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The Correlation between HSP27 Protein Levels and Gene Expression with Symptoms Severity in COVID-19 Patients

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ABSTRACT

Background & Objective: Heat shock proteins (HSPs) have garnered significant interest as a potential host factor in COVID-19. By exerting control over HSP levels, the invading virus can effectively manipulate the destiny of host cells, capitalizing on their essential roles in cellular pathways and viral life cycles. Within this investigation, we present novel findings elucidating the variations in HSP27 protein and mRNA expression between patients exhibiting mild symptoms and those manifesting moderate-to-severe symptoms of COVID-19, juxtaposed against a control cohort.

Materials & Methods: A total of 102 patient samples were included in the study, comprising 54 individuals with moderate-to-severe COVID-19 symptoms and 48 with mild symptoms. Additionally, 42 samples from healthy individuals constituted the control group. HSP27 protein levels were quantified using ELISA, while the transcript content was assessed using Real-Time PCR.

Results: Our initial findings revealed a statistically significant reduction in serum HSP27 levels among patients displaying mild COVID-19 symptoms when compared to the control group ($P< 0.05$). Nonetheless, this disparity did not achieve statistical significance in patients with moderate-to-severe symptoms. In contrast, the transcriptomic profile of HSP27 exhibited striking similarity across all groups, including mild, moderate-to-severe, and controls ($P= 0.25$ and $P= 0.56$, respectively).

Conclusion: The present study, to date, is the first to investigate *HSP27* gene expression levels in COVID-19 patients. Conducting further studies on HSP27 is of considerable help to clarify the importance of this molecule in SARS-CoV-2 infection.

Keywords: COVID-19, HSP27, Immune System, SARS-CoV-2

Introduction

The 2019 coronavirus disease (COVID-19), an infectious illness brought on by a brand-new RNA virus, caused a pandemic and was initially identified in the province of Wuhan, China, in December 2019 (1). The diverse spectrum of clinical manifestations of SARS-CoV-2 infection, ranging from no symptoms to mild flulike symptoms, anosmia, fever, nonproductive cough, dyspnea, and fatigue to pneumonia, sepsis, and acute respiratory distress syndrome, is one of the most troublesome characteristics of the disease (2). The World Health Organization (WHO) reported 6,938,353-6,952,522 fatalities and up to 768,560,727 cases of coronavirus illness 2019 (COVID-19) on July 26, 2023 (3).

Given the ongoing lack of complete information regarding the molecular pathogenesis of SARS-CoV-2 infection and its status as a newly emerged disease, there is a compelling need to investigate various molecular aspects. Investigating the host-dependent factors of SARS-CoV-2 may help to solve the world's current challenge, namely the lack of effective antiviral agents for this life-threatening virus. Similar to other obligate pathogens, human coronaviruses depend on cellular machinery for viral infection and spread (4). Among the molecular chaperones, HSPs play a pivotal role in numerous fundamental cellular processes, including cell survival, cellular stress response, cell cycle control, immune responses, and even the life cycle of viruses through extensive regulation of intracellular proteins (5, 6). Conversely, viruses can exert control over HSPs at various levels, including transcription, translation, and post-translational modifications (7). Recent studies have unveiled a systemic disorder associated with severe

COVID-19 infection: a relative deficiency in the Heat Shock Response (HSR). Research indicates that this inadequate heat shock response is potentially linked to unfavorable outcomes, particularly among high-risk groups vulnerable to COVID-19 mortality (8). These findings have prompted researchers to focus on studying HSPs as indispensable host factors in the context of COVID-19 disease (9, 10).

A subgroup of molecular chaperones, known as small HSPs (sHSPs or HSPBs), are distinguished by their low molecular weight (14–43 kDa) and significant conservation (11). HSP27 is widely expressed in all human tissues and assumes multifaceted roles under both physiological and stressful conditions. These roles encompass indirect cooperation in protein refolding or degradation, interactions with cellular cytoskeletal elements, and the facilitation of anti-apoptotic processes at various levels. (12) HSP27 has been mentioned as a biomarker in certain diseases, including chronic obstructive pulmonary disease (COPD) (13). Additionally, some studies have illuminated the interactions between numerous viral proteins and HSP27, influencing the modulation of NF-kB signaling pathways, interferon (IFN) production, and autophagy processes (14).

