

Article

Predictive Relationships Between *AGTR1* and *ACE2* Polymorphisms for Hypertension and COVID-19 in Patients at a Tshwane Academic Hospital: A Preliminary Study

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus disease 2019 (COVID-19), exploits angiotensin-converting enzyme 2 (ACE2) for cell entry, implicating the renin–angiotensin system (RAS) in disease pathogenesis. Hypertension (HT), a major comorbidity, is strongly influenced by genetic factors within RAS, including angiotensin ii receptor type 1 (AGTR1) and ACE2 polymorphisms. However, data on these variants in African populations remain scarce. This study investigated associations between AGTR1 and ACE2 single-nucleotide polymorphisms (SNPs), HT, and COVID-19 severity in patients at a Tshwane Academic Hospital. **Methods:** We genotyped AGTR1 and ACE2 SNPs in 94 PCR-confirmed COVID-19 patients using Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight (MALDI-TOF) mass spectrometry. Clinical data were extracted from hospital records. Ordinal logistic regression models assessed relationships between SNPs, HT, and COVID-19 severity. **Results:** The cohort (mean age: 53.9 years; HT prevalence: 54.9%) exhibited mild (54.9%), moderate (18.6%), and severe (26.5%) COVID-19. Although the rs2106809 A genotype appeared to be associated with lower odds of severe disease (OR = 0.39, 95% CI: 0.14–1.08, $p = 0.04$), this observation should be interpreted with caution given the limited sample size of this study. Other SNPs and clinical variables showed no significant associations. **Conclusion:** This exploratory study represents the first description of AGTR1 and ACE2 SNP patterns in COVID-19 patients from Tshwane. While the rs2106809 variant may indicate a possible protective trend, the evidence remains preliminary. Age correlated with severity. Larger, multi-ethnic studies are needed to confirm these findings.

Keywords: AGTR1; ACE2; genotypes; polymorphisms; hypertension; COVID-19

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1. Introduction

COVID-19, caused by SARS-CoV-2, presents a wide clinical spectrum, with most individuals experiencing mild to moderate respiratory illness that resolves without specialized care [1]. The initial cases of this respiratory illness were identified in Wuhan, Hubei Province, China, in late December 2019, with SARS-CoV-2 classified as a positive-sense single-stranded RNA virus [2]. The first confirmed case of COVID-19 in South Africa was documented on March 5, 2020, involving a traveler who had recently returned from Italy [3]. Transmission occurs primarily via aerosols, respiratory droplets, and close contact. Disease severity is strongly influenced by age, immune status, and comorbidities such as hypertension (HT) and diabetes [2,4].

SARS-CoV-2 enters host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, a key component of the renin-angiotensin system (RAS). ACE and ACE2 are central to blood-pressure regulation and inflammatory responses, while AGTR1 (encoding the angiotensin II type 1 receptor) regulates the classical RAS signalling cascade and contributes to vascular homeostasis [5–7].

Genetic variation within ACE, ACE2, and AGTR1 has been implicated in modulating HT risk and COVID-19 outcomes. Associations between SNPs in ACE and ACE2 and increased HT susceptibility have been reported, and ACE2 variants on the X chromosome may contribute to sex-specific differences in COVID-19 prevalence and severity [8]. However, findings across studies are inconsistent, with some reporting robust genotype–phenotype associations and others observing minimal or no effects [9]; conflicting results have also been described for specific loci such as rs2106809 [10,11].

Despite expanding international literature [12], AGTR1 and ACE2 SNPs remain markedly understudied in Sub-Saharan African populations, including South Africa. Existing data are dominated by some cohorts from Northern and West Africa [13–15], limiting insight into the distribution and clinical relevance of RAS-pathway variants across the continent’s heterogeneous ancestries, an important gap given Africa’s high HT burden and genomic diversity [16].

This study addresses this gap by evaluating key AGTR1 and ACE2 SNPs in patients at a Tshwane academic hospital in South Africa to determine their relationships with HT and COVID-19 severity. The findings aim to inform population-specific biomarkers and advance our understanding of host genetic factors that contribute to severe disease outcomes.

2. Materials and Methods

2.1. Study Population and Specimen Collection

A total of 94 laboratory-confirmed COVID-19 patients at a Tshwane Academic Hospital exhibiting varying degrees of disease severity (mild, moderate and severe) were enrolled in this study. The COVID-19 severity framework established by the Tshwane Academic Hospital was employed, with its criteria detailed in Supplementary Table S2. Each participant had a nasopharyngeal swab collected using DNA/RNA Shield reagent, in addition to blood drawn into a DNA/RNA Shield Blood Collection Tube. These procedures were carried out by a qualified phlebotomist registered with the Health Professions Council of South Africa (HPCSA), following standardized techniques.

2.2. Hypertension and Other Comorbidities

Confirmed pre-existing HT information was obtained from the participants’ hospital records during their visits, with HT defined in accordance with the South African Hypertension Society (SAHS) guidelines as a reading of $\geq 140/90$ mmHg [17]. Additionally, in-

formation on age, gender, diabetes mellitus (DM) and estimated glomerular filtration rate (eGFR) dichotomized as normal (>60 mL/min/m²) or low (<60 mL/min/m²) were collected.

2.3. Nucleic Acid Extraction & Genotyping

The ExtractMe viral RNA kit (EM39) from Blirt (172 Gdańsk, Poland) was used to extract viral RNA according to the method of Kgtle et al. [18]. The Quick-DNA/RNA™ Blood Tube Kit (R1151) from Zymo Research (Irvine, California) was used to extract DNA from patient samples following the manufacturer's instructions. SARS-CoV-2 genotyping was performed using a previously described method [19]. AGTR1 and ACE2 SNP genotyping was conducted using MALDI-TOF mass spectrometry, as previously outlined by Chalwe et al. [20]. This study focused on the rs5183 [21], rs5185 [22], and rs5186 [23] SNPs within AGTR1, as well as the rs2106809 [24] SNPs in ACE2, which were selected due to their reported associations with the RAS, HT, and COVID-19.

