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ACE2 Gene Expression in Patients with COVID-19 Compared to Multiple Sclerosis Patients

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Abstarct

Introduction: Angiotensin-converting enzyme 2 (ACE2) is a receptor with a high affinity for the COVID-19 virus and its gene expression varies across different tissues and individuals. Variations in ACE2 gene expression have been linked to disease severity, particularly in individuals with immune conditions such as Multiple Sclerosis (MS).

Methodology: Participants were divided into four Groups; Group A (hospitalized severe patients), Group B (outpatients with mild COVID-19 symptoms), Group C (healthy individuals), and Group D (patients with MS). Following RNA extraction and cDNA synthesis, ACE2 gene expression levels were measured using Real-time PCR. Correlations between ACE2 expression, age, and sex were analyzed.

Results: ACE2 gene expression was significantly elevated in Groups A (3.52±1.45) and B (2.54±1.345) compared to Groups C (0.33±0.13) and D (0.90±1.45). There were also significant differences between most of the studied Groups. A significant positive correlation was also found between ACE2 gene expression and age ($r = 0.368$, $p < 0.001$), suggesting a moderate yet robust relationship.

Conclusions: The highest level of ACE2 gene expression was observed in Group A, while Group B exhibited lower ACE2 expression. Groups C and D showed the lowest ACE2 expression level. These findings suggest that ACE2 gene expression is a potential marker for COVID-19 severity and may provide insights into the interplay between COVID-19, MS, age, and sex.

Keywords: ACE2, COVID-19, Multiple Sclerosis, MS, Gene expression

1. Introduction

COVID-19 has infected over a hundred million people and caused more than two million deaths. This disease, caused by the SARS-CoV-2 virus, leads to severe respiratory distress syndrome in humans (1). The lungs are particularly affected, as the virus targets the epithelial cells of the bronchi and alveoli, which results in symptoms such as fever, dry cough, and shortness of breath (2). This virus binds to ACE2 (Angiotensin-converting enzyme 2) receptors in the epithelial cells of alveoli and airway cells through the receptor-binding domain on its spike protein (3). The affinity of SARS-CoV-2 for ACE2 is about 10 to 20 times higher than that of other types of coronaviruses in this family (4). ACE2 can be found in membranous ACE2 (mACE2) and soluble ACE2 (sACE2). mACE2, which is found on the membranes of various organs, including the intestines, kidneys, testis, gallbladder, and heart, functions as a receptor. sACE2 is derived from mACE2 through the enzyme ADAM-17 (A Disintegrin and Metalloprotease-17) (5-7). The virus entry process into target cells is critical in disease progression (8). Endocytosis of the virus reduces mACE2 receptors on cell surfaces, decreasing the production of sACE2 by the ADAM-17 enzyme. sACE2 converts the vasoconstrictor Angiotensin II (Ang-2) into the heptapeptide Angiotensin (1-7), which binds to the Mas receptor (MasR), leading to vasodilation and anti-inflammatory effects (Figure 1) (9-11).

