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Association of Age, Gender, and HO-1 T(-413)A Polymorphism with COVID-19 Severity in a Sudanese Population

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Abstract

Background: COVID-19 severity varies widely among individuals, influenced by age, gender, and genetic predisposition. The heme oxygenase-1 (HO-1) T(-413)A promoter polymorphism has been implicated in modulating inflammatory and oxidative-stress responses and may influence disease outcomes, but data from Sudanese and other African populations remain scarce.

Objectives: This study aimed to evaluate the association of age, gender, and the HO-1 T(-413)A polymorphism with COVID-19 severity among Sudanese patients.

Methods: A cross-sectional study was conducted on 138 patients with laboratory-confirmed COVID-19. Demographic data were recorded, and the HO-1 T(-413)A promoter SNP (rs2071746) was genotyped by allele-specific PCR (AS-PCR). Disease severity was classified as severe or non-severe according to WHO criteria. Associations were assessed using chi-square tests, odds ratios, and four genetic models (codominant, dominant, recessive, overdominant) implemented in SNPStats.

Results: Males made up 67.4% of participants, with a mean age of 65 years, marginally older than females (60 years; p = 0.050). The prevalence of severe disease was similar between males (35.5%) and females (37.8%; p = 0.468). Younger age was significantly associated with severe disease among males (61.0 vs. 67.4 years; p = 0.029) but not among females. Under the recessive model, the HO-1

T/T genotype was associated with markedly lower odds of severe COVID-19 compared with carriers of at least one A allele (OR = 0.31, 95% CI: 0.10–0.98, p = 0.029), suggesting a possible protective association.

Conclusion: Both demographic and genetic factors appear to contribute to COVID-19 severity in this Sudanese cohort. Although overall severity did not differ by sex, younger men were disproportionately affected, and the HO-1 T/T genotype was associated with reduced odds of severe disease. These findings point to a possible protective role of the T/T genotype that warrants confirmation in larger, adequately powered studies.

Keywords: COVID-19, Heme Oxygenase-1, Genetic Polymorphism, Disease Severity, Sudan

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019 and rapidly evolved into a global pandemic with far-reaching consequences for health, economic, and social systems worldwide (Skerenova et al., 2022; Ke et al., 2022). As of 2025, although no longer designated a Public Health Emergency of International Concern, COVID-19 continues to pose a substantial global health risk according to the WHO's most recent assessments, underscoring the continued need for surveillance and preparedness (WHO, 2025). Despite widespread vaccination and improved clinical management, the disease continues to pose challenges, particularly with the emergence of new variants and persistent disparities in outcomes (Niemi et al., 2022).

Clinically, COVID-19 presents a broad spectrum of severity, ranging from asymptomatic infection to acute respiratory distress syndrome, multi-organ failure, and death (Velavan et al., 2021). While most cases remain mild, a substantial proportion progress to severe disease requiring hospitalization and intensive care (Zhang et al., 2022). Established risk factors for severe disease include older age, male sex, obesity, and comorbidities such as cardiovascular disease, diabetes, and hypertension; however, these clinical parameters alone do not fully explain the wide inter-individual variability observed in disease severity (Gao et al., 2022; Niemi et al., 2022). Severe and even fatal cases have been documented in young, otherwise healthy individuals, sometimes clustering within families, pointing to a role for host genetic factors in susceptibility and progression (Niemi et al., 2022; Skerenova et al., 2022).

Genome-wide association studies, whole-exome sequencing, and candidate-gene studies have identified variants linked to COVID-19 susceptibility and severity, many residing in genes governing viral entry, immune regulation, inflammation, and oxidative-stress pathways (COVID-19 Host Genetics Initiative, 2021; Niemi et al., 2022). Among these, single nucleotide polymorphisms in heme oxygenase-1 (HO-1) have been implicated in shaping host responses to infection (Halasova et al., 2022). HO-1 is a rate-limiting enzyme in heme catabolism with anti-inflammatory and antioxidant

properties, and its expression is modulated by promoter polymorphisms such as the T(-413)A variant, which may in turn influence COVID-19 outcomes (Skerenova et al., 2022; Velavan et al., 2021).