Evidence from prior studies indicates the anti-inflammatory effects of HSP27. Consequently, recent research has proposed the possible involvement of this molecule in COVID-19 treatment, sparking interest in further investigation of HSP27 as an immunotherapeutic agent for managing the disease (15, 16). While HSP27 has demonstrated effectiveness in controlling virus infection, its precise role in SARS-CoV-2 infection remains unclear. Therefore, the current study aims to shed some light on the differences in HSP27 protein and mRNA levels among patients with mild COVID-19, those with moderate-to-severe COVID-19, and individuals in the normal population.

Materials and Methods

Study design

The study encompassed 102 adult patients with COVID-19, alongside 42 age-, gender-, and BMI-matched healthy individuals from the identical geographical area as the control group. (Zanjan city in Zanjan province located in the northwest of Iran). The age range of participants in all three groups was 40–80 years. RT-PCR determined SARS-CoV-2 positivity for all of the COVID-19 trial participants. Based on the disease severity, the patient cohort was categorized into two distinct groups. A total of 48 patients who were included in the COVID-19 mild group (16 females, 32 males) exhibited oxygen saturations surpassing the threshold of 95% along the disease progression and did not require hospitalization. In contrast, the COVID-19 moderate-to-severe group included 54 patients (20 females, 34 males) who displayed oxygen saturations falling below the threshold of 93% and arterial blood oxygen partial pressure (PaO2)/oxygen concentration (FiO2) < 300 mmHg (17). The control group consisted of 42 healthy individuals (16 females and 26 males), all with no recent history of significant sicknesses or infections. Additionally, none of the participants had underlying diseases such as cardiovascular diseases, asthma, blood lipids, cancer, diabetes, autoimmune diseases such as rheumatoid arthritis, lupus erythematosus, or other inflammatory disorders. Furthermore, all subjects selected for this study were confirmed not to be taking steroidal, non-steroidal anti-inflammatory, or cytotoxic drugs at the time of sampling. The Research Ethics Committee of Zanjan University of Medical Sciences approved the research protocol (IR. ZUMS.REC.1400.250 and IR.ZUMS.REC.1400.427).

Samples collections

Blood samples were taken from all the subjects after visiting and admission. Three milliliters of blood were collected using K-EDTA tubes for RNA extraction and gene expression analysis. Another three milliliters of blood were collected in clotted tubes, which were centrifuged at room temperature for 10 minutes at 4000× g. After centrifugation, sera were isolated and aliquoted samples were stored at -80 °C until the HSP27 protein concentration assay tests were performed.

HSP27 protein concentration assay

ELISA kits for human HSP27 (0.5-100 ng/ml) were purchased (Crystal Day Biotech Co., Ltd., China). Then, the analyses were conducted in accordance with the manufacturer's instructions for the ELISA kit. Stat Fax-2100 microplate reader made by Awareness Technology Inc., USA, was used to read the absorbances.

HSP27 gene expression assay

RNA extraction

Following the manufacturer's instructions, whole blood was used to extract total RNA using the column kit method (Viragene, Iran). Next, 30 µL of RNase-free water was utilized to dissolve the RNA. The quality of the RNA samples (A260/280 ratio) and their concentrations were calculated by Nanodrop (Thermo Scientific, USA).

Complementary DNA Synthesis and RT-PCR

The total RNA extracted from each patient sample (1 µg) underwent reverse transcription using a cDNA synthesis kit (Yekta Tajhiz Azma) in a final 20 µL volume according to the manufacturer's guidelines. The reaction commenced at 70°C for 5 minutes, followed by a 2-minute incubation on ice and adding the second mixed reagents to each well, at 42°C for 60 minutes and at 70°C for 5 minutes by thermocycler (FlexCycler2 PCR Thermal Cycler, Germany). Relative HSP27 expression was examined by a two-step qRT-PCR which was done by SYBR Green Master Mix (Amplicon, Denmark) and ABI step one plus System (ABI, USA) in a 20 mL total reaction volume, incorporating specific primer sets. The qRT-PCR entailed a three-phase process, following this program for both HSP27 and *GAPDH* genes: initial