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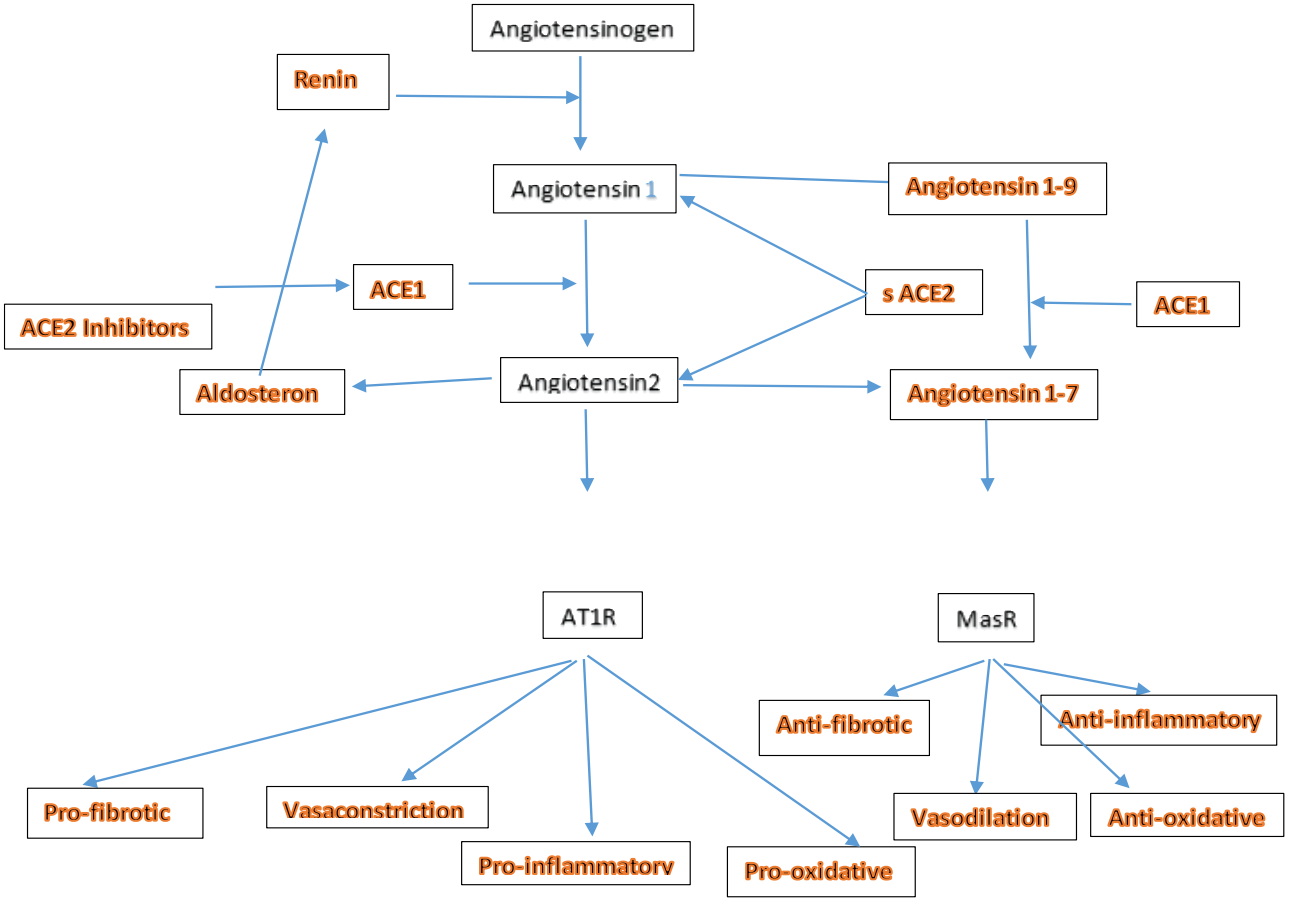


Figure 1. Pathways of ACE2 functions in RAS.

ACE2 gene expression varies across different tissues and organs. High expression levels are found in the small intestine, testicles, heart, adipose tissue, and thyroid glands, while low levels are present in the blood, spleen, bone marrow, brain, blood vessels, and muscles. Moderate expression levels are observed in the lungs, colon, liver, bladder, and adrenal glands (12). Additionally, ACE2 expression levels vary according to sex, race, age, and the presence of underlying, autoimmune, or inflammatory conditions, influenced by single-nucleotide polymorphisms (SNPs). High mACE2 expression is associated with severe SARS-CoV-2 infections in patients with underlying illnesses (13-15). MS is a chronic autoimmune disease that affects the central nervous system, leading to demyelination and neurodegeneration (16). Patients with MS have a dysregulated immune system, which may influence the expression of various genes, including ACE2 (17). Understanding the interaction between SARS-CoV-2 and ACE2 in both COVID-19 and MS patients is crucial, as it may provide insights into the differential impacts of the virus on individuals with pre-existing autoimmune conditions.Since these two diseases are in opposition to each other concerning the expression of the ACE2 gene, this research aimed to compare the level of ACE2 gene expression in patients with COVID-19 and those with MS to elucidate potential variations in their response to the virus.