2.4. Statistical Analysis and Modelling

Characteristics were outlined using summary statistics, including mean, standard deviation (SD), proportions, and percentages of missing data. To address the issue of missing data, we utilized 10 multiple imputations via the Amelia II software (version 9.0) package in R [25]. Specifically, we imputed datasets for age, gender, and DM. The results of our multivariable analysis were derived from these imputed datasets, which were combined according to Rubin's rules [26]. COVID-19 severity was modeled as an ordinal outcome with three levels: Mild, Moderate, and Severe. Ordinal logistic regression (OLR) models were fitted using the MASS package [27], presuming a proportional odds logistic link. Our models were constructed separately for each imputed dataset. To tackle issues of quasi-complete separation and sparse genotype categories, we developed dominant genetic models for SNPs rs5183, rs5185, rs5186, and rs2106809 by merging heterozygous and homozygous categories. Under this approach, the combined genotype categories were compared against major-allele homozygotes. This modeling strategy was chosen not only to reduce sparse-data bias and improve model convergence, but also to enhance statistical power given the limited sample size. Moreover, applying a dominant model is biologically plausible for ACE2 SNPs, where the presence of even a single minor allele may be sufficient to influence gene expression or functional activity. Therefore, this approach provides a balance between statistical robustness and mechanistic interpretability. An adjusted OLR model was specified to include age, gender, DM, HT, eGFR and selected SNPs. Model coefficients and standard errors were extracted from each imputed dataset and pooled using Rubin's rules to generate combined estimates, standard errors, confidence intervals, and *p*-values. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by exponentiating the pooled log-odds estimates. Crude models were also fitted for each predictor individually to evaluate unadjusted associations with COVID-19 severity. These models were similarly pooled across imputations using Rubin's rules. SNPs that did not converge or exhibited poor estimation in the adjusted models were excluded. Model performance was assessed using the Akaike Information Criterion (AIC), averaging the AIC values across imputations and computing AIC weights (AICw) to identify the most parsimonious model. The top-performing model underwent further analysis, and its findings, along with those from the crude analyses, were reported. Collinearity was also evaluated in the adjusted models using variance inflation factors (VIFs).

3. Results

3.1. Study Population

A total of 94 patients were enrolled in the study. Table 1 summarizes the demographic and clinical characteristics of the cohort, including SNPs and COVID-19 severity classifications. The mean age of participants was 53.9 years (SD = 12.8), with a nearly equal distribution between males (52.9%) and females (47.1%). The ethnic composition of the cohort included 50 Black patients, 3 Indian patients, 3 mixed/biracial patients, and 38 White patients. Comorbidities were prevalent, with 26.5% of participants diagnosed with DM and 54.9% with HT. eGFR abnormalities were present in 20.6% of participants. Genotypic distributions for the SNPs were assessed. The performance of the genotyped SNPs showed variability across key quality metrics, including coverage, expected heterozygosity and Hardy–Weinberg equilibrium (HWE) *p*-values. These parameters cooperatively reflect assay robustness and the reliability of genotype calls in population-level analyses. rs5183 showed the highest frequency for allele A (42.2%), followed by GA (22.5%), None (26.5%), and G (8.8%). A similar trend in variability was observed across other SNPs, including rs5185, rs5186 and rs2106809, which is indicative of genetic heterogeneity within the cohort. Regarding COVID-19 severity, 54.9% of participants experienced mild disease, 18.6% had moderate disease, and 26.5% had severe illness.

Table 1. Study Summary Statistics.

Variable	Value	Missing Percentage
Age (mean ± sd)	53.9 ± 12.8	----
Gender n(%)		
Male	54 (52.9%)	---
Female	48 (47.1%)	
DM n(%)		
No	71 (69.6%)	3.9
Yes	27 (26.5%)	
HT n(%)		
No	43 (42.2%)	2.9
Yes	56 (54.9%)	
eGRF n(%)		
No	81 (79.4%)	---
Yes	21 (20.6%)	
rs5183 n(%)		
None	27 (26.5)	
A	43 (42.2)	---
GA	23 (22.5)	
G	9 (8.8)	
rs5185 n(%)		
None	41 (40.2)	
T	4 (3.9)	---
GT	57 (55.9)	
rs5186 n(%)		
None	65(54.2%)	
A	51(42.5%)	
CA	4(3.3%)	
rs2106809 n(%)		
None	25 (24.5%)	
A	61 (59.8%)	---
AG	12 (11.8%)	
G	4 (3.9%)	
COVID-19 Grades, n(%)		
Mild	56 (54.9%)	
Moderate	19 (18.6%)	---
Severe	27 (26.5%)	

