS-CoV-2 represents the pathogen for COVID-19, a very contagious virus with a single strand of genetic material. The immune response to SARS-CoV-2 has been very variable and dependent on immunopathogenesis, gender, inflammatory response, and age—the main determinants in disease progression [1, 2]. The virus may cause an overactive response of the immune system, a cytokine storm syndrome, which then would result in the overexpression of pro-inflammatory cytokines, chemotactic mediators such as ACE-2, FASL, RBD, and TLR-2, and high levels for immunoglobulins [3, 4]. Infections with SARS-CoV-2 and other respiratory viruses are often repleted with secondary bacterial infections, such as those by Klebsiella pneumoniae, Staphylococcus aureus, and Acinetobacter baumannii, which further complicate the clinical outcomes of the disease. Both saliva and oropharyngeal samples are shown to have higher sensitivity and specificity [5, 6].

In this respect, the cycle threshold value of RT-PCR tests is inversely proportional to the viral RNA load and proves very vital in the monitoring of COVID-19 infection, especially in asymptomatic and symptomatic cases [7, 8]. CT Values fit tightly into the severity of illness and outcomes of patients. This is one of the factors underlining the necessity of diagnosis tools' accuracy. In the same regard, many studies have pointed to the critical role of structural and non-structural viral proteins in evaluating viral load and prognosis in patients [9, 10].

This work would, therefore, wish to focus more intently on the respiratory microbiome, immune responses, and molecular alterations occurring during SARS-CoV-2 infection. The influences exerted by recombinant SARS-CoV-2 Spike, nucleocapsid, and envelope proteins, as well as immunological markers for these, are what we are particularly interested in. Research into diagnostic and prognostic factors of COVID-19 has been conducted, focusing mainly on secondary bacterial infection and its contribution to altering disease outcomes.

2. Materials and methods

2.1. Study population and clinical data collection

The study recruited patients aged 15 years or older with COVID-19 symptoms or at increased risk of COVID-19

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from Samarra General Hospital during 2022-2023. Nasopharyngeal swab samples were evaluated for viruses and bacteria using reverse transcriptase polymerase chain reaction and bacterial culture using Vitek 2 Compact (Biomerieux, France). Case data, medical history, and comorbidities were collected at admission and the first positive nasal swab for SARS-CoV-2 for each patient included in this study.

2.2. Sample collection and vaccination status classification

Samples were taken from diverse sites from which SARS-CoV-2 infected patients were aged from 10 to 70 years; this included both vaccinated and non-vaccinated patients, according to Iraq's health ministry. Vaccinated participants received varied types and dosages of vaccines and were classified accordingly. Nasopharyngeal swabs were preserved in 3 mL of VTM, which consists of a balanced salt solution (pH 7.4), 1% Penicillin G (100 U/mL), Amphotericin B (15µg/mL), and Streptomycin (50µg/mL).

2.3. SARS-CoV-2 PCR testing

A partial genome test for COVID-19 was performed by real-time reverse transcriptase polymerase chain reaction (RT-PCR) [Soft Biotech, Seoul, Korea] using specific primer sets targeting the Nucleocapsid (N), Envelope (E), and Spike (S) genes. Samples with a cycle threshold (Ct) value higher than 45 cycles were considered negative. Cycle threshold (Ct) values of the converted viral RNA were normalized to absolute amounts in order to produce a standard curve and estimate the diagnostic value of SARS-CoV-2. The detection of SARS-CoV-2 in patient samples was performed using conventional PCR with specific primer sets targeting the N, S, E, and H.K genes. The sequences of these primers are detailed in Table 1, which provides the basis for the molecular assays used throughout this study.

2.4. Statistical analysis

The statistical analysis for this study was conducted using the SPSS statistical software (version 20.0 for Windows). Spearman's rank correlation coefficient was used to assess the relationship between molecular variants and immunological parameters.