2. Methods

The study population was categorized into four Groups: hospitalized patients with severe COVID-19 (Group A), outpatients with mild COVID-19 symptoms (Group B), healthy individuals (Group C), and patients with MS without COVID-19 (Group D). MS patients with COVID-19 were searched in several hospitals and were not found. Each group consisted of a total of 10 participants.

2.1. Eligibility Criteria

Participants were selected based on PCR test results. Individuals with a negative PCR test for the presence of the COVID-19 virus genome were included as healthy controls. Participants taking ACE inhibitors, angiotensin receptor blockers (ARBs), or corticosteroids were excluded to avoid potential confounding effects on ACE2 expression. Common comorbidities were recorded, and individuals with severe uncontrolled comorbidities were not included in the analysis.

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2.2. Sample Collection

Participants ranged in age from 15 to 88 years, including males and females. For COVID-19 patients, blood samples were collected within 48 hours of diagnosis and before initiation of any antiviral or corticosteroid treatment. For MS patients and healthy controls, blood samples were collected during routine visits. Blood samples (5 mL each) were collected from all participants at Imam Khomeini Hospital in Tehran.

2.3. RNA Extraction

RNA was extracted from 5 mL of whole blood from each participant using the QIAzol Lysis Kit (Qiagen, Frankfurt, Germany). The quantity and purity of the extracted RNA were assessed using a Nanodrop spectrophotometer.

2.4. cDNA Synthesis

cDNA was synthesized from the extracted RNA using a commercial kit (Tajhiz Azma Teb Company, Tehran, Iran), according to the manufacturer's protocol.

2.5. Real-Time PCR

Real-time PCR was performed on the ABI 7500 system using ACE2 and GAPDH primers with TaqMan reagent master mix, following the manufacturer's instructions. Primer sequences were designed to target a unique region of the ACE2 transcript. Specificity was verified using NCBI BLAST to confirm the absence of significant homology with other human transcripts, and single-product amplification was confirmed by melt curve analysis. The primer sequences for ACE2 and GAPDH (used as a reference gene) are provided in Table 1. The thermal cycle conditions for cDNA synthesis are presented in Table 2, and the real-time PCR program is outlined in Table 3.

Table 1. Specifications of used primers in Real-Time PCR.

Primers	Primer Sequences
ACE2 Forward	CAGGGAACAGGTAGAGGACATT
ACE2 Reverse	CAGAGGGTGAACATACAGTTGG
GAPDH Forward	GACAACTTTGGTATCGTGGAAGG
GAPDH Reverse	AGGCAGGGATGATGTTCTGG

Table 2. Thermal cycle of cDNA synthesis.

Stage	Temperature °C	Time (min)
1	25	10
2	47	60
3	85	5

Table 3. Real-Time PCR programing.

Stage	Temperature °C	Time	Cycle repeat
Enzyme activation	95	10 min	1
Denaturation	95	15 sec	30-35
Annealing	60	60 sec	1

The ΔCt of the target gene was calculated as Ct (ACE2) − Ct (GAPDH). The ΔΔCt value was obtained by subtracting the ΔCt of the healthy control group from that of each experimental group (severe vs healthy, mild vs healthy, and MS vs healthy). Gene expression fold change was determined using the formula: fold change = $2^{(-\Delta\Delta Ct)}$. All qPCR reactions were performed in duplicates.