3.2. Crude and Adjusted Predictors of COVID-19 Severity

Ordinal logistic regression analyses were conducted to evaluate the association between clinical and genetic predictors and COVID-19 severity. Because the genotype distribution exhibited quasi-constant patterns, it was not feasible to reliably evaluate the proportional odds assumption across the imputations. Table 2 summarizes the results from both crude and adjusted models following multiple imputations (MIs). The dataset exhibited minimal missingness, with only 3.9% of DM data and 2.9% of HT data unavailable. To ensure methodological rigor, MI was employed instead of complete-case (CC) analysis, as MI maximizes statistical power and minimizes bias by incorporating information from partially observed records, an especially important consideration given the study's relatively small sample size. The imputation model in Amelia was used, which employs the expectation-maximization bootstrap (EMB) algorithm. The EMB combines the classic EM algorithm with a bootstrap approach to draw from the posterior. For each draw, the data are bootstrapped to simulate estimation uncertainty, and then the EM algorithm is run to find the mode of the posterior for the bootstrapped data, yielding fundamental uncertainty as well. Furthermore, a sensitivity analysis was conducted to validate the robustness and consistency of the primary findings, the results of which are presented in Supplementary Table S1. Collectively, these methodological choices strengthen the reliability and scientific merit of the study's preliminary findings. All predictors also demonstrated VIF values below conventional thresholds (e.g., $VIF < 5$), indicating no evidence of problematic multicollinearity as shown in Table 2. In the crude model, increasing age was significantly associated with higher odds of severe COVID-19 ($OR = 1.06$, 95% CI: 1.02–1.10, $p = 0.001$). Male gender also showed a significant association ($OR = 1.47$, 95% CI: 0.95–2.27, $p = 0.04$), although the confidence interval was wide. Low eGFR was also a significant predictor ($OR = 1.96$, 95% CI: 1.21–3.13, $p = 0.002$). In the adjusted model, age remained a significant predictor ($OR = 1.06$, 95% CI: 1.03–1.09, $p < 0.001$). However, the associations for gender and eGFR were attenuated and no longer statistically significant. Notably, although the rs2106809 A genotype showed an association with reduced odds of severe disease ($OR = 0.39$, 95% CI: 0.14–1.08, $p = 0.04$), this finding should be interpreted cautiously. The limited sample size and exploratory nature of the study mean that this observation may not reflect a true underlying relationship. Larger, well-powered studies are needed to verify whether this apparent protective trend is reproducible and clinically meaningful. Other SNPs, including rs5183, did not show significant associations in the adjusted model. Model selection based on AICw identified age as the most informative predictor (AICw $OR = 0.86$, 95% CI: 0.77–0.97, $p = 0.005$), supporting its inclusion in the final model.

3.3. Sensitivity Analysis

A sensitivity analysis was performed using an alternative adjusted model that included dominant coding for SNPs with sparse genotype distributions (Supplementary Table S1). The model demonstrated a slightly improved fit ($AIC = 227.28$). Other clinical variables, including age, gender, DM, HT and eGFR were not statistically significant in this sensitivity model. Most SNPs, including rs5183 and rs5185, did not show consistent associations across models.

Table 2. Ordinal logistic regression analysis of crude and adjusted models for COVID-19 severity after multiple imputation of model-selected variables.

Variable	Crude			Adjusted			AICw			Mean_VIF
	OR	95%CI	<i>p</i> -value	OR	95%CI	<i>p</i> -value	OR	95%CI	<i>p</i> -value	
Age	1.06	1.02–1.10	0.001	1.06	1.03–1.09	0.000	0.86	0.77–0.97	0.005	1.361
Gender (Female)	Reference	Reference	Reference	Reference	Reference	Reference				1.397
Gender (Male)	1.47	0.95–2.27	0.04	0.89	0.45–1.75	0.69				
Diabetes (No)	Reference	Reference	Reference	Reference	Reference	Reference				1.173
Diabetes (Yes)	1.14	0.60–2.13	0.65	1.08	0.60–1.94	0.77				
HT (No)	Reference	Reference	Reference	Reference	Reference	Reference				1.334
HT (Yes)	1.47	0.91–2.38	0.06	0.78	0.37–1.69	0.43				
eGFR (Normal)	Reference	Reference	Reference	Reference	Reference	Reference				1.288
eGFR (Low)	1.96	1.21–3.13	0.002	1.89	0.87–4.09	0.06				
rs5183	Reference	Reference	Reference	Reference	Reference	Reference				1.385
rs5183 (A)	1.74	0.52–5.85	0.30	1.66	0.29–9.60	0.51				
rs5183 (GA)	1.40	0.50–3.95	0.46	1.79	0.57–5.61	0.28				
rs5183 (G)	1.84	0.81–4.20	0.09	0.70	0.22–2.21	0.49				
rs2106809	Reference	Reference	Reference	Reference	Reference	Reference				1.292
rs2106809 (A)	1.37	0.57–3.31	0.41	0.39	0.14–1.08	0.04				
rs2106809 (AG)	0.93	0.39–2.21	0.85	0.88	0.38–2.03	0.73				
rs2106809 (G)	1.61	0.69–3.79	0.20	0.99	0.26–3.72	0.96				

Note: Statistical significance set at $p < 0.05$; AIC = 235.056; VIF = variance inflation factor.

4. Discussion

The present study aimed to investigate the predictive relationships between the AGTR1 and ACE2 SNPs (rs5183, rs5185, rs5186, rs2106809) in relation to pre-existing HT and the severity of COVID-19 among patients at a Tshwane Academic Hospital in Pretoria, South Africa. Among our participants, 54.9% experienced mild illness, 18.6% experienced moderate illness, and 26.5% experienced severe disease. These findings are consistent with those from a multicenter survey conducted in Osaka, Japan, by Imoto et al. [28]. In previous reports, the high prevalence of mild COVID-19 cases has been attributed to widespread population immunity, which may be due to vaccination and/or prior infections [29], the reduced virulence of the dominant variants during the study period [18,19] and the age of the participants [30]. This may help explain the results observed in our study.

The demographic composition of the cohort, predominantly Black patients with additional representation from Indian, mixed/biracial, and White participants, provides a critical context for interpreting both HT status and COVID-19 severity. Racial differences in HT risk are well documented: Black populations exhibit higher rates of HT, altered renal sodium handling, and distinct vascular responses compared with White populations. Additional work further highlights physiological and environmental contributors, including inflammation, gut microbiota changes, and social determinants of health, which reinforce these disparities [31–33].

