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Original article

Role of *CD27* and *SAMHD1* and their genetic susceptibility to COVID-19

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ABSTRACT

SARS-CoV-2, which initiated the worldwide COVID-19 epidemic in 2019, has rapidly emerged and spread, resulting in significant public health challenges worldwide. The COVID-19 severity signs and their association with specific genes have been investigated to better comprehend this phenomenon. In this study, several genes were investigated to see whether they correspond with COVID-19 sickness severity. This research aims to determine and evaluate certain gene expression levels associated with the immune system, as these genes were reported to play important roles in immune control during the COVID-19 outbreak. We analyzed two immunity-linked genes: *CD27* and *SAMHD1* in COVID-19 patients' samples using RT-PCR, compared them to the samples from recovered, immunized, and healthy individuals. These data were examined to determine the potential relationships between clinical patterns, illness severity, and progression, and SARS-CoV-2 infection immunology.

We observed that *CD27* gene expression was higher in COVID-19 vaccinated and control groups, but lower in active and recovered COVID-19 patients. On the other hand, *SAMHD1* gene expression was elevated in infected and recovered COVID-19 groups. According to our study, the proteins CD27 and SAMHD1 are essential for controlling the immunological response to COVID-19. Changes in their expression levels could increase the susceptibility of patients to severe complications associated with the disease. Therefore, the gene expression level of these proteins could serve as viable prognostic markers for COVID-19.

1. Introduction

The World Health Organization (WHO) classified the 2019 coronavirus disease (COVID-19) epidemic on March 11 to be a worldwide pandemic since it began in China and rapidly became a public health crisis worldwide. The virus causing the coronavirus epidemic in 2019 (COVID-19) is named the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This virus has appeared and increased rapidly, causing public health issues all over the globe. The implications of COVID-19 symptom severity are not well understood. To control the outbreak of COVID-19, several countries around the world implemented lockdowns and household quarantines. This was done because even though mild to moderate symptoms are present in the majority of COVID-19 patients, the condition can still result in serious medical problems and even death in those with preexisting chronic disease (Wu, 2020). Coronaviruses (CoVs), members of the family Coronaviridae, are encapsulated RNA viruses linked with pulmonary and additional illnesses (e.g., gastrointestinal and neurological) in a variety of animal species (Glass, et al., 2004).

There are several immunological problems linked to severe COVID-19 patients, including T-cell deficiency and cytokine release syndrome. These defects can be life-threatening and are a significant concern during the pandemic (Ni et al., 2020). Recently, There have been reports of SARS-CoV-2-specific T cells in COVID-19 cases

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(Ni et al., 2020), and their possible defensive function has been concluded from studies of patients recovering from SARS (Li et al., 2008) and MERS (Zhao et al., 2017). Host responses to viral infections are reliant on the contact of the body's innate and adaptive immune systems. T lymphocytes, including CD4 T lymphocytes and CD8 T lymphocytes, are essential for the immune system's successful antiviral responses against pathogens (Jung & Pape, 2002). However, the mechanism by which T-cell dysregulation contributes to the etiology of severe COVID-19 is poorly understood.

A variety of cells, including memory B cells and plasma cells (PCs) that produce antibodies, exhibit a more frequent and similar response to antigens compared to naive B cells. This response plays a crucial role in maintaining immunological memory within the immune system. The production of pathogen-specific B cells and antibodies is essential for protective immunity against infections and vaccines (Blanchard-Rohner et al., 2009). In human, about 40% of the B cells of peripheral blood were found to express CD27 in a basic manner (Klein et al., 1998). The majority of T cells, including naive T cells and Treg cells, constitutively express CD27 at high levels, making it unique as a T cell co-stimulatory molecule (Hintzen et al., 1993).