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2.6. Statistical Analysis

Statistical analysis was conducted using SPSS version 28 software. P-value < 0.05 was considered significant. Data were analyzed using one-way ANOVA, with Tukey's post hoc test for pairwise comparisons between Groups, the independent t-test for comparing two Groups, and the Mann-Whitney test as applicable. Graphs were generated using GraphPad Prism software.

3. Results

3.1. Gene Expression Results

The ACE2 expression levels in the four studied Groups are presented in Table 4.

The results indicate that the ACE2 expression level in the healthy control Group (Group C) was very low (0.33 ± 0.13), whereas it was very high in the severe COVID-19 patient Group (Group A) (3.52 ± 1.46). In the mild COVID-19 patient Group (Group B), ACE2 expression was moderate (2.54 ± 1.34), and in the MS patient Group without COVID-19 (Group D), it was low (0.90 ± 1.45). Significant differences were observed between most Groups (P < 0.001), except between Groups A and B (P = 0.147) and between Groups C and D (P = 0.913) (Table 4 and Figure 2).

Table 4. Comparison of Significant differences in expression level between the four studied Groups

	Groups				P-value					
Groups	A	B	C	D	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
ACE2	3.52± 1.46	2.54± 1.34	0.33 ± 0.13	0.90±1.45	0.147	< 0.001	<0.001	<0.001	< 0.001	0.913

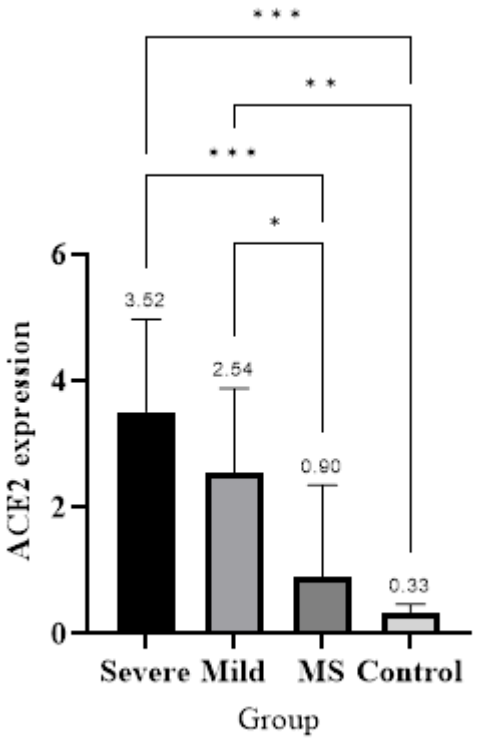


Figure 2. Comparison of ACE2 gene expression between all studied groups

3.2. Correlation of Gene Expression with Age and Sex

There was no statistically significant difference in gender distribution across the studied Groups, indicating homogeneity in gender frequency (P = 0.323) (Table 5, Figure 3).

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Table 5. Comparison of the relationship between genders and the four studied Groups

		Group				P-value
		MS	Sever	Mild	Control	
Gender	Female	50.0%	50.0%	60.0%	20.0%	0.323
	Male	50.0%	50.0%	40.0%	80.0%	