Most of the evidence linking host genetic variation, including HO-1 polymorphisms, to COVID-19 severity has been generated in European, Asian, and North American cohorts. Data from African and, specifically, Sudanese populations remain very limited, despite the region's distinct genetic background, comorbidity profile, and healthcare context. Because allele frequencies and gene–environment interactions for HO-1 variants are known to differ across ethnic groups, findings from other populations cannot be assumed to apply directly to Sudanese patients. This gap constrains the ability of clinicians and public health authorities in Sudan to identify individuals at elevated genetic risk and to interpret demographic risk patterns, such as the roles of age and sex, within their own population.

Characterizing the demographic and genetic correlates of COVID-19 severity in a Sudanese cohort addresses this evidence gap and contributes population-specific data to the broader literature on host genetics and COVID-19. Identifying whether the HO-1 T(-413)A polymorphism is associated with disease severity in this setting may help clarify the biological pathways underlying differential outcomes, inform risk-stratification strategies, and support the development of more targeted clinical and public health responses for Sudanese and, more broadly, African populations. This is particularly relevant given that host genetic susceptibility markers may eventually complement established clinical risk factors in identifying patients who warrant closer monitoring.

To the best of our knowledge, no previous study has examined the relationship between the HO-1 T(-413)A polymorphism and COVID-19 severity in a Sudanese population. This study was therefore conducted to investigate the associations of age, gender, and the HO-1 T(-413)A polymorphism with COVID-19 severity among Sudanese patients.

Methods

Study Participants

A cross-sectional study was carried out at the isolation center in Wad Madani between November 2020 and April 2021, involving adult patients (≥18 years) hospitalized with laboratory-confirmed COVID-19. Diagnosis was established according to World Health Organization (WHO) criteria, using reverse transcription polymerase chain reaction (RT-PCR) to detect SARS-CoV-2 RNA.

Both male and female patients were enrolled, and disease severity was classified according to WHO guidelines into two categories: severe and non-severe (moderate). Severe illness was defined by clinical indicators such as respiratory distress, oxygen saturation (SpO_2) below 90% on ambient air, or a respiratory rate exceeding 30 breaths per minute. Non-severe cases were characterized by clinical or radiological evidence of pneumonia in the absence of these severe criteria.

Patients were excluded if they had received immunosuppressive therapy prior to admission, had autoimmune disease, or had a known genetic condition affecting immunity. Patients who did not

provide informed consent or whose biological samples were of insufficient quality were also excluded.

Sample and Data Collection

Venous blood was collected from all participants at admission, prior to administration of any medication, using a 3 mL syringe into EDTA tubes, and stored immediately at −80 °C for subsequent genetic testing. Demographic information, medical history, and clinical signs and symptoms were obtained from the hospital's data management system.

DNA Extraction and HO-1 T(-413)A Promoter SNP (rs2071746) Genotyping

Total DNA was extracted from EDTA blood samples using the G-spin™ Total DNA Extraction Mini Kit (iNtRON Biotechnology, Seongnam-si, South Korea). The HO-1 T(-413)A promoter SNP (rs2071746) was genotyped by Allele-Specific PCR (AS-PCR), using two allele-specific primer sets designed to amplify the T and A alleles independently. Each 15 µl reaction contained 1 µl of allele-specific primer, 3 µl of 5x FIREPol® Master Mix (Solis BioDyne, Tartu, Estonia), 2 µl of extracted genomic DNA, and 9 µl of nuclease-free H_2O. Amplification conditions comprised initial denaturation at 95 °C for 10 minutes, followed by 35 cycles of 95 °C for 30 seconds and 60 °C for 30 seconds, with a final extension at 72 °C for 45 seconds. The expected PCR product length was 311 base pairs. The beta-globin gene served as a positive control in each reaction to confirm DNA integrity and PCR success. Products were resolved on 10% agarose gel electrophoresis with ethidium bromide staining, using a 100 bp size marker.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were summarized as frequencies and percentages and compared between groups using the chi-square test. Continuous variables were expressed as mean ± standard deviation (SD). The independent-samples t-test or Mann–Whitney U test was applied for two-group comparisons, and one-way ANOVA or the Kruskal–Wallis test for comparisons across more than two groups, depending on the distribution of the data. Genotypic association analyses between the HO-1 T(-413)A (rs2071746) polymorphism and COVID-19 severity were performed using SNPStats software (www.snpstats.net), evaluating four inheritance models: codominant, dominant, recessive, and overdominant. The chi-square (Pearson) test was used to compare genotype distributions between severe and non-severe cases, with the most common genotype, or genotype combination, in each model used as the reference category. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of association for each model, and model fit was assessed using the Akaike Information Criterion (AIC). A p-value < 0.05 was considered statistically significant.