SAMHD1 is a molecule that participate in the pathways of COVID-19-related neurological issues (Khan and Sergi 2020). The virus-induced upregulation of the coding protein in infected cells suggests that it may help to prevent pro-inflammatory reactions brought on by tumor necrosis factor (TNF) (Khan & Sergi, 2020). According to recent research, SAMHD1 is a potent antiviral restriction factor that can target a variety of different therapeutically relevant viruses (Majer et al., 2019). SAMHD1, like other innate immunity proteins, by disrupting the virus's life cycle, it plays a vital role in producing innate and adaptive immune responses to protect animals against viruses (Roux et al., 2019).

There has been limited research has been conducted to compare the importance of *CD27* and *SAMHD1* genes in immunity among COVID-19 patients who have received two doses of the vaccine and recovered from COVID-19, versus healthy controls. Also, the infection may influence gene expression (Peterson et al., 2023). Therefore, this research aims to determine and evaluate certain gene expression levels associated with the immune system including SAMHD1 and CD27 in patients with COVID-19, as these genes were reported to play important roles in immune control during the COVID-19 outbreak.

2. Materials and methods

2.1. Patients and control

The study has been conducted on 63 adults grouped into four categories as: 36 diagnosed as confirmed COVID-19 cases (C-19) in accordance with the diagnostic recommendations founded by the Ministry of Health in Saudi Arabia, by positive detection of respiratory specimens for SARS-CoV-2 on a clinical, radiological, and laboratory level by (RT-PCR) with LightCycler 480 II Roch, Germany. Between March 2021 and July 2021, they received admission to King Abdulaziz Hospital in Jeddah, Saudi Arabia. Nine cases of that have received two doses of COVID-19 vaccines, because of the administration of the second dose while collecting the sample (C2V-19), 13 cases who have recovered from COVID-19 during 6 months after infection (CR-19) and 5 healthy controls (Control) from King Abdulaziz Hospital Healthy medical staff that tested negative for SARS-CoV-2 using RT-PCR. Since the majority of the population was either currently or formerly COVID-19-infected, the limited size of the control group was assigned to the unavailability of healthy individuals who could serve as controls (those not infected with COVID-19 and not immunized) available during the pandemic. The following standards were used to choose all of the participants: Participants were all Saudis (aged 20–60) who signed a permission form. Exclusion criteria included a history of pulmonary disease and chronic diseases.

2.2. Consent form and ethical approval

The research was conducted with the approval of the Research and Studies Department – Jeddah Health Affairs Institutional Review Board (IRB) registration number with KACST, KSA: H-02-J-002 research number 1373 in March 2021. This research was carried out in agreement with the guidelines of the International Medical Association's code of ethics (Declaration of Helsinki) and Good Clinical Practice guidelines. Patients were asked to sign a permission form before collecting specimens.

2.3. Quantitative real-time PCR (RT-PCR) analysis

Total RNA has been extracted from whole blood sample (10––20 ml) using a QIAamp RNA Blood Mini Kit (cat. No. 52304, Qiagen, Germany). cDNA was synthesized from isolated RNA samples (300 ng) using cDNA reverse transcription kit (cat. No. 4368814, Thermo Fisher Scientific, USA). RNAse inhibitor (cat. No. N8080119, Thermo Fisher Scientific, USA) was used with the cDNA reagent to prevent RNA degradation. The purity and quantity of the total RNA was detected with DeNovix DS-11 highly sensitive spectrophotometer at 260 nm.

A specifically designed primers for RT-PCR reaction (Livak and Schmittgen, 2001) were designed to measure the mRNA expressions from *CD27*, NM_001242.5 (Cat. No. PCR-CDA-HSA-CD27-11, Haven Scientific, Saudi Arabia) and *SAMHD1*, NM_001363729.2 (Cat. No. PCR-CDA-HSA-SAMHD1-11, Haven Scientific, Saudi Arabia). To perform RT-PCR, SteadyTaq PCR Master Mix (PCR9505) for end-point PCR, and with EverGreen Universal qPCR Master Mix (PCR5505) for dye-based real-time qPCR according to the following in Table 1.

