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Remdesivir Modulates *CASP8* and *CASP9* Expression in COVID-19 Patients: Impact on Apoptotic Pathways and Immune Response

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ABSTRACT

Introduction: COVID-19, caused by SARS-CoV-2, is associated with alterations in apoptotic signaling pathways, which influence disease progression and immune function. *CASP8* and *CASP9* are key regulators of apoptosis. This study aimed to evaluate the expression levels of the *CASP8* and *CASP9* genes in COVID-19 patients compared to healthy controls, and to investigate the effect of Remdesivir treatment on their expression. **Methods**: Blood samples were collected from 30 hospitalized patients infected with the SARS-CoV-2 Omicron variant before and after Remdesivir treatment, and from 20 healthy controls. Patients received intravenous Remdesivir therapy (200 mg on day one, followed by 100 mg daily for 4 days). RNA was extracted from blood leukocytes, and real-time quantitative PCR (qPCR) was conducted to assess gene expression, normalized to *GAPDH*. **Results**: No significant difference was observed in *CASP8* expression between untreated COVID-19 patients and controls. However, *CASP8* expression increased 2.5-fold in Remdesivir-treated COVID-19 patients compared to untreated patients ($P < 0.001$). *CASP9* expression was reduced to 10% of healthy control levels in COVID-19 patients ($P < 0.001$) but increased to 80% of control values after Remdesivir therapy ($P < 0.001$). A modest positive correlation was observed between *CASP8* and *CASP9* expression ($r = 0.333$; $P = 0.05$), and between *CASP8* expression and total white blood cell (WBC) count ($r = 0.356$; $P = 0.05$). **Conclusions**: Remdesivir modulates apoptosis-related gene expression, upregulating *CASP8* and partially restoring *CASP9* expression in COVID-19 patients. These findings suggest that Remdesivir influences apoptotic pathways, which may contribute to immune regulation during SARS-CoV-2 infection and enhance therapeutic outcomes.

INTRODUCTION

COVID-19, caused by SARS-CoV-2, has triggered a global health crisis with diverse clinical presentations [1]. COVID-19 ranges from asymptomatic to severe cases, with symptoms including fever, cough, and dyspnea, and causes complications in multiple organ systems, including pneumonia, acute respiratory distress syndrome (ARDS), and cardiovascular, neurological, gastrointestinal, and dermatological disorders [2-5].

SARS-CoV-2 enters host cells primarily through the angiotensin-converting enzyme 2 (ACE2) receptor [6]. This interaction can trigger inflammatory cell death, potentially initiating a cytokine storm, which contributes to ARDS and multi-organ failure [1]. This interaction can trigger inflammatory cell death, potentially initiating a cytokine storm, which contributes to ARDS and multi-organ failure.

COVID-19 infection is associated with significant alterations in apoptotic pathways. SARS-CoV-2 can induce apoptotic or necrotic cell death directly through viral entry and indirectly via a cytokine storm [7]. This cell death contributes to severe inflammation and is a secondary consequence of the hyperinflammatory cytokine storm, worsening prognosis in COVID-19.

Cell death pathways, particularly apoptosis, a regulated form of programmed cell death, play a critical role in SARS-CoV-2 pathogenesis. Pathogens, including SARS-CoV-2, can manipulate host cell fate by modulating apoptotic pathways, including the intrinsic and extrinsic pathways involving caspases [8]. *CASP8* and *CASP9* are

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critical regulators of apoptotic pathways, particularly in viral infections. *CASP8* primarily drives the extrinsic apoptosis pathway, triggered by cell surface death receptors such as TNF receptor superfamily members. Upon ligand binding, these receptors recruit adaptor proteins like FADD (FAS-associated death domain) to form the death-inducing signaling complex (DISC), which activates *CASP8* through oligomerization and self-cleavage [4]. Activated *CASP8* directly cleaves and activates downstream effector caspases, such as *CASP3* and *CASP7*, thereby executing apoptosis [2, 3].

SARS-CoV-2 triggers increased apoptosis, particularly in T-cells, contributing to lymphopenia and enhancing disease severity [9]. Inhibiting caspase activation may mitigate this immunodeficiency [10]. SARS-CoV-2 infection disrupts the endothelium, causing endothelial dysfunction, cell death, and vascular hyperpermeability, which exacerbate COVID-19 pathogenesis [11]. Additionally, SARS-CoV-2 infection may increase the risk of type 2 diabetes through mechanisms including β-cell dysfunction and apoptosis of pancreatic β-cells. This could lead to metabolic syndrome, renin-angiotensin-aldosterone system dysregulation, oxidative stress, and systemic inflammation [12].