denaturation at 95°C for 15 minutes, 45 cycles of denaturation at 95C for 20 seconds; primer annealing temperature at 59°C for 20 seconds, and elongation at 72°C for 20 seconds. After each run, the melting curves obtained were analyzed. Amplification specificity was confirmed by the existence of singular peaks in the melting curves, and Unambiguous bands on agarose gel electrophoresis with the correct size. Duplicate runs were made for each qPCR reaction. ABI step one plus Series Software 2.3 was used to analyze the results and transform them into threshold cycle values. To normalize the data, the reference gene *GAPDH* was employed.

Table 1. Primer sequences utilized for RT-PCR

Gene	Primer sequences (5' to 3' direction)	Amplified fragment size (bp)
HSP27	F: AAGGATGGCGTGGTGGAGATC R: TCGTTGGACTGCGTGGCTAG	194
GAPDH	F: ATCACCATCTTCCAGGAGCG R: CCTTCTCCATGGTGGTGAAGAC	103

Statistical analysis

Relative HSP27 expression within patient samples, juxtaposed against the control group, was gauged through Ln [Efficiency$^{\wedge\Delta\Delta CT}$] value calculations. The assessment of data normality was executed via the Shapiro-Wilk test. Statistical analyses were performed utilizing R version 4.2.1. The potential influence of confounding variables, including age and sex, was examined using the Quantile regression model. Using the brms and ggplot2 packages in R Stan, Bayesian modeling was employed to scrutinize discrepancies between patients and the control group. Statistical significance was set at p-values less than 0.05. The receiver operating characteristic (ROC) curve was harnessed for disease status classification based on protein levels to evaluate suitability.

Results

No statistically significant variations were observed regarding age and sex distributions when comparing the patients to the control group. The transcript contents of HSP27 were analyzed in blood samples using RT-PCR, with the *GAPDH* gene serving as an internal reference for normalizing gene expression. The transcript content of the *HSP27* exhibited near-identical levels across the mild, moderate-to-severe, and control groups. Consequently, no variations were detected among these groups ($p = 0.25$ and $p = 0.56$, respectively) (Figure 1). Moreover, the average gene expression level in women was higher than that of the men in all groups. The amplification efficiencies of *HSP27* and *GAPDH* were estimated to be 1.92 and 1.98, respectively. The study power was evaluated to be 0.84 based on the results obtained.

Although a significant decrease in the mean serum levels of HSP27 was observed in the group of patients with mild symptoms compared to the control group, this value was not significant at a statistical level in the patients with moderate-to-severe symptoms (Figure 3). To assess biomarkers' prognostic values and compare their predictive values, a receiver operating characteristic (ROC) study was conducted. The ROC curve analysis was also demonstrated on an area under the curve (AUC) value of 0.517 for HSP27 protein, as depicted in Figure 4, with a 95% confidence interval ranging from 0.42 to 0.61.

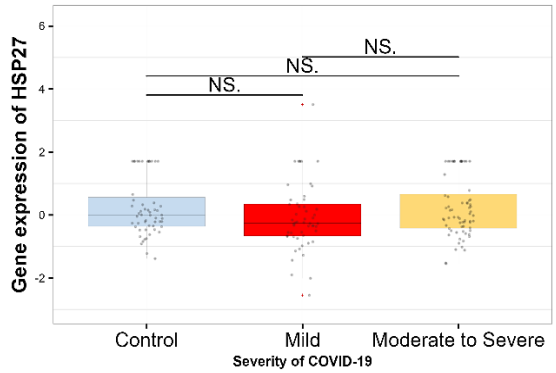

Figure 1. Relative HSP27 expression was scrutinized within blood specimens derived from COVID-19 patients stratified into mild and moderate-to-severe symptom groups, juxtaposed against the control group. Utilizing the Pfaffl method ($E^{-\Delta\Delta CT}$), the mean fold change was calculated for each cohort. Evaluation of HSP27 gene expression between the COVID-19 patient groups and the control cohort did not reveal any statistically significant disparities. The $P<0.05$ was considered a significant level.
(NS: No Significant)