Genetically, key HT-associated genes such as SCNN1B, GRK4, ARMC5, and CACNA1D show ancestry-specific patterns in individuals of African descent, contributing to low renin phenotypes and increased susceptibility to end-organ damage [34,35]. These genetic and physiological traits are particularly relevant because HT remains one of the strongest predictors of severe COVID-19 outcomes. Racial and ethnic disparities in HT prevalence and control contribute to broader inequities that may amplify vulnerability to severe COVID 19 [36,37]. Given this background, the predominance of Black participants in the cohort underscores the importance of interpreting SNP-based findings within an ancestry-informed framework. This diversity also strengthens the study's contribution to potential precision medicine efforts by helping identify ancestry-specific variants that may influence cardiometabolic and infectious disease outcomes.

In the crude model, advancing age was notably linked to increased chances of experiencing severe COVID-19. This is consistent with findings from Mueller et al. [30] and Hossain et al. [38]. They reported that the severity of COVID-19 and its outcomes are closely correlated with age, indicating that older adults (particularly those over 65) may face significantly greater risks of hospitalization, severe illness (e.g., multi-organ failure), and mortality. These studies attribute this mainly to factors like age-related immune decline (immunosenescence), a higher prevalence of pre-existing health issues and elevated baseline inflammation, among others [30,38]. This may provide insight into the results observed among our participants. These findings underscore the importance of age as a consistent and significant predictor of disease severity, corroborating previous literature that identifies older age as a major risk factor for adverse outcomes related to COVID-19 [30].

The male gender demonstrated a notable association as well. This aligns with findings from Zaher et al. [39] and Beegle et al. [40], who indicated that men are at a greater risk of experiencing severe illness, hospitalization, and mortality when compared to women, who may have higher incidences of long COVID. They linked this discrepancy to differences in immune responses across genders, hormonal influences (such as the protective effect of estrogen), and lifestyle factors (including higher smoking prevalence among

men), which likely lead to men being more susceptible to severe health outcomes [39,40]. This finding may provide a plausible explanation for our results.

A low eGFR emerged as a significant predictor within our study population. Our results share similarities with those reported by Boruga et al. [41] and Cornelissen et al. [42], who also observed that COVID-19 infection correlates with a decreased eGFR. The kidneys are often affected by infections through both direct and indirect mechanisms. Ahmadian et al. [43] noted that kidney involvement related to COVID-19 primarily presents as proteinuria and acute kidney injury (AKI). Damage to the kidneys caused by SARS-CoV-2 is likely to be multifaceted; it can directly infect podocytes and proximal tubular cells, and via the ACE2 pathway, can result in acute tubular necrosis, protein leakage into Bowman's capsule, collapsing glomerulopathy and mitochondrial dysfunction. The dysregulation of immune responses driven by SARS-CoV-2, including cytokine storms, macrophage activation syndrome, and lymphopenia, may also contribute to AKI. Additional potential mechanisms for AKI include organ interactions, endothelial dysfunction, hypercoagulability, rhabdomyolysis, and sepsis [41–43]. These factors could help explain the findings presented in this paper.

HT emerged as the most prevalent underlying condition, affecting 54.9% of the participants in our study. This finding aligns with numerous reports in the literature, including those by Batiha et al. [44] and Sohrabivafa et al. [45]. Previous research has proposed several mechanisms through which COVID-19 may contribute to the worsening of pre-existing hypertension [37,46]. For instance, SARS-CoV infection triggers inflammation that can harm blood vessels and the heart, consequently resulting in elevated blood pressure [47]. Furthermore, the virus binds to the transmembrane protein ACE2, a key component of the RAAS, which is crucial for regulating blood pressure. Disruption of this receptor can lead to higher BP values and increased difficulty in managing the condition [37]. Finally, COVID-19 can induce fluid imbalances within the body, causing either fluid retention or dehydration, both of which can influence blood pressure [48]. These factors may contribute to a clearer understanding of the findings presented in our study.

In addition to the previously mentioned factors, we performed an analysis examining the relationship between DM and the severity of COVID-19. Our findings did not reveal any statistically significant correlations that would support the conclusions drawn by Legris et al. [49].

Interestingly, in the adjusted model, only age continued to be a significant predictor when analyzing these same variables. The relationships for gender and eGFR weakened and were no longer statistically significant. The process of model selection, utilizing Akaike Information Criterion weights (AICw), determined that age was the most informative predictor, which justifies its inclusion in the final model.

The ACE 2 gene located on chromosome X (Xp22) has 18 exons and 20 introns that are identical to ACE exons [9,50]. The AGTR1 gene, in addition to ACE2, is located on chromosome 3 (3q21-25) and comprises 5 exons and 4 introns [51]. The ACE2 gene contains genetic polymorphisms that influence the clinical presentation of COVID-19. Specific SNPs such as rs2074192, rs1978124, rs2074809, and rs2074666 have been reported to contribute to the disease's severity and its pathological effects across various organs [11]. In the context of HT, ACE gene SNPs such as rs4341, rs4343, and rs4344 have demonstrated varying degrees of association with the condition. Multiple SNPs within the AGTR1 gene such as rs5183, rs5185, and rs5186 have been identified as being associated with differing levels of severity in individuals affected by both COVID-19 and HT [6,11]. The genotypic distributions for these SNPs were assessed in our population. The rs5183 showed the highest frequency for allele A (42.2%), followed by GA (22.5%), None (26.5%), and G (8.8%). A similar trend in variability was observed across other SNPs, including rs5185, rs5186 and rs2106809, which is indicative of genetic heterogeneity within the cohort.