CASP9, an initiator caspase, is essential to the intrinsic apoptotic pathway. During some viral infections, *CASP9* can be activated independently of other initiator or effector caspases (*e.g.*, *CASP3* and *CASP8*), indicating its potential to contribute independently to apoptosis [13]. Beyond its apoptotic role, *CASP9* contributes to the innate immune response against viral infections. For instance, it regulates type I interferons (IFNs), critical for antiviral defense [14]. Additionally, *CASP9* modulates host antiviral signaling by fine-tuning cytokine levels and immune cell activation. Thus, *CASP9*'s dual role in apoptosis and immune regulation underscores its significance in host defense against viruses [15].

Antiviral therapies are essential for managing COVID-19, with Remdesivir among the antiviral drugs initially granted emergency use authorization by the by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) [16]. Other antivirals, such as molnupiravir, ribavirin, favipiravir, and lopinavir/ritonavir, have been explored [17]. These agents employ diverse mechanisms, including inhibition of RNA polymerase and viral proteases [18]. While some show potential in preliminary studies, large-scale clinical trials are required to confirm their safety, efficacy, and optimal dosing for COVID-19 treatment [19].

Despite the urgent need for effective COVID-19 therapies, supportive care remains the primary management strategy [18]. Ongoing research and clinical trials are evaluating antiviral drugs and other potential treatments to enhance COVID-19 outcomes [16, 20, 21]. Our previous study on gene expression in COVID-19 patients revealed that *CCND1* expression rose ninefold in COVID-19 patients compared to controls, unaffected by Remdesivir, whereas *TP53* expression fell by 50% but doubled following Remdesivir treatment [22]. Building on this, the present study aimed to evaluate *CASP8* and *CASP9* gene expression in COVID-19 patients relative to healthy controls and to assess their expression before and after Remdesivir therapy.

MATERIAL AND METHODS

Blood sample collection. Blood samples were obtained from 30 hospitalized COVID-19 patients, aged 20–70 years, infected with the Omicron variant of SARS-CoV-2 at Masih Daneshvari Hospital, Tehran, Iran. Additionally, samples were collected from 20 healthy controls within the same age range without a history of COVID-19. Participants had no pre-existing conditions, including diabetes, cancer, hypertension, or prior heart disease or stroke. COVID-19 patients received Remdesivir therapy (200 mg on day 1, followed by 100 mg daily for 4 days). Blood samples from COVID-19 patients were collected before treatment and five days after completing the Remdesivir regimen. Control samples were collected once. Laboratory analyses included WBC counts and C-reactive protein (CRP) levels.

RNA extraction and cDNA synthesis. Total RNA was extracted from blood leukocytes using RiboEX™ reagent (Cat. No. RiboEX302-001, GeneALL, Seoul, South Korea), according to the manufacturer's protocol. RNA quality and integrity were assessed via 1% agarose gel electrophoresis, and RNA concentrations were quantified using a BioPhotometer spectrophotometer (Eppendorf, Hamburg, Germany). Reverse transcription of 0.5 μg RNA per reaction was performed using oligo(dT) and random hexamer primers with SuperScript II reverse transcriptase in the Easy cDNA Synthesis Kit (Cat. No. A101161, Pars Toos, Mashhad, Iran). The resulting cDNA was stored at −20°C for subsequent analysis.

Real-time quantitative PCR. Primer sequences for *CASP8*, *CASP9*, and *GAPDH* were designed using Oligo 7 software to minimize secondary structures (*e.g.*, hairpins or primer-dimers) and ensure melting temperatures within 1°C. Specificity was confirmed via BLASTn analysis on the NCBI platform (https://blast.ncbi.nlm.nih.gov). Primer sequences are listed in Table 1. *GAPDH* served as the reference gene for normalization. Primer performance was verified by agarose gel electrophoresis, confirming a single amplicon. qPCR was conducted using the StepOne™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Samples were analyzed in duplicate using SYBR Green as the fluorescent dye.