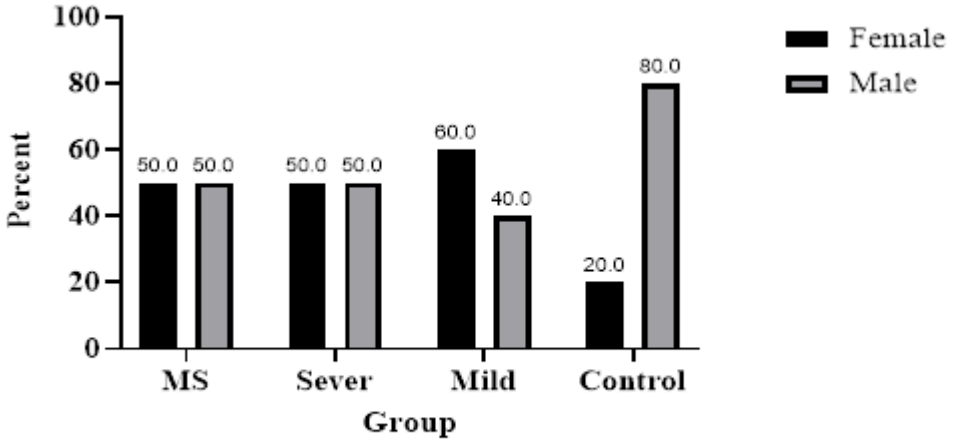


Figure 3. Comparison of the relationship between genders in the four studied groups.

Although ACE2 expression levels were higher in women (2.16 ± 1.92) compared to men (1.54 ± 1.58), this difference was not statistically significant (P = 0.266) (Table 6, Figure 4).

Table 6. Comparing the relationship between gender and ACE2 gene expression.

	Gender	Mean	Std. Deviation	P-value
ACE2 expression	Female	2.16472	1.921172	0.266
	male	1.54018	1.580232	

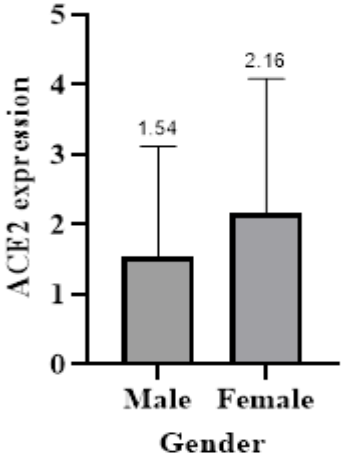


Figure 4. Comparison of ACE2 gene expression between women and men.

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The studied Groups showed a significant difference in average age (P < 0.001) (Table 7). The average age in the severe COVID-19 Group (Group A) was significantly higher than in the MS Group (Group D) and the control Group (Group C) (P < 0.001) (Table 7, Figure 5).

Table 7. Comparison of the average age between the studied Groups.

	Groups				P-value
	MS	Sever	Mild	Control	
Age	25.30 (5.74)	56.0 (28.63)	45.10 (22.72)	30.70 (7.48)	< 0.001

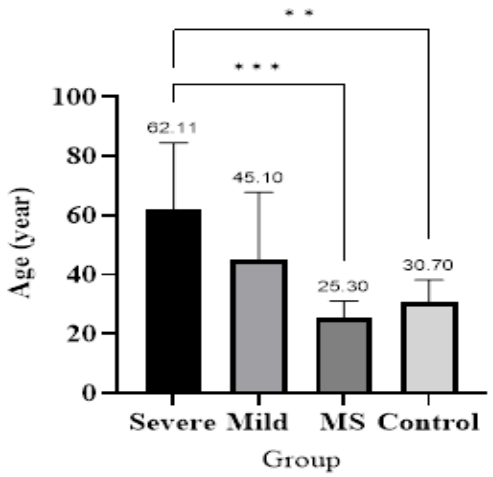


Figure 5. Comparison of the average age between the studied groups.

Additionally, age was significantly correlated with ACE2 gene expression (P = 0.014, r = 0.36), indicating that ACE2 expression levels increase considerably with age (Table 8, Figure 6).

Table 8. The relationship between ACE2 gene expression and age.

		ACE2 expression
Age	Correlation Coefficient	0.386*
	P-value	0.014

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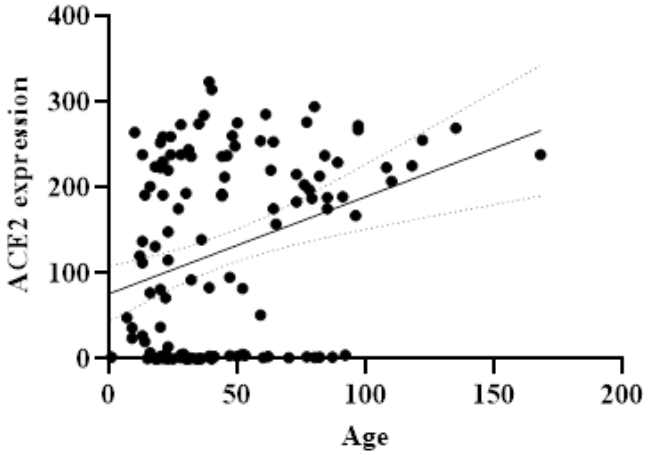