The 2 − ΔΔCt method)fold change) was adopted (Livak and Schmittgen, 2001), this is a practical method for examining the relative changes in gene expression from RT-PCR experiments, and the relative expressions for *CD27* and *SAMHD1* were normalized accordingly against the following housekeeping genes (B2M, GAPHD and RPL13A). Three separate experimental replicates were used for each assay.

2.4. Statistical analysis

Processing the data and creating the graphics were done using GraphPad Prism v7.0 (GraphPad Software, USA), dataset outliers were excluded for 2 − ΔΔCt using the ROUT (robust regression and outlier removal). Data has been analyzed using the appropriate statistical analysis as *t* test, for multiple comparisons, ANOVA and Kruskal-Wallis test with Dunn correction was chosen, if the *p*-value is<0.05, it is judged as significant.

Table 1
qPCR cycling parameters.

Component	Volume per reaction	Final concentration
SteadyTaq MM(2X) OR EverGreen MM (2X)	10 μL	1 X
CD27/*SAMHD1* assay (20X)	1 μL	1 X
Template cDNA	Variable	10 pg – 100 ng
PCR-grade water	Up to 20 μL	–

3. Results

In the current study, initially 63 samples were collected, (COVID-19 patients from King Abdulaziz Hospital and the rest from King Fahad Medical Research Center from December 2020 to June 2022.

Simplex RT-PCR was used to test all of the primers and probes. To produce the best fluorescence signal, the RT-PCR apparatus was carefully calibrated before to performing the reactions. The simplex reactions for *CD27* and *SAMHD1* genes, as well as housekeeping genes, were then carried out in triplicate.

The study subjects were only evaluated by gender, not further characteristics, and by their Ct and $2 - \Delta\Delta Ct$ values no correlation with age is given. In the 63 subjects, 33 (52%) and 30 (48%) were female and male, respectively.

3.1. Relative changes in CD27 gene expression from RT-PCR

Table 2 presents the mean cycle threshold (Ct) value accompanied by the corresponding standard deviations (SD). The mean Ct value for *CD27* level in the control was 26.09 ± 7, 24.42 ± 1.26 for C2V-19, 26.28 ± 7.75 for CR-19 and 30.36 ± 7.76 for C-19. After applying the $2 - \Delta\Delta Ct$ method and excluding outliers, the average – $2\ \Delta\Delta Ct$ value with standard deviations (SD) are shown in Table 3.. The mean of $2 - \Delta\Delta Ct$ value for *CD27* level in the control was 98.08 ± 98.59, 97.56 ± 87.79 for C2V-19, 4.467 ± 4.63 for CR-19 and 1.685 ± 1.61 for C-19 and. Fig. 1 shows the comparison of $2 - \Delta\Delta Ct$ among the test group. Multiple comparison test revealed statistically significant differences for *CD27* gene expression level among all test group in ($p < 0.05$).

3.2. Relative changes in SAMHD1 gene expression from RT-qPCR

Tables 4 shows the average cycle threshold (Ct) value with standard deviations (SD). The mean Ct value for *SAMHD1* level in the control was 24.84 ± 3.7, 20.64 ± 0.75 for C2V-19, 28.28 ± 7.35 for CR-19 and 29.42 ± 11.07 for C-19. After applying the $2 - \Delta\Delta Ct$ method and excluding outliers, the average – $2\ \Delta\Delta Ct$ value with standard deviations (SD) are shown in Table 5.. The mean of $2 - \Delta\Delta Ct$ value for *SAMHD1* level in the control was 8.84 ± 5.41, 4.5 ± 1.4 for C2V-19, 15.6 ± 7.12 for CR-19 and 11.4 ± 11 for C-19. Fig. 2 shows the comparison of $2 - \Delta\Delta Ct$ among the test group. Multiple comparison test revealed no statistically significant differences for *SAMHD1* gene expression level among all test group except for the control and C-19 group ($p < 0.05$).