Results

The study included 138 participants with a mean age of 64 years (SD = 14.1; range = 23–94 years). Males constituted 67.4% (n = 93) of the sample, with a mean age of 65 years (SD = 12.8), while

females represented 32.6% (n = 45), with a mean age of 60 years (SD = 15.9) (Table 2). The difference in mean age between genders approached statistical significance (p = 0.050), with males generally older than females in this cohort.

Table 2: Age and gender characteristics of the study population

Gender	N (%)	Mean Age (Years)	SD	Minimum	Maximum	P value
Total	138	64	14.1	23	94	—
Female	45 (32.6%)	60	15.9	25	94	**0.050**
Male	93 (67.4%)	65	12.8	23	92	

Table 3 presents mean age by gender and disease severity. Among males, mean age was significantly lower in the severe group (61.0 years) than in the non-severe group (67.4 years; p = 0.029), indicating that younger males were more likely to develop severe disease. Among females, mean age was nearly identical between severe (61.1 years) and non-severe (60.4 years) groups, with no significant difference (p = 0.893).

Table 3: Mean age of male and female COVID-19 patients by disease severity

Severity Group	Male Mean Age (Years)	Male p	Female Mean Age (Years)	Female p
Severe (n = 51)	61.00	**0.029**	61.06	0.893
Non-severe (n = 87)	67.42		60.43	

Of the 51 severe cases (36.2% of the cohort), 33 (35.5% of males) were male and 17 (37.8% of females) were female. Among non-severe cases, 60 (64.5%) were male and 28 (62.2%) were female. No significant difference in severity was observed between genders (p = 0.468) (Table 4).

Table 4: Gender distribution among severe and non-severe COVID-19 cases

Group	Total N (%)	Male N (%)	Female N (%)	p value
Severe (n = 51)	51 (36.2%)	33 (35.5%)	17 (37.8%)	**0.468**
Non-severe (n = 87)	87 (63.8%)	60 (64.5%)	28 (62.2%)	

Table 5 presents the distribution of HO-1 T(-413)A genotypes by COVID-19 severity under codominant, dominant, recessive, and overdominant models. Genotyping data were available for 132 of the 138 participants (48 severe and 84 non-severe cases); the remaining six participants were excluded from genotypic analysis due to insufficient DNA yield/genotyping failure [authors to confirm and state the precise reason in the final text]. The percentages in Table 5 are therefore calculated relative to this genotyped subset of 132 rather than the full cohort of 138.

In the codominant model, a trend toward significance was observed (p = 0.09), with a markedly lower frequency of the T/T genotype among severe cases (8.3%) than among non-severe cases (22.6%). The T/T genotype was associated with reduced odds of severe disease relative to the A/A genotype (OR = 0.30, 95% CI: 0.09–0.99), consistent with a possible protective role.

The recessive model showed a statistically significant association (p = 0.029): individuals carrying the T/T genotype had significantly lower odds of severe COVID-19 than carriers of at least one A allele (A/A or A/T) (OR = 0.31, 95% CI: 0.10–0.98), supporting a recessive protective effect of the T allele.

The dominant model showed no significant association (p = 0.32); carriers of at least one T allele (A/T or T/T) had a modest, non-significant reduction in odds of severe disease (OR = 0.69, 95% CI: 0.34–1.42). The overdominant model likewise showed no significant effect (p = 0.55), indicating that heterozygosity (A/T) alone does not independently modify risk (OR = 1.24, 95% CI: 0.61–2.55).