3. Results

This study investigated the relationship between microbiological samples from the respiratory system and the immunological and molecular changes in patients with SARS-CoV-2 in Iraq. The main findings are summarized below:

3.1. Bacterial isolates in COVID-19 patients

Patients with SARS-CoV-2 viral pneumonia frequently experience secondary respiratory bacterial infections, most commonly caused by *Streptococcus pneumoniae, Staphylococcus aureus*, and *Haemophilus influenzae*. This study aimed to elucidate the relationships between vaccination status, prior infections, the composition of the respiratory microbiome, and immune responses. Notably, a greater diversity of Gram-negative pathogens, including *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, was detected among the patient cohort.

The distribution of Gram-positive bacterial isolates among COVID-19 patients is summarized in Table 2. Notably, *Staphylococcus aureus* and Fusobacterium were predominantly found in oral cavity samples, while Streptococcus pneumoniae was the most common isolate in nasopharyngeal samples, highlighting the potential for secondary bacterial infections in different anatomical sites.

A comprehensive overview of Gram-negative bacterial isolates identified in the oral cavity and nasopharynx of COVID-19 patients is presented in **Table 3**. *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Moraxella catarrhalis* were among the most frequently detected pathogens, emphasizing the diversity and clinical significance of Gram-negative co-infections in this cohort.

The significant differences in bacterial prevalence between groups, confirmed by chi-square tests (Gram-positive: Chi-Square = 26.284, P-Value = 0.0008; Gram-

Table 1. Primer sequences used for SARS-CoV-2 gene detection by conventional PCR.

No.	Gene	Primer Sequence (5′–3′)
1	N	F: AACACAAGCTTTCGGCAGAC
		R: GCACCTGTGTAGGTCAACCA
2	S	F: GCACCAAAGGTCCAACCAGA
		R: CARATGTTAAASACACTATTAGCATA
3	E	F: ACTCATTCGTTTCGGAAGAGACA
		R: CAGATTTTTAACACGAGAGTAAACG
4	H.K	F: GTTTTGTAGTTTTTGGAGTTAGTGTTGTGT
		R: CTCAACCTACAATCAAAAACAACACAAACA

Table 2. Distribution of Gram-positive bacterial isolates in oral cavity and nasopharyngeal samples from COVID-19 patients.

Isolated Source	Bacteria	No. of Isolates	%	(Total) %
Oral cavity	Staphylococcus aureus	14	63.6	
	Fusobacterium	5	22.7	
	H. influenzae	3	13.6	41.5
Nasopharynx	Streptococcus pneumoniae	31	100%	58.4
(Total)		53		

Chi-Square = 26.284, P-Value = 0.0008

Table 3. Prevalence of Gram-negative bacterial pathogens in oral and nasopharyngeal samples of COVID-19 patients.

Isolated Source	Bacteria	No. of Isolates	%	(Total) %
Oral cavity	Klebsiella pneumoniae	4	3.0	
	Klebsiella oxytoca	6	4.4	7.40
Nasopharynx	Klebsiella pneumoniae	27	20.0	
	Klebsiella oxytoca	9	6.7	
	Acinetobacter baumannii	8	5.9	
	Pseudomonas aeruginosa	20	14.8	
	Moraxella catarrhalis	13	9.6	
	Lactococcus lactis	10	7.4	
	Escherichia coli	3	2.2	64.40
(Total)		135	100%	

Chi-Square = 51.267, P-Value = 0.00002.

Table 4. Demographic Characteristics of SARS-CoV-2 PCR-Positive Patients.

	Group	Number (n)	Percentage (%)
Sex	Male	**71**	**57.7%**
	Female	**52**	**42.2%**
Age	**Mean ± SD**	**Minimum**	**Maximum**
	49± 10.108	**15**	**70**

negative: Chi-Square = 51.267, P-Value = 0.00002), highlight the need for targeted antimicrobial therapies in these patients.