3.3. Relative changes in ($2 - \Delta\Delta Ct$) between CD27 and SAMHD1 gene expression

Fig. 3 shows the comparison of $2 - \Delta\Delta Ct$ between *CD27* and *SAMHD1* among the test group. T test revealed no statistically significant differences between *CD27* and *SAMHD1* in the control group ($p > 0.05$). To the contrary statistically significant differences between *CD27* and *SAMHD1* were reported in CR-19 ($p < 0.001$), CR-19 ($p < 0.0001$) and C2V-19 ($p < 0.01$).

Table 2
The Ct value revealed in qPCR assay for *CD27*.

Characteristics	N	Ct-value for *CD27* (Mean ± SD)
Control	5	26.09 ± 7
C2V-19	9	24.42 ± 1.26
CR-19	13	26.28 ± 7.75
C-19	36	30.36 ± 7.76

Table 3
The $2 - \Delta\Delta Ct$ value revealed in *CD27* qPCR assay for the subject after excluding outliers.

Characteristics	N	$2 - \Delta\Delta Ct$ for *CD27* (Mean ± SD)
Control	5	98.08 ± 98.59
C2V-19	9	97.56 ± 87.79
CR-19	11	4.467 ± 4.63
C-19	29	1.685 ± 1.61

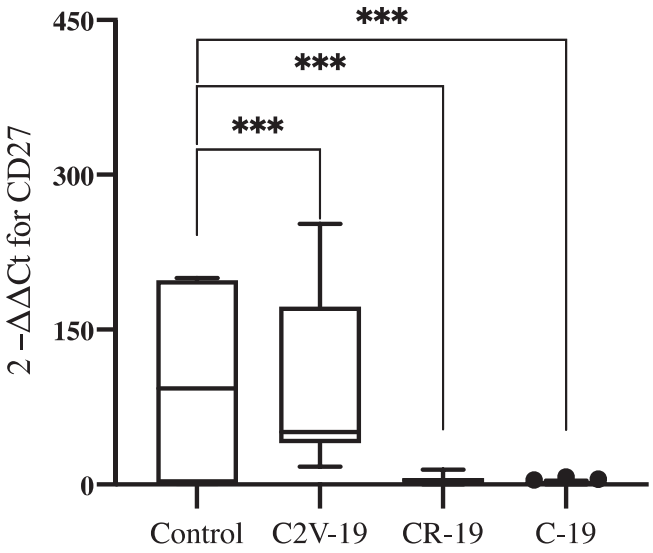

Fig. 1. Box plot showing a comparison of ($2 - \Delta\Delta Ct$) in *CD27* expression through quantitative RT-PCR in different test group. A significant difference is denoted by $^{*}p < 0.05^{***}$.

Table 4
The Ct value revealed in qPCR assay for the *SAMHD1*.

Characteristics	n	Ct-value for *SAMHD1* (Mean ± SD)
Control	5	24.84 ± 3.7
C2V-19	9	20.64 ± 0.75
CR-19	13	28.28 ± 7.35
C-19	36	29.42 ± 11.07

Table 5
The $2 - \Delta\Delta Ct$ value revealed in *SAMHD1* qPCR assay for the subject after excluding outliers.

Characteristics	n	$2 - \Delta\Delta Ct$ for *SAMHD1* (Mean ± SD)
Control	5	8.84 ± 5.41
C2V-19	9	4.5 ± 1.4
CR-19	11	15.6 ± 7.12
C-19	29	11.4 ± 11

4. Discussion

The COVID-19 pandemic has had an extraordinary impact on healthcare systems worldwide, with high mortality rates in hospitalized patients, while some patients remain asymptomatic or have mild symptoms (Docherty et al., 2020; Rivett et al., 2020). The ultimate purpose of this research assesses the expression levels of genes using RT-qPCR associated with the immune system, including SAMHD1 and CD27, in patients with COVID-19, as these genes are known to serve as important role in immune control.