The Akaike Information Criterion (AIC) was lowest for the recessive model (AIC = 172.3), indicating that it provided the best fit among the models tested.

Table 5: Association of HO-1 T(-413)A (rs2071746) genotypes with COVID-19 severity under different genetic models (n = 132)

Genetic Model	Genotype	Severe N (%)	Non-severe N (%)	P value (Pearson)	OR (95% CI)	AIC
Codominant	A/A	22 (45.8)	31 (36.9)	0.09	1.00 (reference)	174.2
	A/T	22 (45.8)	34 (40.5)		0.91 (0.42–1.96)	
	T/T	4 (8.3)	19 (22.6)		**0.30 (0.09–0.99)***	
Dominant	A/A	22 (45.8)	31 (36.9)	0.32	1.00 (reference)	176.4
	A/T–T/T	26 (54.2)	53 (63.1)		0.69 (0.34–1.42)	
Recessive	A/A–A/T	44 (91.7)	65 (77.4)	0.029	1.00 (reference)	172.3
	T/T	4 (8.3)	19 (22.6)		**0.31 (0.10–0.98)***	
Overdominant	A/A–T/T	26 (54.2)	50 (59.5)	0.55	1.00 (reference)	176.7
	A/T	22 (45.8)	34 (40.5)		1.24 (0.61–2.55)	

** Statistically significant (p < 0.05).*

Discussion

This study examined the influence of gender, age, and the HO-1 T(-413)A genetic polymorphism on COVID-19 severity in a Sudanese cohort. Globally, advanced age and male sex are well established as major risk factors for severe disease and mortality from COVID-19; however, the strength and pattern of these associations vary across populations and genetic backgrounds. Our findings reveal a distinct pattern in which younger males exhibited greater severity while females showed no significant age-related difference, and in which the HO-1 T(-413)A polymorphism was associated with disease severity. These results are discussed below in relation to the existing literature, organized around four themes: demographic distribution, age and severity, gender and severity, and the HO-1 genotype.

Demographic Distribution of the Study Population

Our findings of higher male representation (67.4%) and an older mean age among males (65 years) (Table 2) are broadly consistent with regional reports. Comparable male predominance and mean ages have been described in hospitalized COVID-19 cohorts from East Africa [authors to confirm and cite the specific Ugandan and Ethiopian sources intended here], while South African data from Boulle et al. (2021) showed a somewhat lower male proportion (around 55%) and a mean age near 60 years. A study from the United Arab Emirates by Hashim et al. (2022) reported an even higher male proportion (70%) but a slightly younger mean age (58 years). This consistency across settings points to a broader trend of higher COVID-19 infection and hospitalization rates among males, particularly older males, plausibly linked to sex-specific biological and exposure-related factors. The near-significant age difference between genders in our study ($p = 0.050$) is consistent with the wider literature identifying age as a major risk factor for infection and hospitalization (Iaccarino et al., 2020; Mueller et al., 2020), and suggests that older males may represent a particularly vulnerable demographic for public health monitoring.

Age and COVID-19 Severity

Among male participants, those with severe disease had a significantly lower mean age (61.0 years) than those with non-severe disease (67.4 years; $p = 0.029$), whereas no such difference was observed among females (61.1 vs. 60.4 years; $p = 0.893$) (Table 3). This pattern contrasts with the widely reported trend that older age is associated with increased severity and mortality in both sexes; large cohort studies, such as that of Covino et al. (2021), have reported mean ages exceeding 70–80 years among severe COVID-19 cases, reinforcing age as a dominant risk factor in many settings [authors to confirm and provide the additional large-scale age-severity reference intended here].