3.2. Distribution characteristics of patient outcomes

The prevalence of secondary bacterial pneumonia was highest among patients older than 50 years (26.02%), followed by those aged 40–50 years, with progressively lower rates observed in the 30–40 and 20–30-year age groups. Male patients were at increased risk for severe COVID-19 outcomes compared to females. Additionally, the prevalence of acute infection was notably higher in older age groups.

The distribution of secondary bacterial pneumonia across different age groups is illustrated in Figure 1. This figure highlights the increased prevalence of secondary bacterial infections among older patients, with the highest rates observed in individuals over 50 years of age.

3.3. Association of SARS-CoV-2 Ct values with patient demographics

Of the 240 patients included, 123 (51.2%) tested positive for SARS-CoV-2 using PCR tests. Among these, 57.7% (n=71) were male and 42.2% (n=52) were female, with ages ranging from 15 to 70 years (mean age: 49 ± 10.108 years). Lower cycle threshold (Ct) values, indicating higher viral loads, were observed among these patients.

The demographic characteristics of the study population, including sex and age distribution among PCR-positive COVID-19 patients, are shown in Table 4. This table provides essential context for interpreting the clinical and microbiological findings reported in this study.

3.4. Gene expression analysis via RT-qPCR

The study demonstrated that higher Ct values in patient samples were associated with lower viral loads, likely reflecting the effect of pre-existing antibodies in vaccinated individuals. RT-qPCR analysis revealed an inverse correlation between viral load and IgM levels, with symptomatic patients-both fully infected and vaccinated-exhibiting higher IgM titers. Conversely, IgG levels were positively associated with higher Ct values in infected patients, consistent with previous findings. This suggests that elevated anti-SARS-CoV-2 spike protein antibodies contribute to a reduction in viral load, as reflected by increased Ct values, highlighting the impact of immune response on viral dynamics.

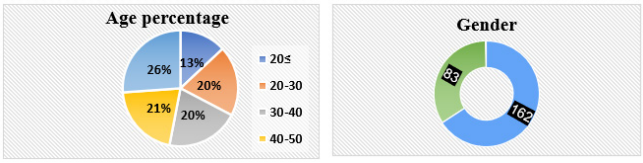

Fig. 1. Prevalence of secondary bacterial pneumonia by age group.

Gene expression analysis following varying degrees of SARS-CoV-2 exposure revealed significant differences in the expression of the spike, envelope, and nucleocapsid (N) genes among severe, moderate, and mild infection groups, as well as vaccinated and control groups. Notably, samples with higher viral RNA loads exhibited lower Ct values, consistent with the principle that increased viral copy number results in earlier detection during amplification. Patients with severe symptoms, particularly those in intensive care, had higher viral loads compared to those with mild or asymptomatic infection. Furthermore, viral load was observed to peak during the initial week of illness. The Ct values obtained from nasopharyngeal and oropharyngeal samples reliably reflected the viral burden in SARS–CoV–2–positive patients. Importantly, survivors were often identified by initial Ct values below 20, with one noted case presenting a Ct value of 17.4. These findings underscore the prognostic value of gene expression and Ct measurements in assessing disease severity and patient outcomes.

Amplification curves generated from RT-qPCR assays for selected SARS-CoV-2 genes are shown in Figure 2.

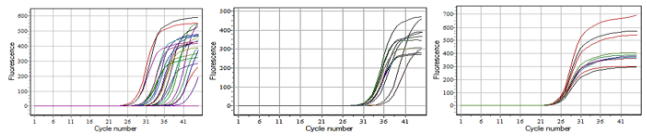

Fig. 2. Representative gene expression profiles and amplification curves for selected SARS-CoV-2 genes.

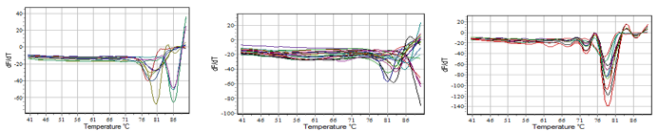

Fig. 3. Representative melting curves for selected SARS-CoV-2 genes detected in patient samples.

These curves demonstrate the typical gene expression profiles observed in patient samples, providing insight into the molecular detection and quantification of viral RNA.