Our genetic analysis in the adjusted model suggested a possible protective effect of the rs2106809 A genotype, which was significantly associated with reduced odds of severe disease. This observation remains preliminary and should therefore be interpreted with caution. The role of the rs2106809 gene variant in COVID-19 severity is complex and shows conflicting results across different populations and studies, with some finding that it is associated with increased severity while others suggest a potential protective effect in specific contexts [11,52]. The rs2106809 SNP is located at chromosomal position X:15599938 (GRCh38.p14) [24], and its allele frequency in African populations has been reported as 0.1159 [53]. Differences between populations and interactions between genes and environmental factors may explain the inconsistencies in the rs2106809 findings reported across studies. For instance, Matic et al. [10], reported the rs2106809 allele as a prominent protective factor for in-hospital death due to COVID-19, but only among females while Molina et al. [11] found that the rs2106809 SNP was associated with hospitalization. Our findings correspond well to those of Matic et al. [10] who also reported a possible protective role of the rs2106809 SNP. As evidenced by these reports, the effect of the rs2106809 variant on COVID-19 severity appears to be population-specific and may be influenced by complex factors such as sex, ethnicity, and gene-environment interactions. The present findings emphasize the need for further research in larger and more diverse populations to determine the exact role of the rs2106809 SNP.

Intriguingly, we found no significant relationship between HT and the other SNPs investigated in this study. This is in-line with the findings from Jafary et al. [54], who also reported no significant association between the SNPs and the risk of being hypertensive with other diseases and the risk of DM in unadjusted and adjusted models in patients with COVID-19. Our results, however, contradict those of other studies that indicated an association between ACE2 polymorphisms, HT and COVID [55,56]. Jafary et al. [54] indicated that one of the possible reasons for this result is that these SNPs are not in the coding region on ACE2 and therefore do not play a role in the structure and function of ACE2 receptor. The findings within our population may reflect these contextual factors; however, it is also plausible that the study was underpowered and could not detect subtle genetic effects. Consequently, the absence of statistically significant associations should not be interpreted as definitive evidence of no underlying relationship. Rather, these results highlight the need for larger, adequately powered studies to clarify whether these apparent null findings represent true biological effects.

This study did not include key clinical endpoints such as ICU admission, mechanical ventilation, or mortality, which may also limit the clinical interpretability of the findings and potentially attenuate detectable genotype–phenotype relationships. As such, these observations should be viewed as exploratory and interpreted with appropriate caution.

5. Conclusions & Recommendations

To the best of our knowledge, this study provides the first report of the rs5183, rs5185, and rs5186 (AGTR1) and rs2106809 (ACE2) SNPs in relation to HT and COVID-19 among patients at a Tshwane Academic Hospital. While our findings indicate that age is consistently associated with COVID-19 severity, the apparent protective trend observed for the rs2106809 A genotype should be interpreted with caution due to the exploratory design and limited sample size. These preliminary observations underscore the need for larger and more diverse cohorts to verify these associations and to better delineate the potential roles of these SNPs in disease susceptibility and progression.

6. Limitations

This exploratory study had some limitations that warrant cautious interpretation of the findings. Some SNPs exhibited sparse genotype distributions, leading to quasi-complete separation and unstable estimates. The small sample size further increases the likelihood of type I and type II errors and limits the strength of the conclusions, particularly in the complex field of disease genetics. Generalizability is also constrained by the single-center setting, which may introduce unmeasured confounding related to COVID-19. Additionally, missing data were handled using multiple imputations, which, while appropriate, adds another layer of possible uncertainty. As a result, these preliminary findings should be viewed as specific to the cohort studied and not necessarily reflective of the broader South African population.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/covid6030040/s1>, Table S1: Ordinal Logistic Regression Adjusted Model Results with Imputed Data for Predicting the Odds of COVID Severity. Table S2: COVID-19 Severity Classification: Tshwane Academic Hospital Complex.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Dataset available on request from the authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AIC	Akaike Information Criterion
ACE2	Angiotensin-converting enzyme 2
AGTR1	Angiotensin II Receptor Type 1
COVID-19	Coronavirus disease 2019
DM	Diabetes mellitus
eGRF	estimated glomerular filtration rate
HPCSA	Health Professions Council of South Africa
HT	Hypertension
NuMeRI	Nuclear Medicine Research Infrastructure
OLR	Ordinal logistic regression
ORs	Odds ratios

RAS	Renin–angiotensin system
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SNPs	Single-Nucleotide Polymorphisms
SAHS	South African Hypertension Society
UP	University of Pretoria