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Table 1. Primer sequences for human *CASP8*, *CASP9*, and *GAPDH* used in qPCR

Gene	Forward	Reverse
CASP8	5'-ATTCAGCAAAGGGGAGGAGT-3'	5'-TTCAAAGGTCGTGGTCAAAG-3'
CASP9	5'-GGGAAATGCAGATTTGGCTTAC-3'	5'-CATTTTCTTGGCAGTCAGGTCG-3'
GAPDH	5'-CTCCAAAATCAAGTGGGGCG-3'	5'-TGGTTCACACCCATGACGAA-3'

Statistical analysis. Data normality was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics, including means and standard deviations, summarized qPCR results. Group comparisons were performed using one-way ANOVA with Tukey's post-hoc test to correct for multiple comparisons. Correlations between variables were assessed using Pearson or Spearman correlation methods, based on data distribution. All analyses were conducted in SPSS software (version 20.0, IBM, Armonk, NY, USA), with a statistical significance threshold of $P < 0.05$.

RESULTS

Changes in *CASP8* gene expression between control, patients, and treatment groups

CASP8 expression in COVID-19 patients showed no significant change compared to controls, but Remdesivir treatment increased *CASP8* expression of 2.5-fold (P<0.001) (Figure 1).

Changes in *CASP9* gene expression between control, patients, and treatment groups

The *CASP9* expression was reduced by 90% in comparison to the control group (P <0.001). Treatment with Remdesivir restored *CASP9* expression up to 80% of the control level (P <0.001) (Figure 2).

Correlation of *CASP8* with *CASP9* gene expression

Due to non-normal data distribution, the Spearman rank correlation test was applied in the patient group to assess the correlation between the gene expressions of *CASP8* and *CASP9*. The examination revealed a positive correlation between the gene expressions of *CASP8* and *CASP9* (r=0.333; P=0.05) (Figure 3).

Correlation of apoptotic gene expression with WBC

The Spearman test revealed a significant positive correlation between the *CASP8* gene expression and WBC in the COVID-19 group (r=0.356; P=0.05) (Figure 4).

graph of changes gene expression with COVID-19 after treatment Remdesivir, the control group

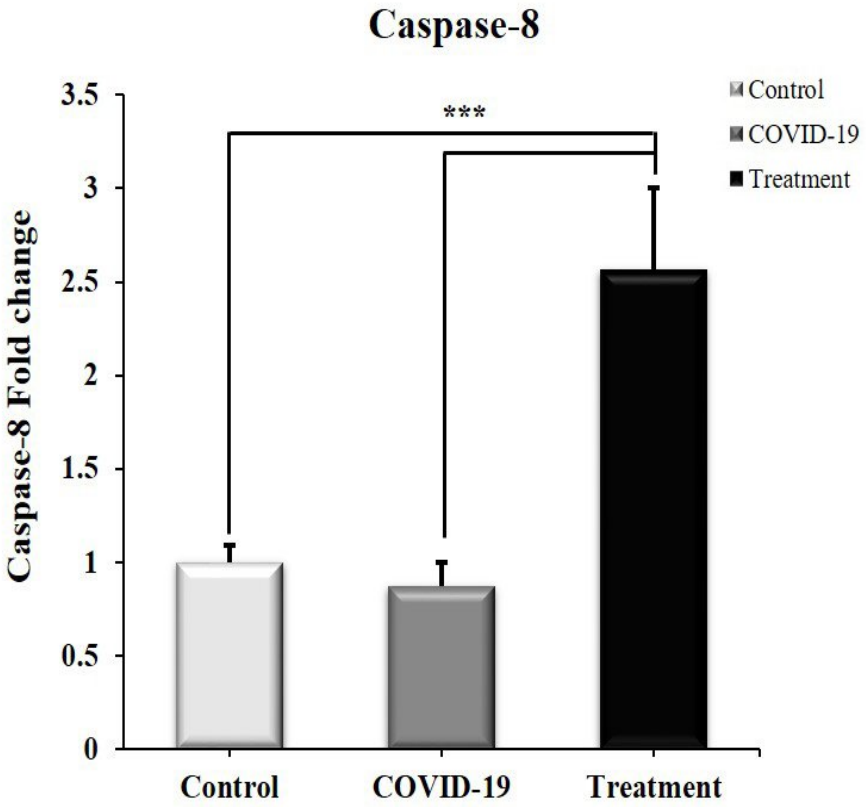

Fig. 1. Bar in *CASP8* in patients before and with compared to (P<0.001).