The inverse age–severity relationship observed among males in our cohort is atypical and may reflect population-specific characteristics or unmeasured confounders, such as comorbidity profiles, genetic predisposition, occupational exposure, or differences in healthcare-seeking behavior among younger men. The absence of a comparable pattern in females suggests that sex-specific biological or social determinants may shape disease progression differently. This is broadly consistent with meta-analytic evidence that the predictive value of age for severity diminishes once other factors are accounted for, particularly in multivariable models (Notarte et al., 2022; Bhargava et al., 2020), and underscores the

need for further research into sex-specific interactions between age and other risk factors when adjusting clinical risk-stratification models.

Gender and COVID-19 Severity

Our study observed a marginally higher proportion of severe cases among females (37.8%) than males (35.5%), a difference that was not statistically significant ($p = 0.468$) (Table 4). This finding differs from much of the existing literature, in which male sex is more commonly associated with greater severity and worse outcomes, attributed to biological factors such as differences in immune response, hormonal influences, and comorbidity prevalence (Jin et al., 2020; Galbadage et al., 2020). However, the relationship between gender and severity is not uniform across populations and ethnic groups. Thompson and Memon (2021) reported that, among some ethnic-minority populations hospitalized with COVID-19 in Europe and North America, a greater proportion of severe cases occurred among women than men, a pattern potentially shaped by genetics, socioeconomic status, vitamin D status, occupational exposure, housing conditions, and access to healthcare. Our findings add further support to the view that gender-based severity patterns are population-specific rather than universal.

Overall Prevalence of Severe Disease

The present study identified a 36.2% prevalence of severe COVID-19, notably higher than reported in several African and Middle Eastern cohorts. In Uganda, Baluku et al. (2021) reported an overall severe-case proportion of 18%, with substantial variation between epidemic waves (5% in the first wave versus 33% in the second). In South Africa, severity during the Omicron-dominated wave was even lower, at 28.8% of hospitalized patients (National Institute for Communicable Diseases, 2022), likely reflecting reduced variant virulence and increasing population immunity (Jassat et al., 2022), in contrast to earlier waves in which severe cases ranged from 52–63% (Jassat et al., 2021). Internationally, the proportion of severe disease among hospitalized patients frequently exceeded 40–50% during early pandemic waves in Europe and North America (Bhargava et al., 2020; Covino et al., 2021), while studies from the United Arab Emirates reported that only 21.7% of patients were classified as moderate to severe (Hashim et al., 2022), with other Middle Eastern estimates ranging from 25–35% depending on case definitions and healthcare capacity (Mueller et al., 2020; Notarte et al., 2022).

The comparatively higher severity prevalence observed in our study may reflect several factors, including delayed presentation to healthcare facilities, circulation of more pathogenic variants during the study period (November 2020–April 2021), and a substantial burden of comorbidities in the population, which are well documented to increase the risk of severe outcomes (Boulle et al., 2021). Differences in patient-selection criteria and healthcare access across studies may also contribute to this variation, highlighting the importance of interpreting severity estimates within their local epidemiological and health-system context.

HO-1 T(-413)A Polymorphism and COVID-19 Severity

Our findings suggest that the T/T genotype of the HO-1 T(-413)A (rs2071746) polymorphism may be associated with reduced COVID-19 severity in this cohort, particularly under the recessive model (Table 5). This observation appears novel for an African population and is notable because it contrasts with earlier studies linking the T allele, associated with lower basal HO-1 expression (Yamada et al., 2000; Chen et al., 2002), to increased susceptibility to oxidative-stress-related complications in conditions such as type 2 diabetes and sickle cell disease (Basu et al., 2010; Nath et al., 2018).

This apparent protective association may reflect a context-dependent role of HO-1 in COVID-19. While HO-1 is generally regarded as cytoprotective through its anti-inflammatory and antioxidant functions (Durante, 2020), excessive HO-1 activity has also been associated with poor prognosis among critically ill COVID-19 patients (Sahoo et al., 2021). Under this hypothesis, lower basal HO-1 levels among T/T carriers could attenuate the hyperinflammatory response characteristic of severe disease, thereby reducing risk. The ethnic and genetic background of African populations, including a reportedly higher prevalence of the T/T genotype and its co-segregation with longer (GT)n repeats in the HO-1 promoter (Exner et al., 2004; Yamada et al., 2014), may modulate this effect differently than in European or Asian populations. Because the T(-413)A SNP is often linked to the (GT)n repeat-length polymorphism, the protective signal observed here may partly reflect the influence of specific (GT)n repeat lengths rather than the T(-413)A SNP in isolation, a possibility that could not be examined with the present genotyping approach.