The specificity of the RT-qPCR assays was confirmed through analysis of melting curves, as depicted in Figure 3. These melting curves validate the amplification of target genes and help distinguish specific products from non-specific amplification.

The mean fold change in expression levels of key SARS-CoV-2 genes across different patient groups is presented in Figure 4. This comparison reveals significant differences in gene expression associated with infection severity and vaccination status.

3.5. ROC analysis and discrimination between groups

ROC curve analysis was done to evaluate the accuracy of several in vitro diagnostic biomarkers like the cycle threshold levels for RT-PCR assay, IgM, and IgG antibodies for SARS-CoV-2 by using parameters like sensitivity, specificity, and AUC, which were the critical factors with respect to the determination of their efficacy for proper clinical diagnosis.

To assess the diagnostic performance of various biomarkers, ROC curve analysis was conducted for RT-PCR Ct values, IgM, and IgG antibody levels. The sensitivity, specificity, AUC, and optimal cutoff values for each marker are summarized in Table 5, demonstrating their utility in distinguishing between vaccinated and infected individuals.

The diagnostic performance of RT-PCR Ct values, IgM, and IgG antibody levels in distinguishing between vaccinated and infected individuals was evaluated using ROC curve analysis, as shown in Figure 5. The figure summarizes sensitivity, specificity, and AUC values for each marker.

Figure 6 presents the ROC curve analysis for IgM antibody levels, highlighting their effectiveness as a diagnostic marker for differentiating between vaccinated and infected patients.

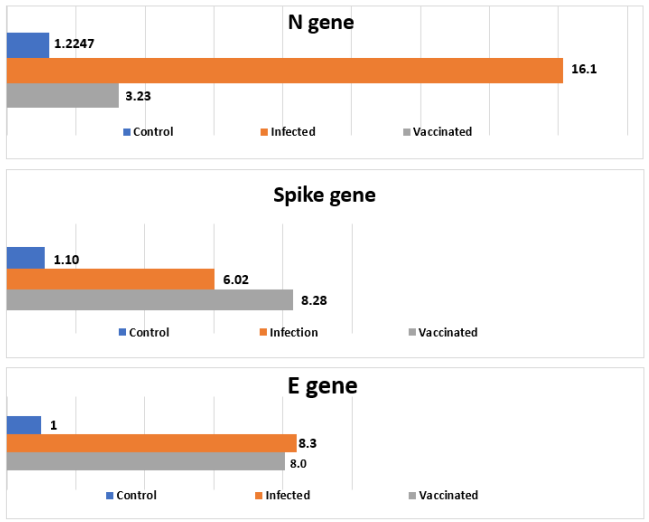

Fig. 4. Average fold change in expression of SARS-CoV-2-related genes among patient groups.

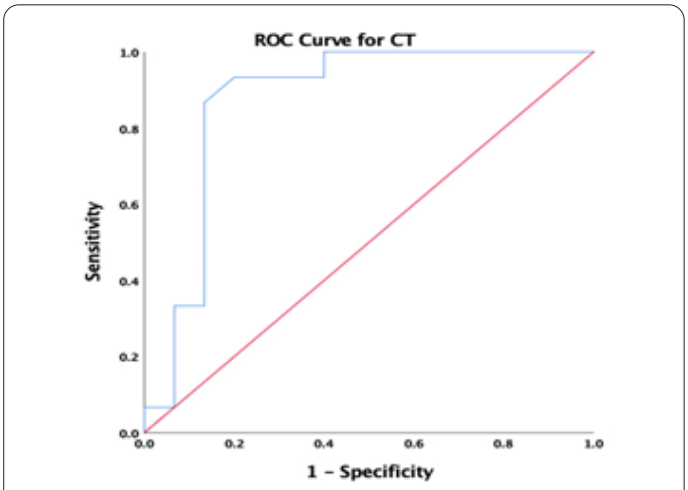

Fig. 5. ROC curve analysis of Ct value, IgM, and IgG for differentiating vaccinated and infected individuals.