Figure 6. The relationship between ACE2 gene expression and age.

4. Discussion

Our study revealed that ACE2 gene expression is significantly associated with the severity of COVID-19 (18). The highest expression levels were found in Group A (hospitalized patients with severe COVID-19), while the lowest levels were observed in Group C (healthy individuals). Group B (patients with mild COVID-19) had ACE2 expression higher than Group C but lower than Group A. Group D (MS patients without COVID-19) exhibited lower ACE2 expression than all Groups except Group C. These findings highlight the critical role of ACE2 expression in disease progression, with elevated levels linked to more severe manifestations of COVID-19.

Our results are consistent with several studies indicating that ACE2 expression is upregulated in severe COVID-19 cases. For example, Gheware, A. et al. reported that ACE2 expression is significantly increased in the lungs of patients with severe COVID-19, contributing to the virus's pathogenicity and respiratory complications (19). Similarly, Li, G. et al. found that higher ACE2 expression correlates with increased severity of COVID-19 symptoms, particularly in older adults and individuals with underlying disorders, including angiocardiopathy, type 2 diabetes, certain malignancies, pneumonia, and hypertension (20, 21). A study conducted by Ipekci highlights that lung involvement and, accordingly, ARDS development and mortality rate were found to be higher in older-aged patients as a result of higher ACE2 expression (22). In our study, a significant correlation was observed between age and ACE2 expression across all Groups, indicating a modest but reliable association. Older individuals exhibited higher levels of ACE2 expression, which is associated with higher rates of severe COVID-19 (Table 8, Figures 5 and 6). This finding aligns with research by AlGhatrif M et al., which demonstrated that ACE2 expression increases with age, potentially due to age-related changes in pulmonary physiology and comorbidities (23). In addition, Bartleson, J.M. et al. suggested that the interaction between aging, chronic conditions, and ACE2 upregulation might explain the higher vulnerability of elderly populations to severe COVID-19 (24).

Interestingly, some studies have found an inverse relationship between age and ACE2 expression in specific contexts. For instance, Leung et al. reported a decrease in ACE2 expression with age in individuals with chronic airway diseases, which might be due to disease-specific regulatory mechanisms (25). This highlights the complex interplay between age, underlying health conditions, and ACE2 expression. Our study showed no significant difference in ACE2 gene expression between sexes (P=0.266). Despite higher expression levels in women compared to men, the difference was not statistically significant (Table 6 and Figure 3). This finding is supported by the work of Sama et al., who reported no significant sex-based differences in ACE2 expression across various tissues (26). However, other studies suggest that sex hormones, such as estrogen, may modulate ACE2 expression and influence COVID-19 outcomes. For instance, COVID-19 severity has been linked to androgen-driven TMPRSS2 expression, which facilitates viral entry into cells (27).

In Group A, the highest ACE2 expression was linked to severe lung involvement. In underlying respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), ACE2 expression is increased in the alveolar epithelium, leading to severe symptoms and complications such as acute respiratory distress syndrome (ARDS) and potentially death due to reduced blood oxygen levels and surfactant production (28, 29), This is consistent with the mechanism where the virus binding to mACE2 triggers an inflammatory response and subsequent pneumocyte apoptosis.