References

1. CDC. “About Covid-19.” Centers for Disease Control and Prevention. Available online: <https://www.cdc.gov/covid/about/index.html> (accessed on 13 August 2025).
2. Cascella, M.; Rajnik, M.; Aleem, A.; Dulebohn, S.C.; Di Napoli, R. *Features, Evaluation, and Treatment of Coronavirus (Covid-19)*; StatPearls Publishing LLC: Tampa, FL, USA, 2023. Available online: <https://www.ncbi.nlm.nih.gov/books/NBK554776/> (accessed on 22 December 2025).
3. Modisenyane, M.; Madikezela, L.; Mngemane, S.; Ramadan, O.P.; Matlala, M.; McCarthy, K.; Govender, N.; Nemungadi, T.; Silali, S.P. Covid-19 Response in South African Communities: Screening, Testing, Tracing and Movement Modelling. *SAMJ South Afr. Med. J.* **2022**, *112*, 366–370.
4. Brodin, P. Immune Determinants of Covid-19 Disease Presentation and Severity. *Nat. Med.* **2021**, *27*, 28–33. <https://doi.org/10.1038/s41591-020-01202-8>.
5. Herrera, P.; Cauchi, R.J. Cauchi. Ace and Ace2: Insights from *Drosophila* and Implications for Covid-19. *Heliyon* **2021**, *7*, e08555. <https://doi.org/10.1016/j.heliyon.2021.e08555>.
6. Tayler, H.M.; MacLachlan, R.; Güzel, Ö.; Fisher, R.A.; Skrobot, O.A.; Abulfadl, M.A.; Kehoe, P.G.; Miners, J.S. Altered Gene Expression within the Renin–Angiotensin System in Normal Aging and Dementia. *J. Gerontol. Ser. A* **2023**, *79*, glad241. <https://doi.org/10.1093/gerona/glad241>.
7. Xu, H.; Zhong, L.; Deng, J.; Peng, J.; Dan, H.; Zeng, X.; Li, T.; Chen, Q. High Expression of Ace2 Receptor of 2019-Ncov on the Epithelial Cells of Oral Mucosa. *Int. J. Oral Sci.* **2020**, *12*, 8. <https://doi.org/10.1038/s41368-020-0074-x>.
8. Faustine, I.; Marteka, D.; Malik, A.; Supriyanto, E.; Syafhan, N.F. Genotype Variation of Ace and Ace2 Genes Affects the Severity of Covid-19 Patients. *BMC Res. Notes* **2023**, *16*, 194. <https://doi.org/10.1186/s13104-023-06483-z>.
9. Al-Eitan, L.; Al-Khaldi, S.; Ibdah, R.K. Ace Gene Polymorphism and Susceptibility to Hypertension in a Jordanian Adult Population. *PLoS ONE* **2024**, *19*, e0304271. <https://doi.org/10.1371/journal.pone.0304271>.
10. Matic, S.; Milovanovic, D.; Mijailovic, Z.; Djurdjevic, P.; Stefanovic, S.; Todorovic, D.; Vitosevic, K.; Canovic, V.; Popovic, S.; Dimitrijevic, N.M.; et al. Ace2 and Tmprss2 Genetic Polymorphisms as Potential Predictors of Covid-19 Severity and Outcome in Females. *Front. Med.* **2024**, *11*, 1493815.
11. Sabater Molina, M.; Rocamora, E.N.; Bendicho, A.I.; Vázquez, E.G.; Zorio, E.; Rodriguez, F.D.; Ortuño, C.G.; Rodríguez, A.I.; Sánchez-López, A.J.; Rubio, R.J.; et al. Polymorphisms in Ace, Ace2, Agtr1 Genes and Severity of Covid-19 Disease. *PLoS ONE* **2022**, *17*, e0263140. <https://doi.org/10.1371/journal.pone.0263140>.
12. Cafiero, C.; Rosapepe, F.; Palmirotta, R.; Re, A.; Ottaiano, M.P.; Benincasa, G.; Perone, R.; Varriale, E.; D’Amato, G.; Cacciamani, A.; et al. Angiotensin System Polymorphisms’ in Sars-Cov-2 Positive Patients: Assessment between Symptomatic and Asymptomatic Patients: A Pilot Study. *Pharmgenomics Pers. Med.* **2021**, *14*, 621–629.
13. Adimulam, T.; Arumugam, T.; Gokul, A.; Ramsuran, V. Genetic Variants within Sars-Cov-2 Human Receptor Genes May Contribute to Variable Disease Outcomes in Different Ethnicities. *Int. J. Mol. Sci.* **2023**, *24*, 8711.
14. Atiku, S.M.; Kasozi, D.; Campbell, K.; Olatunji, L.A. Single Nucleotide Variants (Snvs) of Angiotensin-Converting Enzymes (Ace1 and Ace2): A Plausible Explanation for the Global Variation in Covid-19 Prevalence. *J. Renin-Angiotensin-Aldosterone Syst.* **2023**, *2023*, 9668008.
15. El Yousfi, F.-Z.; El Hilali, S.; Belayachi, J.; Ennibi, K.; Razine, R.; Abouqal, R.; Bouhouche, A. Association of Renin–Angiotensin Pathway Gene Polymorphisms with Covid-19 Susceptibility and Severity in Moroccans: A Case–Control Study. *Biochem. Genet.* **2025**, *63*, 2225–2243. <https://doi.org/10.1007/s10528-024-10813-6>.
16. Mabhida, S.E.; Mashatola, L.; Kaur, M.; Sharma, J.R.; Apalata, T.; Muhamed, B.; Benjeddou, M.; Johnson, R. Hypertension in African Populations: Review and Computational Insights. *Genes* **2021**, *12*, 532.
17. Rayner, B.; Jones, E.; Veriava, Y.; Seedat, Y.K. South African Hypertension Society Commentary on the American College of Cardiology/American Heart Association Hypertension Guidelines. *Cardiovasc. J. Afr.* **2019**, *30*, 184–187.