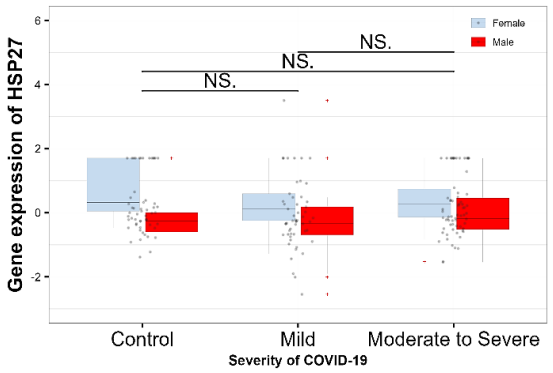

Figure 2. Relative expression of HSP27 in both groups of COVID-19 patients with mild and moderate-to-severe symptoms compared to the control group by gender. As illustrated in this figure, no statistically significant disparities in disease severity were observed between the patient and healthy control groups. The average gene expression in women is higher than that of the men in all groups studied. (NS: No Significant)

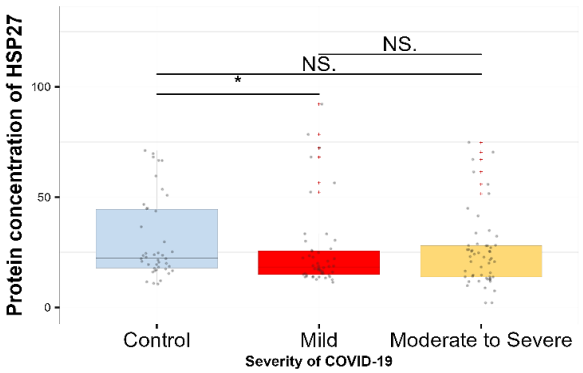

Figure 3. Serum levels of HSP27 protein in two groups of COVID-19 patients with mild and moderate-to-severe symptoms vs. the control group. A significance threshold of $P< 0.05$ was employed. (NS: No Significant) *$P< 0.05$

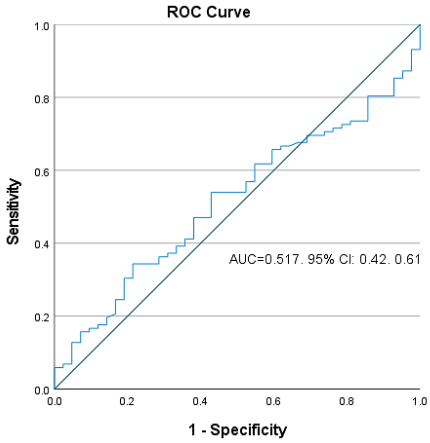

Figure 4. ROC curve analysis for evaluating the biomarker value of HSP27 protein in patients with COVID-19.

Discussion

Prior examinations of HSP27's involvement in COVID-19 have been somewhat limited in scope. To the best of our knowledge, the current investigation represents the pioneering effort to delve into the intricacies of HSP27 gene expression within individuals afflicted by the SARS-CoV-2 virus. Within this comprehensive inquiry, we meticulously scrutinized HSP27 protein and transcript levels across two distinct cohorts of COVID-19 patients, classified based on the severity of their symptoms, and juxtaposed them with a control group. Strikingly, our study's outcomes unveiled a noteworthy reduction in HSP27 protein content among patients displaying mild symptoms, a significant departure from the control group. Conversely, while a parallel downtrend was evident in HSP27 transcript levels among patients exhibiting both mild and moderate-to-severe symptoms, no statistically significant variance was discernible when contrasted with the control group. HSP27 exhibits dual roles in viral infections: it demonstrates antiviral activity in some instances while acting as a promoter in others (18, 19). Numerous investigations have illuminated the pivotal role of the interaction between viruses and HSP27, functioning as molecular chaperones, in the intricate regulation of viral infections. These multifaceted processes encompass viral entry into host cells and nuclei, replication, and the expression of viral genes (7, 9). The dynamics of HSP27 during viral infections are proposed in several studies, presenting three scenarios. In certain viral infections, there is an upsurge in HSP27 levels, while in others, a concurrent decrease is observed, and in some cases, HSP27 levels remain unaltered. For instance, Dan et al. reported a surge in