Molecular diagnostics is a more sensitive method allowing diagnosis of etiology and PCR is the most widely used molecular

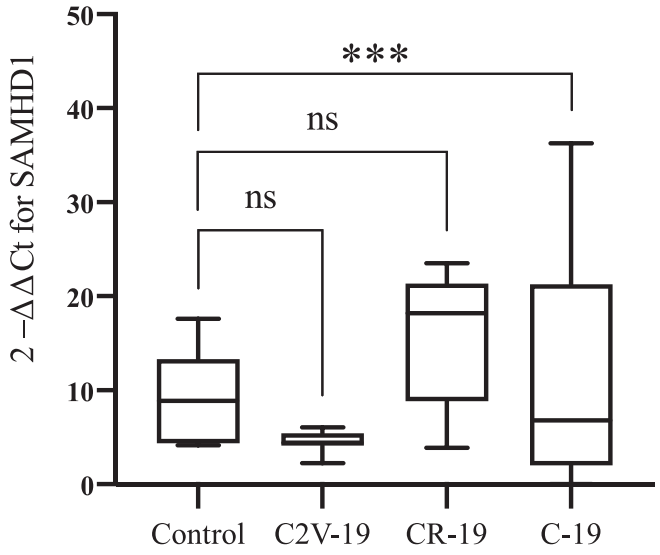

Fig. 2. Box plot showing comparison of (2 − ΔΔCt) in *SAMHD1* expression through quantitative RT-PCR in different test group. A significant difference is denoted by $^{*}p < 0.05^{***}$, Ns = Not significant.

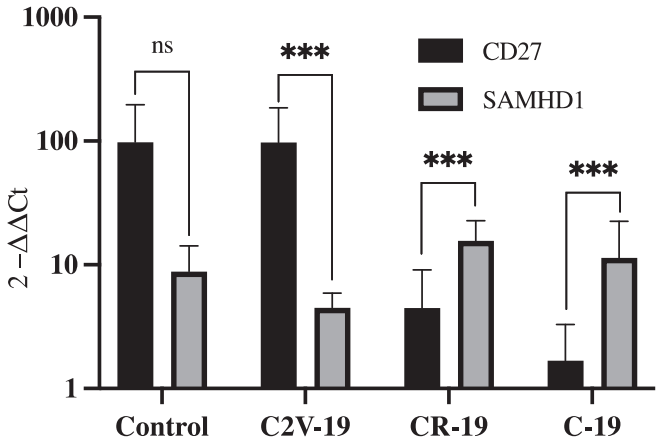

Fig. 3. Bar chart showing comparison of (2 − ΔΔCt) between *CD27* and *SAMHD1* gene expression among the test group. A significant difference is denoted by $^{*}p < 0.05^{***}$, Ns = Not significant.

diagnostic technique. Therefore, there is an urgent need to find a prognostic molecular biomarker for COVID-19. In order to identify SARS-CoV-2 in 63 clinical samples, expression for both *CD27* and *SAMHD1* gene were examined using qRT-PCR. Our work is constrained by sample size, insufficient demographic data, and the requirement for an independent validation cohort. Our cases were devided into four groups: COVID-19 cases, cases of that have received two doses of COVID-19 vaccines, cases who have recovered from COVID-19 and healthy controls. Regardless, our findings provide emphasis on the specific characteristics of COVID-19′s prognostic genes and offer input into molecular pathogenesis.

Having a severe COVID-19 infection is not completely reliant on having the virus because the majority of infections are mild or moderate (Guan et al., 2020). Because this disease characterized by the development of excessive inflammation, which involved in the production of cytokines (Burke et al., 2020), immature monocyte influx (Mann et al., 2020), and activation of T-lymphocyte (+). The limited studies in the literature on COVID-19 and gene expression is generally consistent with our findings (Jain et al., 2021, Kwan et al., 2021).