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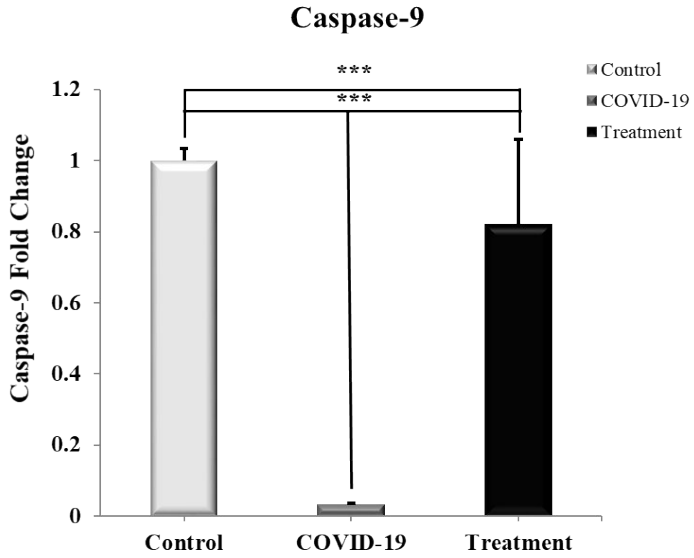

Fig. 2. Bar graph showing changes in *CASP9* gene expression in COVID-19 patients before and after Remdesivir treatment compared to healthy controls (P<0.001).

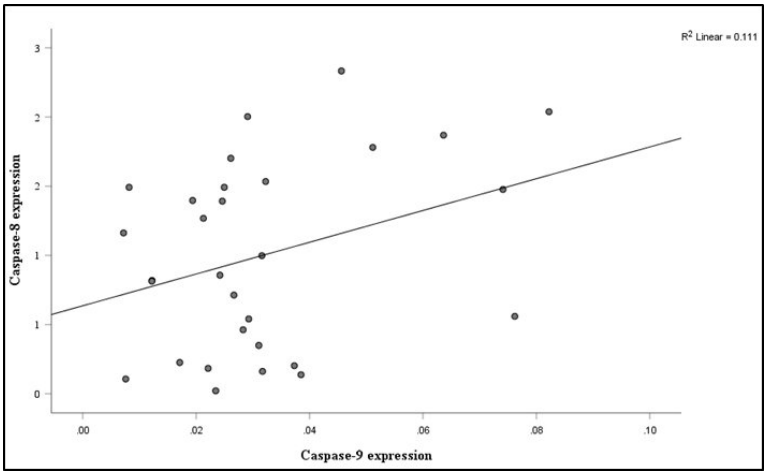

Fig. 3. Scatter plot showing the positive correlation between the gene expressions of *CASP8* and *CASP9* (r=0.333; P=0.05)

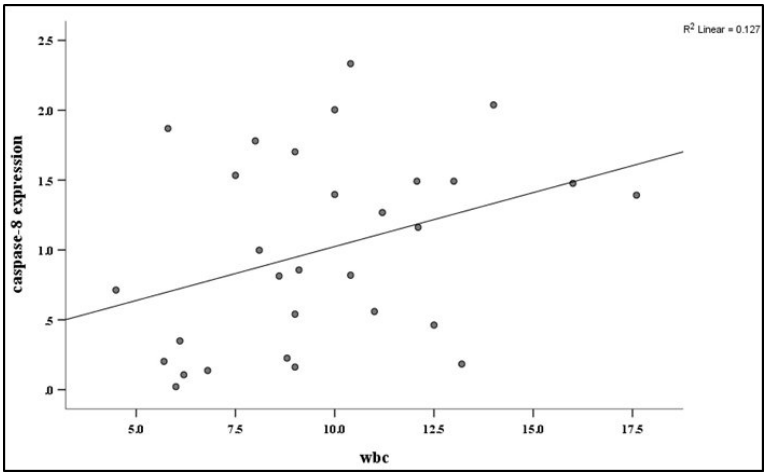

Fig. 4. Scatter plot showing a positive correlation between *CASP8* gene expression and WBC count in the COVID-19 group (r=0.356; P=0.05)

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DISCUSSION

Caspases, in particular *CASP8* and *CASP9*, play a key role in the process of apoptosis, which is central to SARS-CoV-2 pathogenesis. The alteration in levels of these caspases in COVID-19 patients correlates with disease severity and with the response to immunity. Emerging experimental and clinical evidence points to cell death and autophagy caused by SARS-CoV-2 as key processes in virus infection and pathogenesis [23].