The role of ACE2 in autoimmune diseases like MS is not well-documented. Our study found that MS patients (Group D) had lower ACE2 expression levels than all other Groups except for Group C, suggesting a potential protective effect against COVID-19. This is consistent with research on other autoimmune conditions, such as IgA nephropathy and type 1 diabetes, where reduced ACE2 expression was observed (30). This reduced expression might decrease susceptibility to severe COVID-19, as fewer ACE2 receptors are available for the virus to bind.

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As discussed previously, in autoimmune diseases such as MS, reducing membrane ACE2 (mACE2) receptors due to endocytosis leads to a decrease in sACE2 production. This reduction in sACE2 results in lower levels of its ligand, angiotensin (1-7), which has anti-inflammatory and antioxidant properties. Consequently, the reduced production of angiotensin (1-7) also diminishes the blockade of Ang-2 type 1 receptor (AT1R). This unopposed binding of Ang-2 to AT1R promotes the generation of pro-inflammatory, pro-oxidant, and pro-fibrotic products. These factors contribute to the exacerbation of inflammation and the progression of autoimmune diseases, including MS (31-33).

In various underlying conditions, increased ACE2 expression is often observed, likely due to upregulation of mACE2 (34-39). For instance, patients with diabetic heart disease and diabetes show significant increases in ACE2 expression, making them more susceptible to COVID-19. This supports the hypothesis that individuals with higher ACE2 expression are at greater risk of severe COVID-19 (40).

Research suggests that individuals with Multiple Sclerosis (MS) might have a reduced susceptibility to contracting COVID-19. This hypothesis stems from the observation that MS patients tend to exhibit lower expression levels of the ACE2 gene, a critical receptor for the entry of SARS-CoV-2 into human cells, potentially reducing their risk of infection (41). However, to substantiate this theory, further investigations are needed, such as analyzing blood samples from MS patients to assess their immune responses, viral load, and other relevant biomarkers (42). Although studies have explored ACE2 expression and its relationship to COVID-19 in different conditions, specific research connecting decreased ACE2 expression in MS patients with lower susceptibility to the virus remains limited (43).

5. Conclusion

Our research observed an association between ACE2 gene expression and the severity of COVID-19, with the highest expression levels detected in hospitalized patients and the lowest in healthy individuals. MS patients exhibited relatively low ACE2 expression, which may indicate a potential relationship with reduced COVID-19 susceptibility; however, this observation requires confirmation in larger, longitudinal studies. Age showed a significant positive correlation with ACE2 expression, while no significant difference was observed between the sexes. Further targeted research is warranted to clarify the link between ACE2 expression in MS patients and COVID-19 risk, and to determine whether ACE2 can serve as a reliable prognostic biomarker. These findings contribute to understanding the role of ACE2 in COVID-19 pathogenesis and may inform future studies exploring its potential relevance in disease prognosis and therapeutic strategies.

Acknowledgments

This research was conducted independently, and no acknowledgments are required.

Data Availability Statement

All data from this study will be made available by the author if needed and requested by the editor.

Abbreviations

1. ACE2: Angiotensin-converting enzyme 2
2. MS: Multiple Sclerosis
3. mACE2: membranous angiotensin-converting enzyme 2
4. sACE2: Soluble angiotensin-converting enzyme 2
5. TMPRSS2: Transmembrane protease, serine 2
6. ADAM-17: A Disintegrin and Metalloprotease- 17
7. Ang-2: Angiotensin-2
8. MasR: Mas receptor
9. ARDS: Acute respiratory distress syndrome

Statements & Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by [F. A., A.S., H. A., and B. Z. S.]. The first draft of the manuscript was written by [F. A., and A.S.] .The final draft was written and edited by F.A. All authors read and approved the final manuscript.

Conflict of Interest

All authors declare no conflicts of interest that might be relevant to the contents of this article.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Department of Biochemistry and Biophysics, Faculty of Advanced Sciences and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran (2022.3.10/IR.IAU.PS.REC.1401.168).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Not applicable

Data Availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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