HSP27 levels upon Enterovirus A71 infection, suggesting its potential to bolster the IRES-dependent translation process and influence viral protein translation a novel avenue for countering EV-A71 infection (20). Conversely, Sun et al. documented a notable decline in HSP27 mRNA content during porcine epidemic diarrhea virus infection using RT-PCR. This reduction in HSP27 expression was postulated as a strategy employed by the virus to evade the host's antiviral mechanisms (21). In a different context, Li et al. conducted a study observing the stable gene expression of HSP27 following encephalomyocarditis virus infection, while its protein levels decreased from 9 hours post-infection. Intriguingly, their research identified viral proteins 2Cpro and 3Apro as key contributors to the degradation and loss of HSP27 protein during infection (14).

The marked reduction in HSP27 protein levels within the mild symptom group, in contrast to the control group, can plausibly be attributed to viral replication in these afflicted individuals (22, 23). As the disease progresses and symptoms worsen, the predominant causative factor shifts from the virus itself to the host immune system's response. It is noteworthy to acknowledge that HSP27 is a molecule known for its responsiveness to estrogen. Consequently, the observed lower expression levels of HSP27 in males compared to females align with established expectations (15).

Prior research has posited that IFN-γ exerts regulatory control over the HSP27 gene via specific regulatory regions, effectively downregulating HSP27 expression by activating intricate signaling pathways (24). Intriguingly, recent investigations have unveiled elevated IFN-γ levels in individuals afflicted by SARS-CoV-2 compared to a control cohort (25). In light of these antecedent findings, the observed lack of significant alteration in HSP27 levels among COVID-19 patients in the present study could potentially be attributed to heightened IFN-γ concentrations, contrary to initial expectations. Conversely, an independent study scrutinizing serum HSP27 levels in severe and critically ill COVID-19 patients admitted to intensive care units revealed a marked elevation in HSP27 concentrations (26). This surge in HSP27 expression likely aligns with its established role in platelet aggregation, mediated through the regulation of actin filament polymerization. It may be associated with thrombo-inflammation and the activation of thrombotic responses (26–28).

To summarize, our patient data revealed that HSP27 levels did not significantly differ from those in the control group. Several plausible explanations for these findings emerge. Firstly, HSP27 levels during COVID-19 may exhibit dynamic fluctuations, possibly rising in the early stages of infection in asymptomatic individuals and subsequently declining in symptomatic patients as they seek medical care (29). Secondly, the modulation of HSP27 activity during COVID-19 disease may occur through post-translational modifications rather than transcriptional and translational alterations. As mentioned, non-phosphorylated HSP27 degrades proteins with defective folding through the proteasomal pathway. At the same time, phosphorylated HSP27 is closely associated with the viral replication immune response of host cells, cell cycle, and apoptosis (30). Thirdly, it is conceivable that our results may be affected by increased levels of inflammatory cytokines or the interference of SARS-CoV-2 proteins (31, 32).

Conclusion

Recent investigations indicate a dynamic modulation of HSP27 expression in response to SARS-CoV-2 infection, exhibiting variations corresponding to the virus replication cycle and disease stage. To comprehensively elucidate the implications of HSP27 in COVID-19 and its intricate expression alterations, additional investigations are imperative to analyze the temporal kinetics of this molecular response in COVID-19. Ultimately, an in-depth comprehension of gene expression patterns across various diseases, particularly the novel context of COVID-19, holds significant promise for identifying novel diagnostic and therapeutic molecular targets.

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Authors' Contribution

A. M.: Supervision, grant acquisition, study design, and review and editing the manuscript. F. E.: Collection and preparation of samples, experimental work, and writing the first draft of manuscript. M. S.: Patient recruitment. Sh. A: Statistical analysis. All the authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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