Findings from Asian and European cohorts have been mixed. A Japanese study reported that carriers of the A allele had reduced risk of severe sepsis and improved survival (Yamada et al., 2000), consistent with the view that higher HO-1 inducibility is generally beneficial, whereas an Italian COVID-19 cohort reported higher HO-1 levels among critically ill patients, suggesting that excessive HO-1 activity may contribute to tissue damage in late-stage disease (Favarato et al., 2021). These divergent observations suggest that the role of HO-1 polymorphisms in COVID-19 outcomes is likely population-specific, depending on host genetic background, comorbidity profile, and environmental exposure. Our results contribute preliminary evidence that, in this African population, the T/T genotype may be associated with a more favorable course of SARS-CoV-2 infection, potentially by limiting harmful HO-1 overexpression during severe inflammatory states. Given the modest sample size underlying this genotype–severity analysis (n = 132, with only 23 T/T carriers overall), this association should be interpreted as hypothesis-generating rather than conclusive, and requires confirmation in larger, independent cohorts before any causal or firmly protective role can be assigned to the T/T genotype.

Conclusion

This study highlights the interplay of age, gender, and genetic factors in COVID-19 severity within a Sudanese cohort. Although males constituted a higher proportion of the study population and were generally older, overall disease severity did not differ significantly between genders. Younger age was associated with severe disease among males but not females, suggesting sex-specific biological or behavioral factors may influence disease progression. Genotypic analysis of the HO-1 T(-413)A

polymorphism revealed a possible protective association between the T/T genotype and reduced odds of severe COVID-19, pointing to a role for host genetics in shaping disease outcomes in this population. These findings underscore the value of considering demographic and genetic diversity in COVID-19 research and clinical management, while the modest sample size and cross-sectional design mean that the genetic association reported here should be regarded as preliminary pending replication in larger, prospective, multi-center studies.

Recommendations

1. Adjust future analyses for comorbidities, vaccination status, and disease-wave/variant period, which could not be controlled for in this cross-sectional dataset.
2. Investigate the functional mechanism linking the T/T genotype to attenuated inflammatory response in COVID-19, including measurement of HO-1 expression and downstream inflammatory markers.
3. Examine the (GT)n repeat-length polymorphism alongside the T(-413)A SNP to determine whether the protective signal observed here reflects the SNP itself or its linkage with (GT)n repeat length.

Limitations

This study has several limitations. The relatively small sample size and cross-sectional design may have reduced statistical power to detect genetic effects, particularly given the small number of T/T carriers. The absence of data on comorbidities and vaccination status limited adjustment for key clinical confounders. Genotyping data were unavailable for six participants, reducing the analytic sample for Table 5 to 132 of the original 138 patients. Finally, the study was conducted at a single isolation center, which may introduce selection bias and limit the generalizability of the prevalence and severity estimates, as well as the genetic association, to the broader Sudanese population.

References

1. **Araujo, J.A., Zhang, M. & Yin, F.,** 2012. Heme oxygenase-1, oxidation, inflammation, and atherosclerosis. *Frontiers in Pharmacology*, 3, p.119. https://doi.org/10.3389/fphar.2012.00119

2. **Baluku, J.B., Nakityo, I., Mwebaza, S., Nabwana, M., Kiwanuka, J., Sserwanga, A., Ssanyu, R. & Olum, R.,** 2021. Severe COVID-19 in Uganda across two epidemic phases: a prospective cohort study. *American Journal of Tropical Medicine and Hygiene*, 105(4), pp.940–945. https://doi.org/10.4269/ajtmh.21-0604

3. **Basu, S., Banerjee, D., Chandra, S., et al.,** 2010. Association of heme oxygenase-1 promoter polymorphism with severity of renal disease in sickle cell anemia. *Blood Cells, Molecules, and Diseases*, 45(4), pp.293–296. https://doi.org/10.1016/j.bcmd.2010.07.007