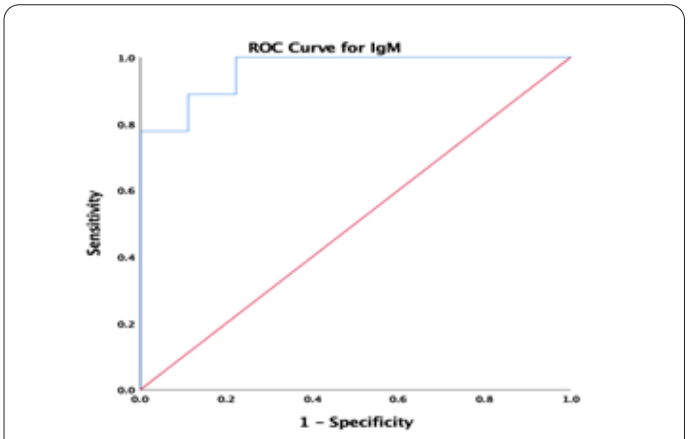

Fig. 6. Diagnostic performance of IgM antibody levels for distinguishing vaccinated from infected patients (ROC analysis).

Table 5. Diagnostic performance of Ct value, IgM, and IgG for differentiating vaccinated and infected individuals (ROC analysis).

Parameter	Cutoff	Sensitivity (SE)	Specificity (SP)	AUC	Standard Error (SE)	95% CI	P-value
Ct	> 31.72	0.9247	0.8572	0.873	0.074	0.728-1.00	0.0014*
IgM	> 7.034	0.9002	0.8997	0.963	0.039	0.886-1.000	0.001*
IgG	> 19.48	0.9947	0.9597	0.990	0.016	0.958-1.00	0.0003*

*Significant (p-value < 0.05).

The ROC curve for IgG antibody levels, depicted in Figure 7, demonstrates the utility of IgG as a biomarker for distinguishing infection status among the study population.

3.6. Comparison of SARS-CoV-2 antibody results and RT-PCR Ct values

To support this observation, a comparative analysis was performed to examine the relationship between average Ct values and the presence of IgM and IgG antibodies across different patients. As shown in Table 6, a general trend emerged: median Ct values in patients with positive IgM and IgG antibodies were lower, indicating higher viral loads. This suggests that the detection of these antibodies, particularly IgM, may serve as an indicator of recent infection and active viral replication.

The relationship between SARS-CoV-2 antibody status (IgM and IgG) and RT-PCR Ct values is detailed in Table 6. This table illustrates that lower Ct values, indicative of higher viral loads, are generally associated with the presence of IgM and/or IgG antibodies, supporting their role as markers of recent or ongoing infection.

The association between SARS-CoV-2 antibody status (IgM and IgG) and RT-PCR Ct values is illustrated in Figure 8. This figure shows that patients with positive antibody results tend to have lower Ct values, indicative of higher viral loads and recent infection.

3.7. Correlations between immunological parameters and bacterial presence

The study also examined correlations between the presence of gram-positive and gram-negative bacteria and various immunological markers, including ACE-2, TLR2, RBD, FASL, IgG, and IgM. Significant correlations were found, indicating complex interactions between bacterial infections and immune responses.

Correlations between the presence of Gram-positive and Gram-negative bacteria and various immunological parameters (including FASL, RBD, ACE, IgG, IgM, and TLR2) are presented in Table 7. These findings suggest complex interactions between bacterial co-infections and host immune responses in COVID-19 patients.

3.8. Immunological parameters

Our study reported a significant difference ($P < 0.05$) between Gram-positive and Gram-negative bacteria concerning the levels of ACE-2.