18. Kgatle, M.; Das, R.; Lawal, I.; Boshomane, T.; Mokoala, K.; Gaspar, C.; Mbokazi, L.; Nkambule, N.; Gow, V.; Ndlovu, H.; et al. The Sars-Cov-2 Seroprevalence among Oncology Patients. *J. Clin. Med.* **2023**, *12*, 529.
19. Kgatle, M.; Chalwe, J.M.; van der Westhuizen, D.; Xu, S.; Damane, B.P.; Mathebela, P.; Ueckermann, V.; Mayaphi, S.; Rodrigues, H.G.; Moura-Alves, P.; et al. Detection of Neutralizing Antibodies in Covid-19 Patients from Steve Biko Academic Hospital Complex: A Pilot Study. *COVID* **2023**, *3*, 999–1010.
20. Chalwe, J.M.; Grobler, C.; Oldewage-Theron, W. Development of a Structural Equation Model to Examine the Relationships between Genetic Polymorphisms and Cardiovascular Risk Factors. *Nutrients* **2023**, *15*, 2470.
21. NCBI. *Rs5183 Snp*; National Library of Medicine: Bethesda, MD, USA, 2024. Available online: <https://www.ncbi.nlm.nih.gov/snp/rs5183> (accessed on 16 February 2026).
22. NCBI. *Rs5185 Snp*; National Library of Medicine: Bethesda, MD, USA, 2024. Available online: <https://www.ncbi.nlm.nih.gov/snp/rs5185> (accessed on 16 February 2026).
23. NCBI. *Rs5186 Snp*; National Library of Medicine: Bethesda, MD, USA, 2024. Available online: <https://www.ncbi.nlm.nih.gov/snp/rs5186> (accessed on 16 February 2026).
24. NCBI. *Rs2106809 Snp*; National Library of Medicine: Bethesda, MD, USA, 2024. Available online: <https://www.ncbi.nlm.nih.gov/snp/rs2106809> (accessed on 16 February 2026).
25. Honaker, J.; King, G.; Blackwell, M. Amelia: A Program for Missing Data. *J. Stat. Softw.* **1998**, *45*, 1–47.
26. Rubin, D.B. *Multiple Imputation for Nonresponse in Surveys*; Wiley: Hoboken, NJ, USA, 2004. Available online: <https://books.google.co.za/books?id=gTGzEAAAQBAJ> (accessed on 16 February 2026).
27. Venables, B.; Ripley, B. *Modern Applied Statistics with S*; Springer: Berlin/Heidelberg, Germany, 2002. Available online: <https://link.springer.com/book/10.1007/978-0-387-21706-2> (accessed on 22 January 2026).
28. Imoto, W.; Yamada, K.; Kawai, R.; Imai, T.; Kawamoto, K.; Uji, M.; Kanda, H.; Takada, M.; Ohno, Y.; Ohtani, H.; et al. A Cross-Sectional, Multicenter Survey of the Prevalence and Risk Factors for Long Covid. *Sci. Rep.* **2022**, *12*, 22413. <https://doi.org/10.1038/s41598-022-25398-6>.
29. Stroz, S.; Kosiorek, P.; Zbroch, E.; Mikoluc, B.; Stasiak-Barmuta, A. Immune Response Variation in Mild and Severe Covid-19 Patients. *Qatar Med. J.* **2024**, *2024*, 11.
30. Mueller, A.L.; McNamara, M.S.; Sinclair, D.A. Why Does Covid-19 Disproportionately Affect Older People? *Aging (Albany NY)* **2020**, *12*, 9959–9981.
31. Elijevich, F.; Kirabo, A.; Laffer, C.L. Salt Sensitivity of Blood Pressure in Black People: The Need to Sort out Ancestry Versus Epigenetic Versus Social Determinants of Its Causation. *Hypertension* **2024**, *81*, 456–467.
32. Lindhorst, J.; Alexander, N.; Blignaut, J.; Rayner, B. Differences in Hypertension between Blacks and Whites: An Overview. *Cardiovasc. J. Afr.* **2007**, *18*, 241–247.
33. Thomas, S.J.; Booth, J.N.; Dai, C.; Li, X.; Allen, N.; Calhoun, D.; Carson, A.P.; Gidding, S.; Lewis, C.E.; Shikany, J.M.; et al. Cumulative Incidence of Hypertension by 55 years of Age in Blacks and Whites: The Cardia Study. *J. Am. Heart Assoc.* **2018**, *7*, e007988.
34. Siddiqui, T.W.; Siddiqui, R.W.; Siddiqui, S.W.; Fatima, S. The Blood Pressure Gap: Confronting Racial and Ethnic Disparities. *Endocr. Pract.* **2025**, *31*, S189. <https://doi.org/10.1016/j.eprac.2025.05.526>.
35. Zilbermint, M.; Hannah-Shmouni, F.; Stratakis, C.A. Genetics of Hypertension in African Americans and Others of African Descent. *Int. J. Mol. Sci.* **2019**, *20*, 1081.
36. Peng, M.; He, J.; Xue, Y.; Yang, X.; Liu, S.; Gong, Z. Role of Hypertension on the Severity of Covid-19: A Review. *J. Cardiovasc. Pharmacol.* **2021**, *78*, e648–e655.
37. Zhang, V.; Fisher, M.; Hou, W.; Zhang, L.; Duong, T.Q. Incidence of New-Onset Hypertension Post-Covid-19: Comparison with Influenza. *Hypertension* **2023**, *80*, 2135–2148.
38. Hossain, S.; Islam, S.; Kamruzzaman, M.; Shekhar, H.U. Exploring Age-Related Influences on Covid-19 Severity and Therapeutic Approaches for Older Patients. *Aging Health Res.* **2025**, *5*, 100259.
39. Zaher, K.; Basingab, F.; Alrahimi, J.; Basahel, K.; Aldahlawi, A. Gender Differences in Response to Covid-19 Infection and Vaccination. *Biomedicines* **2023**, *11*, 1677.
40. Beegle, K.; Demombynes, G.; de Walque, D.; Gubbins, P.; Veillard, J. Covid-19 Increased Existing Gender Mortality Gaps in High-Income More Than Middle-Income Countries. *Int. J. Infect. Dis.* **2024**, *148*, 107167.
41. Boruga, M.; Septimiu-Radu, S.; Nandarge, P.S.; Elagez, A.; Doros, G.; Lazureanu, V.E.; Stoicescu, E.R.; Tanase, E.; Iacob, R.; Dumitrescu, A.; et al. Kidney Function Tests and Continuous Egfr Decrease at Six Months after Sars-Cov-2 Infection in Patients Clinically Diagnosed with Post-Covid Syndrome. *Biomedicines* **2024**, *12*, 950.