Our findings demonstrate significant changes in the regulation of apoptotic pathways in COVID-19 patients, with Remdesivir modulating *CASP8* and *CASP9* expression. Specifically, *CASP8* expression in untreated COVID-19 patients did not differ from controls, but Remdesivir treatment induced a 2.5-fold increase ($P < 0.001$). Conversely, the expression of *CASP9* was reduced to approximately 10% of the controls in COVID-19 patients not receiving Remdesivir but was restored to 80% after its administration ($P < 0.001$). Additionally, we identified modest positive correlations between *CASP8* and *CASP9* expression (r=0.333; P=0.05), as well as between *CASP8* expression and white blood cell count (r=0.356; P=0.05) among COVID-19 patients. These findings suggest that the therapeutic effects of Remdesivir may extend beyond direct antiviral actions to include the regulation of apoptotic pathways, potentially enhancing the immune response in COVID-19 patients.

The unchanged mRNA expression of *CASP8* in COVID-19 patients compared to healthy controls contrasts with previous reports of altered *CASP8* activity in other viral infections. *CASP8*, being an initiator of the extrinsic apoptotic cascade, typically shows alterations in expression in response to viral infections, including SARS-CoV-2, as part of host defense mechanisms [24, 25]. The inability to detect alterations in *CASP8* expression could suggest that SARS-CoV-2 employs mechanisms to suppress or evade this part of the host response in the initial stages of infection. Such evasive mechanisms might be involved in disease development and persistence through failure to activate cell death responses that would otherwise limit virus replication [24]. Other studies have shown that SARS-CoV-2 induces epithelial cell activation of *CASP8* to cause cell death and inflammatory cytokine processing [24]. The discrepancy in findings highlights the complexity of SARS-CoV-2 interactions with host apoptotic pathways, potentially due to viral strain differences or cell-type specificity [26].

The 2.5-fold increase in *CASP8* expression upon Remdesivir treatment is a significant finding with therapeutic implications. The upregulation suggests that Remdesivir may overcome mechanisms of viral suppression and restore normal apoptotic responses. Enhanced *CASP8* activity could allow infected cell removal through programmed cell death and may limit virus spread and tissue damage [27, 28]. Remdesivir, an antiviral drug used to treat COVID-19, has been implicated in modulating CASP8 expression [29, 30]. For example, in prior studies, Remdesivir was found to augment the cleavage of CASP8 in cultured hepatocytes. Additionally, *in vitro* research showed that Remdesivir reduced hepatocyte viability and albumin production and increased *CASP8* cleavage [29].

Apoptosis induced by Remdesivir is associated with activation of signaling pathways such as p38, JNK, and ERK1/2, contributing to mitochondrial injury, autophagy, and apoptosis [31]. *CASP8* plays a pivotal role in initiating the extrinsic apoptotic cascade upon interaction with death receptors and adaptor molecules, FADD or TRADD [32, 33]. Activated *CASP8* can cleave pro-apoptotic molecules such as Bid (truncated Bid, tBid) and cause mitochondrial outer membrane permeabilization (MOMP) and subsequent activation of intrinsic apoptotic pathways through *CASP9* [23].

In many SARS-CoV-2 infections, the virus appears to have a stronger effect on the intrinsic (mitochondrial) pathway with the regulation of *CASP9* rather than *CASP8*. Hence, levels of *CASP8* in COVID-19 patients with no treatment may be near-baseline levels and may not be suppressed or modified to a considerable degree [34, 35].

Following Remdesivir treatment, viral replication decreases, and normal surveillance and signaling pathways can be restored or even amplified. Immune restoration can cause heightened expression of *CASP8* and its related death receptor pathways because the body enhances clearance of residual infected cells, thereby improving immune coordination. Thus, while *CASP8* expression in COVID-19 patients is not very different from normal, it increases upon Remdesivir treatment after the suppressive effects of the virus have been minimized [36, 37].

Aside from its apoptotic role, *CASP8* has inflammatory signaling and cell activation roles in the immune system, and upregulation might be involved in an enhanced and coordinated response to SARS-CoV-2 infection [38]. Restoration of normal apoptotic signaling may represent an underappreciated mechanism of Remdesivir in addition to its well-documented RNA-dependent RNA polymerase inhibition.