To the best of our current knowledge, this work represents the first investigation into the identification of *CD27* and *SAMHD1* gene expression in several donor groups, including those with COVID-19, those who have recovered from COVID-19, and vaccinated individuals serving as controls. Our findings suggest differential expression levels between these samples' groups.

Although markers of inflammation such as C-reactive protein (CRP) and serum IL-6 levels are commonly used to indicate disease severity, they are not perfect predictors (Bentivegna et al., 2021; Bennett et al., 2021). COVID-19 severity is determined by the equilibrium of the host's immune response and viral stimulation. In severe situations, this reaction becomes uncontrollable, resulting in hyperinflammation defined by excessive quantities of cytokines and pro-inflammatory chemicals, known as a cytokine storm (Mangalmurti and Hunter 2020).

The behavior of viruses, such as how they shed or the variation in their genetic sequences, cannot be used to accurately predict clinical outcomes (Liu, 2020). Instead, genome-wide expression profiling is a more effective and unbiased approach that can be used to examine how molecular pathways are activated or suppressed in relation to disease symptoms. This technique can also help identify potential biomarkers that can predict disease severity on an individual level and can be used to discover new therapeutic targets. Developing early predictors that can identify patients at risk of decompensation following SARS-CoV-2 infection would be very beneficial.

This study reports the association between gene expression levels of *CD27* and *SAMHD1* genes and COVID-19 status, severity, and adverse outcomes. We used Simplex qRT-PCR to analyze the gene expression levels of *CD27* and *SAMHD1* in 63 COVID-19 patients, including active COVID-19 patients, vaccinated patients, recovered patients, and controls.

In the current study, we found that *CD27*, a marker for of the early stages of activation and lung tissue destruction, gene expression levels were significantly elevated in the COVID-19 vaccinated and control groups, whereas the expression levels of *CD27* were lower in the active and recovered COVID-19 patients. The level of gene expression of *SAMHD1* was found to be elevated in COVID-19 active and recovered patients. CD27 is a marker of memory B cells, there have been several studies that have investigated the role of humoral immune response and its relation to COVID-19 status. A recent study by Woodruff et al. investigated that severe COVID-19 patients have extrafollicular double negative B cells, which function in pathology of immunity and short-lived immunity following severe SARS-CoV-2 infection (Woodruff et al., 2020). Analysis of B cell populations in these studies revealed that extrafollicular double negative B cells, which are distinguished by the lack of CD27 and igD, were prominently observed in severe cases of COVID-19 (Woodruff et al., 2020; Kaneko et al., 2020).

Wauters et al conducted a study to compare different subsets of B cells in COVID-19 patients. They found an increase in matured naïve B-cells (CD27 negative) and a reduction in memory B-cells (CD27 positive) in COVID-19 patients. However, they did not find any significant correlation between CD27 positive or negative B cells and disease severity (Wauters, 2020). In another study by Hernandez et al, they observed significant changes in double negative B cells in response to COVID-19 infection. They further divided CD27 negative memory B cells into four subsets and discovered a significant decrease in their levels in severe and critical cases of COVID-19 (Sosa-Hernández et al., 2020).

Golchere et al published a case report linking COVID-19 infection to congenital CD27 deficiency in a 20-month-old boy (Golchehre et al., 2023). Furthermore, another study by found increased expression of *CD27* and other B cell genes in the early stages of COVID-19 recovery, indicating its potential as a biomarker for recovery. Finally, Al balushi et al discovered that a lower

percentage of circulating naïve CD27 + T cells in the early stages of SARS-CoV-2 infection independently predicted ICU admission or death in COVID-19 patients (Al Balushi et al., 2021).