42. Cornelissen, M.E.B.; Bloemsma, L.D.; Baalbaki, N.; Twisk, J.W.R.; Downward, G.S.; der Zee, A.-H.M.-V. Estimated Glomerular Filtration Rate in Post Covid-19 Patients at 3–6 Months and 12–18 Months after Infection. *Ren. Fail.* **2025**, *47*, 2551737. <https://doi.org/10.1080/0886022X.2025.2551737>.
43. Ahmadian, E.; Khatibi, S.M.H.; Soofiyan, S.R.; Abediazar, S.; Shoja, M.M.; Ardalan, M.; Vahed, S.Z. Covid-19 and Kidney Injury: Pathophysiology and Molecular Mechanisms. *Rev. Med. Virol.* **2021**, *31*, e2176.
44. Batiha, G.E.-S.; Gari, A.; Elshony, N.; Shaheen, H.M.; Abubakar, M.B.; Adeyemi, S.B.; Al-kuraishy, H.M. Hypertension and Its Management in Covid-19 Patients: The Assorted View. *Int. J. Cardiol. Cardiovasc. Risk Prev.* **2021**, *11*, 200121.
45. Sohrabivafa, M.; Sadeghi, R.; Feiz-Haddad, M.H. Worldwide Prevalence of Hypertension in Patients with Covid-19: A Meta-Analysis and Systematic Review. *Health Scope* **2022**, *11*, e115665.
46. Teymourzadeh, A.; Abramov, D.; Norouzi, S.; Grewal, D.; Heidari-Bateni, G. Infection to Hypertension: A Review of Post-Covid-19 New-Onset Hypertension Prevalence and Potential Underlying Mechanisms. *Front. Cardiovasc. Med.* **2025**, *12*, 1609768.
47. Wong, R.S.Y. Inflammation in Covid-19: From Pathogenesis to Treatment. *Int. J. Clin. Exp. Pathol.* **2021**, *14*, 831–844.
48. Wrona, M.; Skrypnik, D. New-Onset Diabetes Mellitus, Hypertension, Dyslipidaemia as Sequelae of Covid-19 Infection—Systematic Review. *Int. J. Environ. Res. Public Health* **2022**, *19*, 13280.
49. Legris, P.; Vaillard, L.; Nonciaux, C.; Hourdain, P.; Taroux, M.; Petit, J.-M.; Vergès, B.; Bouillet, B. Diabetes Is Not Associated with Covid-19-Related Mortality in Older Institutionalized People. *Diabetes Metab.* **2021**, *47*, 101235.
50. Saponaro, F.; Rutigliano, G.; Sestito, S.; Bandini, L.; Storti, B.; Bizzarri, R.; Zucchi, R. Ace2 in the Era of Sars-Cov-2: Controversies and Novel Perspectives. *Front. Mol. Biosci.* **2020**, *7*, 588618.
51. Liu, J.Y.; Yi, Y.Z.; Guo, Q.W.; Jia, K.X.; Li, X.C.; Cai, J.J.; Shen, Y.L.; Su, G.M.; Chen, X.; Zhang, X.Y.; et al. Associations of Ace I/D and Agtr1 Rs5182 Polymorphisms with Diabetes and Their Effects on Lipids in an Elderly Chinese Population. *Lipids Health Dis.* **2024**, *23*, 231. <https://doi.org/10.1186/s12944-024-02222-w>.
52. Karakaş Çelik, S.; Genç, G.Ç.; Pişkin, N.; Açikgöz, B.; Altinsoy, B.; İşsiz, B.K.; Dursun, A. Polymorphisms of Ace (I/D) and Ace2 Receptor Gene (Rs2106809, Rs2285666) Are Not Related to the Clinical Course of Covid-19: A Case Study. *J. Med. Virol.* **2021**, *93*, 5947–5952.
53. Karczewski, K.J.; Francioli, L.C.; Tiao, G.; Cummings, B.B.; Alföldi, J.; Wang, Q.; Collins, R.L.; Laricchia, K.M.; Ganna, A.; Birnbaum, D.P.; et al. The Mutational Constraint Spectrum Quantified from Variation in 141,456 Humans. *Nature* **2020**, *581*, 434–443. <https://doi.org/10.1038/s41586-020-2308-7>.
54. Jafary, F.; Kazemi, M.; Zarean, M.; Khoshhali, M.; Karimian, M.; Fani, F.; Shahzamani, K. Association of Angiotensin-Converting Enzyme 2 Gene Polymorphisms with Hypertension and Treatment Response to Hydroxychloroquine in Iranian People with Coronavirus Disease 2019: A Cross-Sectional Study. *J. Int. Med. Res.* **2025**, *53*, 03000605251375221.
55. Bosso, M.; Thanaraj, T.A.; Abu-Farha, M.; Alanbaei, M.; Abubaker, J.; Al-Mulla, F. The Two Faces of Ace2: The Role of Ace2 Receptor and Its Polymorphisms in Hypertension and Covid-19. *Mol. Ther. Methods Clin. Dev.* **2020**, *18*, 321–327.
56. Luo, Y.; Liu, C.; Guan, T.; Li, Y.; Lai, Y.; Li, F.; Zhao, H.; Maimaiti, T.; Zeyaweiding, A. Association of Ace2 Genetic Polymorphisms with hypertension-Related Target Organ Damages in South Xinjiang. *Hypertens. Res.* **2019**, *42*, 681–689. <https://doi.org/10.1038/s41440-018-0166-6>.

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