The pronounced 90% reduction in *CASP9* expression relative to controls in COVID-19 patients not on treatment is one of the most striking findings in the current research. The virus and inflammatory microenvironment in SARS-CoV-2 infections can suppress or regulate the host apoptotic machinery to enable virus replication. The virus can make infected cells resistant to early apoptosis through downregulation of *CASP9* expression or activity, and hence extend the period of virus replication. The process follows the trends in other coronaviruses in which virus proteins have direct interference with host apoptotic signaling pathways through mechanisms such as disruption in the functions of the mitochondria, epigenetic regulation, or activation of caspases. The levels of *CASP9* in COVID-19 patients are generally low and have a role

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in reduced apoptosis in infected cells and increased survival in viruses [35].

When Remdesivir inhibits the replication of SARS-CoV-2, the ability of the virus to suppress the intrinsic (mitochondrial) apoptotic process diminishes. Consequently, host cells regain normal or augmented levels of *CASP9* expression [39]. Remdesivir lowers the viral burden and alleviates SARS-CoV-2-mediated suppression of apoptotic gene expression so that levels of *CASP9* recover and facilitate normal apoptosis in infected cells. Restoration of *CASP9* expression is part of the overall recovery to normal immune and cell regulation upon the end of active virus replication [40].

As a key initiator in the intrinsic apoptotic cascade, such widespread downregulation signifies severe disruption in mitochondrial-mediated apoptosis in SARS-CoV-2 infection [41]. This widespread suppression would likely be implicated in dysregulated cell death mechanisms and would be a cause of COVID-19 immunopathology features such as lymphopenia and hyperinflammation [42]. Previous research has established that *CASP9* can be activated independently of other caspases in the process of virus infections and can be a primary initiator in apoptotic responses [43]. The severe reduction observed here signifies that the virus may target this pathway specifically to evade the elimination of infected cells.

The restoration to 80% levels of *CASP9* expression after Remdesivir treatment is a crucial therapeutic effect with significant implications. Beyond its involvement in apoptosis, *CASP9* is involved in type I interferon regulation and antiviral immunity in general [44]. The restoration of *CASP9* expression after treatment may be part of normalizing overall immune function through several pathways. The 8-fold up-regulation over COVID-19 untreated levels indicates the extent of the effect and that Remdesivir may be reversing specific virus-mediated immune evasive mechanisms. Restoration would be part of virus clearance enhancement and mitigation of pathological inflammation through normalization of cell death mechanisms and regulation of the immune system.

The significant positive correlation between *CASP8* and *CASP9* expression ($r = 0.333$; $P = 0.05$) signifies coordinated regulation between both apoptotic indices in COVID-19 and upon Remdesivir treatment. The correlation suggests that rather than being completely independent pathways, the extrinsic and intrinsic apoptotic pathways most likely respond to the same regulating signals in the context of SARS-CoV-2 infection and antiviral treatment [35]. The determination coefficient ($R^2 = 0.111$) signifies that approximately 11% expression variability in *CASP9* can be attributed to *CASP8* expression and vice versa, reflecting a modest association. Other variables, such as pro-inflammatory cytokines, cell type differences, or patient variability, may affect the pathways' expression [45]. The coordinated up-regulation upon Remdesivir treatment indicates a generalized restoration of apoptotic capacity and without effects on pathways per se. The observation conforms to the current perspective on cross-talk between apoptotic pathways, where *CASP8* can activate the intrinsic pathway through Bid cleavage and establish a feedback loop to amplify the apoptotic signal upon virus infection or treatment [24].

Overall, this correlation supports the idea that intrinsic and extrinsic pathways of apoptosis may be triggered or influenced concurrently in COVID-19 patients with common regulating signals, resulting in a moderate but significant correlation between the levels of *CASP8* and *CASP9* [46].

The positive correlation between *CASP8* expression and white blood cell counts ($r=0.356$; $P=0.05$) provides important insight into the interaction between regulation through apoptosis and number of immune cells in COVID-19 [47]. The correlation might be reflective of the role played by *CASP8* in cell death and the activation of immune cells, through inflammasome regulation. Increased *CASP8* expression upon Remdesivir administration may be implicated in augmenting functions of the immune cells, such as lymphocyte survival and adequate neutrophil responses [48]. The correlation supports the hypothesis that adequate regulation through apoptosis is important in sustaining functional leukocytes in the context of viral infection [49]. The observation may be partly responsible for accounting for lymphopenia in severe COVID-19 and suggests that recovery through normal apoptotic signaling by Remdesivir administration may restore normal white blood cell dynamics and functions in disease recovery.