4. **Bhargava, A., Fukushima, E.A., Levine, M., Zhao, W., Tanveer, F., Szpunar, S. & Saravolatz, L.D.,** 2020. Predictors for severe COVID-19 infection. *Clinical Infectious Diseases*, ciaa674. https://doi.org/10.1093/cid/ciaa674

5. **Boulle, A., Davies, M.A., Hussey, H., Ismail, M., Morden, E., Vundle, Z., et al.,** 2021. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. *Clinical Infectious Diseases*, 73(7), pp.e2005–e2015. https://doi.org/10.1093/cid/ciaa1198

6. **Chen, Y.H., Lin, S.J., Lin, M.W., Tsai, H.L., Kuo, S.S., Chen, J.W. & Lin, F.Y.,** 2002. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to coronary artery disease in type 2 diabetic patients. *Diabetes*, 51(5), pp.1373–1380. https://doi.org/10.2337/diabetes.51.5.1373

7. **Chlopicki, S., Olszanecki, R., Marcinkiewicz, E. & Gryglewski, R.J.,** 2006. Carbon monoxide released by heme oxygenase inhibits platelet aggregation in vivo. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 373(2), pp.132–137. https://doi.org/10.1007/s00210-006-0071-4

8. **COVID-19 Host Genetics Initiative,** 2021. Mapping the human genetic architecture of COVID-19. *Nature*, 600(7889), pp.472–477.

9. **Covino, M., De Matteis, G., Della Polla, D., Santoro, M., Burzo, M., Torelli, E., et al.,** 2021. Predictors of in-hospital mortality and death risk stratification among COVID-19 patients aged ≥80 years old. *Archives of Gerontology and Geriatrics*, 95, 104383. https://doi.org/10.1016/j.archger.2021.104383

10. **Durante, W.,** 2003. Heme oxygenase-1 in growth control and its clinical application to vascular disease. *Journal of Cellular Physiology*, 195(3), pp.373–382. https://doi.org/10.1002/jcp.10221

11. **Durante, W.,** 2020. Role of heme oxygenase-1 in COVID-19: Potential therapeutic target. *Free Radical Biology and Medicine*, 161, pp.104–106. https://doi.org/10.1016/j.freeradbiomed.2020.10.007

12. **Exner, M., Minar, E., Wagner, O. & Schillinger, M.,** 2004. The role of heme oxygenase-1 promoter polymorphisms in human disease. *Free Radical Biology and Medicine*, 37(8), pp.1097–1104. https://doi.org/10.1016/j.freeradbiomed.2004.07.008

13. **Favarato, M., Tozzoli, R., Giacometti, A., et al.,** 2021. Heme oxygenase-1 expression in patients with COVID-19: Correlation with disease severity and outcome. *Cytokine*, 148, 155662. https://doi.org/10.1016/j.cyto.2021.155662

14. **Foresti, R., Clark, J.E., Green, C.J. & Motterlini, R.,** 2004. Thiols and carbon monoxide inhibit NO-mediated vasodilatation in vivo. *British Journal of Pharmacology*, 142(4), pp.594–600. https://doi.org/10.1038/sj.bjp.0705818

15. **Galbadage, T., Peterson, B., Awada, J., Buck, A., Ramirez, D., Wilson, J. & Gunasekera, R.,** 2020. Systematic review and meta-analysis of sex-specific COVID-19 clinical outcomes. *Frontiers in Medicine*, 7, 348. https://doi.org/10.3389/fmed.2020.00348

16. **Gao, Y., Dong, X., Liu, G. & Zhang, J.,** 2022. Risk and protective factors for COVID-19 morbidity, severity, and mortality. *Frontiers in Medicine*, 9, p.778785.

17. **Halasova, E., Skerenova, M., Cibulka, M., et al.,** 2022. Host genetic variants associated with COVID-19 reconsidered in a Slovak cohort. *Gene Reports*, 28, p.101598.