Correlations between the presence of Gram-positive and Gram-negative bacteria and various immunological parameters are visualized in Figure 9. The figure provides

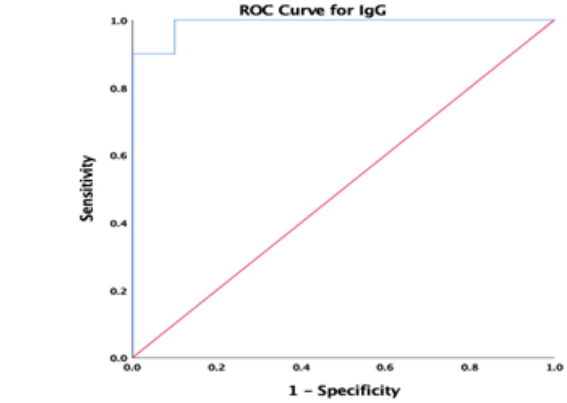

Fig. 7. Diagnostic performance of IgG antibody levels for differentiating vaccinated from infected patients (ROC Analysis).

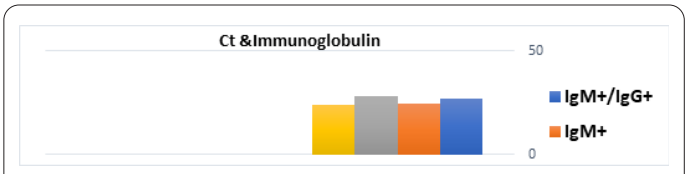

Fig. 8. Relationship between SARS-CoV-2 IgM/IgG antibody status and RT-PCR Ct values.

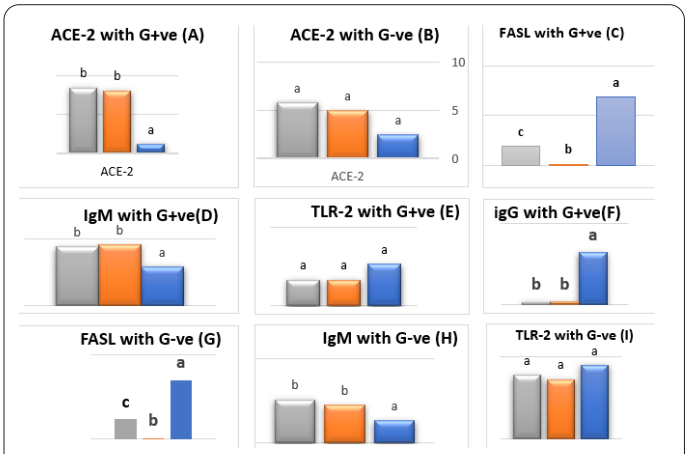

Fig. 9. Associations between bacterial co-infection and key immunological parameters in COVID-19 patients (A-I).

Table 6. Association between SARS-CoV-2 antibody status and RT-PCR Ct values.

Antibody Results	Number (n) & Percentage (%)	Average Ct Value
IgM (+) IgG (+)	110 (45.8%)	26.97
IgM (+) IgG (-)	80 (33.3%)	24.50
IgM (-) IgG (+)	18 (7.5%)	27.90
IgM (-) IgG (-)	32 (13.3%)	23.81

Table 7. Correlations of Gram-positive and Gram-negative bacteria with immunological parameters.

Parameter	Correlation Coefficient	P-value
FASL - RBD	0.469*	0.037
ACE - FASL	0.695**	0.001
ACE - RBD	0.223	0.345
IgG - RBD	-0.301	0.197
IgM - RBD	0.019	0.936
TLR2 - IgG	-0.308	0.187

a comprehensive overview of the complex interactions between bacterial co-infections and host immune responses in COVID-19 patients.

According to the study, an integrated diagnostic and therapeutic approach in managing COVID-19 patients, particularly those suffering from co-infections due to bacteria, could make a big difference and would surely call for targeted treatments with better clinical outcomes.