The Remdesivir-mediated regulation of *CASP8* and *CASP9* expression provides new information about its action beyond direct inhibition of viral replication. While Remdesivir can be best defined as an RNA-dependent RNA polymerase inhibitor that supresses virus genome formation [36], we conclude that Remdesivir may restore normal apoptotic signaling impaired in COVID-19 infection concurrently. The dual action may contribute to Remdesivir's clinical efficacy in patients through targeting both virus replication and immunopathology. Restoration of regulation in the apoptotic pathways may be particularly significant in the prevention of the hyperinflammatory state characteristic of severe COVID-19, where dysregulated cell death results in cytokine storm and tissue injury [50].

The differential expression of *CASP8* and *CASP9* indicates that Remdesivir may have differential impacts on the extrinsic and intrinsic pathways of apoptosis. While *CASP8* expression was increased beyond baseline levels, *CASP9* expression was normalized without exceeding levels seen in controls. The trend suggests rebalancing and not global activation of apoptotic signals, and may be useful in providing optimal immune responses with minimal further cell death [51]. Such fine-tuning is in line with the new perspective that effective COVID-19

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therapies must address both virus clearance and regulation of the immune response.

In conclusion, our study demonstrates that Remdesivir modulates *CASP8* and *CASP9* expression in COVID-19 patients, potentially contributing to its therapeutic effect through restoring normal apoptosis. The 2.5-fold induction in *CASP8* expression and significant recovery in *CASP9* expression upon Remdesivir treatment suggest that Remdesivir may mitigate SARS-CoV-2-mediated dysregulation in cell death pathways. The correlations between *CASP8* and *CASP9* expression and immune markers suggest that modulation of apoptosis may be an underappreciated mechanism of action for Remdesivir. The findings provide insights into how Remdesivir may address viral replication and immunopathology in COVID-19 patients.

Further research is needed to assess whether similar effects on the regulation of the apoptotic pathway occur with other antivirals and whether such effects have implications in clinical response in other patient populations. Additional research on the downstream consequences of restored expression of caspases in inflammatory markers, immune cell function, and virus clearance would further illuminate the implications of the findings. Targeting apoptotic pathway regulation may be a promising adjunctive strategy in COVID-19 management. Our findings in total highlight the complex interaction between viral infection, regulation of the apoptotic pathway, and antiviral treatment and underscore the merit of considering host response modulation in the design and refinement of COVID-19 therapies.

The findings of this study are affected by many significant limitations due to methodological and contextual issues. The study primarily included patients infected with the Omicron variant, though some earlier data collection coincided with the predominance of the SARS-CoV-2 Delta variant, which is associated with worse clinical outcomes and higher virulence [52]. Some of the illness severity among participants in this phase led to mortality before we were able to obtain follow-up blood samples. As a result, some participants did not provide follow-up samples, and the longitudinal data available for a subset of cases is incomplete. Therefore, we extended this longitudinal study into a subsequent wave that included the Omicron variant and, predominantly, Omicron cases. Omicron, in particular, showed an association with lower rates of hospitalization and reduced mortality, especially among vaccinated individuals [53]. This is particularly problematic because there is the potential for confounding due to reduced illness severity and differences in clinical management as the sample progressed through two variants of the disease.

Furthermore, some enrolled patients only received a single dose of Remdesivir and they did not contribute to the research with follow-up samples. Because of this, we lost additional follow-up samples and treatment data. Loss of samples and/or treatment data is a recognized issue in clinical research conducted during periods of high disease burden, where the clinical course of illness is rapid and treatment protocols are evolving, leading to inconsistency of sample collections and study adherence.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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DATA AVAILABILITY

Raw qPCR data and statistical analyses supporting the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL CONSIDERATIONS

This research adhered to medical ethical principles and was approved by the Ethics Committee of Masih Daneshvari Hospital. Before the study, written informed consent was obtained from all eligible participants. The ethics approval code is IR.SBMU.NRITLD.REC.1399.087.

AUTHORS' CONTRIBUTIONS

SA and SM contributed to the conceptualization, methodology, validation, investigation, and writing of the manuscript. Data analysis was conducted by SA. SM also assisted with sample collection and patient information acquisition. Sample collection from the hospital, preparation of materials, and performance of all tests were carried out by SNL. The first draft of the manuscript was written by ZF.

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