SAMHD1 was identified by Laguette et al as a restriction factor that largely prevents HIV-1 infection in human dendritic and myeloid cells (Laguette et al., 2012). The protein SAMHD1 has been implicated in the pathogenesis of Aicardi-Goutieres syndrome, a genetic encephalopathy that presents with symptoms resembling those of congenital viral infection. It has been postulated that SAMHD1 functions as a suppressor of the interferon response. There have been suggestions regarding how SAMHD1 inhibits the replication of HIV-1. One theory is that its inhibitory effect is due to its action as a dNTPase. Another suggestion is that SAMHD1 may limit the replication of HIV-1 through its RNase activity (Oo et al., 2022).

Masood et al conducted a study to report *SAMHD1* expression, a gene involved in the interferon response, in COVID-19. They observed that the level of expression of *SAMHD1* are associated to the difficulty and stage of COVID-19 disease, with upregulation in asymptomatic cases and downregulation in severe cases (Masood et al., 2021). SAMHD1 may be used as a therapeutical target to enhance the immunity in COVID-19 patients by inhibiting its expression (Oo et al., 2022).

SAMHD1 has been shown to be an effective antiviral factor against several medically relevant viruses. However, one study reported that SAMHD1 might be proviral in CHIKV and ZIKV infections, promoting their replication (Wichit, 2019). The contrasting results could be due to the absence of reverse transcription in these viruses. Understanding how SAMHD1 functions in COVID-19 infection is crucial, as it is essential in determining how the innate and adaptive immune response will develop.

It's well evident now that SAMHD1 is an important factor in modulating the body's natural immune responses. It has been proven to effectively hinder many viruses, but viruses have also developed mechanisms to evade SAMHD1′s block (Majer et al., 2019). The significance of SAMHD1′s ability to boost the reproduction of specific viruses by inhibiting the NF-B signaling pathway cannot be overstated. SAMDH1 appears to influence the NF-B pathway, and researchers speculate that SAMHD1 is the molecule responsible for COVID-19-related neurological disorders that could result in death (Khan and Sergi 2020). Therefore, it is crucial to fully comprehend the mechanisms involved in COVID-19 pathogenesis, as this knowledge may help create new medications that act by regulating SAMHD1 activity.

The role of *CD27* and *SAMHD1* in COVID-19 is currently under investigation, and the precise mechanisms through which they impact the disease's severity and status are not yet fully understood. Nevertheless, early research suggests that *CD27* and *SAMHD1* are essential for controlling the immunological response to COVID-19, and changes in their expression levels may render patients more vulnerable to severe disease complications.

Our research sought to investigate the link between *CD27* and *SAMHD1* levels and COVID-19 status. To ensure accurate results, we excluded patients with comorbidities, which are known to increase the risk of severe COVID-19.

In conclusion, CD27 is a crucial protein in regulating the immune response to COVID-19, and recent studies suggest that low levels of *CD27* may be linked to severe symptoms and higher mortality rates. These findings highlight an interesting gene may have implications for the development of effective therapeutics and vaccines strategies for COVID-19. In addition, according to a study, SAMHD1 is the molecule that might be responsible for the neurological side effects of COVID-19. Further research is necessary to better understand the role of *CD27* in COVID-19 and to investigate its potential diagnostic and therapeutic applications. A few of these findings need to be confirmed by protein levels and thorough immunohistochemical staining for these genes.

Author contributions

Maryam H. Al-Zahrani: Project administration, Conceptualization, Visualization, Methodology, Supervision, Validation, Resources, Investigation, Writing – original draft, Writing – review & editing. **Rana A. Alghamdi:** Project administration, Conceptualization, Visualization, Formal analysis, Software, Methodology. **Nesrin I. Tarbiah:** Project administration, Conceptualization, Visualization, Funding acquisition. **Nuha A. Alkhattabi:** Project administration, Conceptualization, Visualization. **Husam M. Joharjy:** Project administration, Conceptualization, Visualization, Data curation. **Reham A. Khalifa:** Project administration, Conceptualization, Visualization, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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