4. Discussion

COVID-19 causes upper respiratory infections that can be mild or severe. Mild cases sometimes get worse and turn into pneumonia. The PCR technique has been used as the main diagnostic method for SARS-COV-2 patients. They also use other methods like computed tomography and blood tests. Scientists are looking into how lab-made SARS-CoV-2 proteins have an impact on immune system markers. The study population was evaluated based on gender, revealing a higher infection rate in males (57.7%) compared to females (42.2%). The Receiver Operating Characteristic (ROC) curve analysis showed that the cycle threshold (Ct) value has a sensitivity of 0.924 and a specificity of 0.857, with an AUC of 0.873, underscoring the efficacy of RT-PCR in estimating viral RNA load [11]. Although RT-PCR represents the gold standard for SARS-CoV-2 diagnosis, it is not as widely available; therefore, radiologic and serologic tests are needed. Serologic tests, in particular, SARS-CoV-2 IgG and IgM antibody tests, could help in the diagnosis of past infections and monitoring for immunity, particularly regarding vaccination. In contrast to RT-PCR, antibody detection is faster and more accessible, but on the other hand, RT-PCR has higher diagnostic sensitivity and specificity. Studies comparing nasopharyngeal and oropharyngeal swabs revealed that both types of samples have equivalent sensitivity in the detection of COVID-19, which correlated well with symptoms and viral load in the presence of IgG antibodies [12]. Detection methods for antibodies also become important for ascertaining symptomatic and asymptomatic carriers of the virus, since they can point to past infection and potential immunity. In the present study, sensitivities and specificities against SARS-CoV-2 of the rapid serological tests measuring specific IgG/IgM levels were 0.9947 and 0.9002, with specificities of 0.9597 and 0.8997, respectively. These findings are in agreement with previous reports [13, 14], where similar serological assays exhibited high sensitivity and specificity, further highlighting their diagnostic utility. Ct value during RT-PCR screening is inversely proportional to the viral load in the sample, while lower Ct values represent higher levels of viral RNA [15]. The threshold cycle value Ct, with the expression of different genes (S, N, E) of SARS-CoV-2 from the current study, was a good predictor of the viral load and infection status. It has recently been found to play a very important role in defense against viral infection and also in secondary bacterial infections, mostly caused by gram-positive bacteria. Recognition of the SARS-CoV-2 envelope protein by TLR2 could activate immune responses, a process thought to lead to a cytokine storm [16]. It has been reported that inhibitors of the TLR2 signaling pathway may attenuate the severity of COVID-19 by intervening in these immune responses[17, 18]. This study showed that, in patients with severe COVID-19, there was an increase in the expression of FASL correlated to lymphocyte apoptosis and overall disease severity [19]. The increase in FASL correlates to the age-related inflammation that takes place through the process of immunosenescence, and therefore it predisposes elderly people more to developing severe complications due to COVID-19 [20]. Vaccination strategies have varied across the world, and their effectiveness may differ with demography, particularly with age. It has been shown that with age increase, there is a loss of efficiency in immune responses, underlining the challenges brought about by immunosenescence [21, 22].

This article underlines the role of SARS-CoV-2 infection, secondary bacterial infection, and host defense response in COVID-19. It enumerates the importance of RT-PCR for diagnosis and assessment of viral load, and serological tests for establishing past infection and immunity. The identification of Streptococcus pneumoniae and Staphylococcus as important co-infections that need targeted therapy is discussed. Immunological markers ACE-2, TLR2, and FASL underpin immune dysregulation with possible severe outcomes, especially in the elderly. This calls for further studies that are aimed at carrying out a comprehensive refinement of diagnosis and therapeutic strategies, besides helping to understand the long-term consequences following SARS-CoV-2 infection.

Informed consent

The authors announced that the patients in this study were used with the ethical approval issued by the Iraqi Ministry of Health-Samarra General Hospital with number (15) dated 8/1/2022.

Availability of data and materials

Data supporting the findings of this study are available from the corresponding author upon reasonable request, based on the analysis of the study patients' data.

Authors' contributions

Waqas Saadi Mahmood, Melda Dölarslan : researcher design and supervision, sahar Abdul wahhab Abdul wahid:implemention of all laboratory precedures, Ammar Mohmed Alwan :sample collection.

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There is no.

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