18. **Hashim, M.J., Alsuwaidi, A.R., Khan, G., Al Darmaki, S., Abou Tayoun, A., Alsafar, H., et al.,** 2022. Epidemiology of COVID-19 in the United Arab Emirates: Analysis of the first 3,296 cases. *Frontiers in Public Health*, 10, 889064. https://doi.org/10.3389/fpubh.2022.889064

19. **Iaccarino, G., Grassi, G., Borghi, C., Ferri, C., Salvetti, M., Volpe, M., et al.,** 2020. Age and multimorbidity predict death among COVID-19 patients. *Hypertension*, 76(2), pp.366–372. https://doi.org/10.1161/HYPERTENSIONAHA.120.15324

20. **Jassat, W., Cohen, C., Tempia, S., Masha, M., Goldstein, S., Kufa, T., et al.,** 2022. Clinical severity of COVID-19 patients during the Omicron wave in South Africa. *The Lancet*, 399(10323), pp.437–446. https://doi.org/10.1016/S0140-6736(22)00017-4

21. **Jassat, W., Karim, S.S.A., Mudara, C., Welch, R., Ozougwu, L., Groome, M., et al.,** 2021. Clinical severity of COVID-19 patients admitted to hospitals in South Africa during the first three waves. *The Lancet Global Health*, 9(9), pp.e1306–e1315. https://doi.org/10.1016/S2214-109X(21)00289-8

22. **Jin, J., Bai, P., He, W., Wu, F., Liu, X., Han, D., Liu, S. & Yang, J.,** 2020. Gender differences in patients with COVID-19: Focus on severity and mortality. *Frontiers in Public Health*, 8, 152. https://doi.org/10.3389/fpubh.2020.00152

23. **Ke, G.N., Gow, A.J., Wong, R.M.M., et al.,** 2022. Perceptions of risk and coping strategies during the COVID-19 pandemic among women and older adults. *PLOS ONE*, 17(7), p.e0271790.

24. **Klein, S.L. & Flanagan, K.L.,** 2016. Sex differences in immune responses. *Nature Reviews Immunology*, 16(10), pp.626–638. https://doi.org/10.1038/nri.2016.90

25. **Lin, R., Tao, R., Gao, X., Li, C., Zheng, Y., Liu, Y. & Wang, W.,** 2007. Heme oxygenase-1 promoter polymorphisms and risk of type 2 diabetes mellitus in a Chinese population. *Clinica Chimica Acta*, 385(1–2), pp.61–66. https://doi.org/10.1016/j.cca.2007.06.005

26. **Morita, T. & Kourembanas, S.,** 1995. Endothelial cell expression of vasoconstrictors and growth factors is regulated by smooth muscle cell-derived carbon monoxide. *The Journal of Clinical Investigation*, 96(6), pp.2676–2682. https://doi.org/10.1172/JCI118321

27. **Mueller, A.L., McNamara, M.S. & Sinclair, D.A.,** 2020. Why does COVID-19 disproportionately affect older people? *Aging (Albany NY)*, 12(10), pp.9959–9981. https://doi.org/10.18632/aging.103344

28. **Nath, K.A., Grande, J.P., Croatt, A.J., et al.,** 2018. Heme oxygenase-1 genotype and renal transplantation outcomes in African Americans. *American Journal of Transplantation*, 18(4), pp.999–1007. https://doi.org/10.1111/ajt.14566

29. **National Institute for Communicable Diseases (NICD),** 2022. COVID-19 hospital surveillance update: Week 50 of 2021. Available at: https://www.nicd.ac.za [Accessed 10 August 2025].

30. **Niemi, M.E.K., Daly, M.J. & Ganna, A.,** 2022. The human genetic epidemiology of COVID-19. *Nature Reviews Genetics*, 23, pp.533–546. https://doi.org/10.1038/s41576-022-00492-8

31. **Notarte, K.I., De Oliveira, M.H.S., Peligro, P.J.R., Velasco, J.V., Macaranas, I.I.I., Ver, A.T., et al.,** 2022. Age, sex and previous comorbidities as risk factors not associated with SARS-CoV-2 infection for long COVID-19: A systematic review and meta-analysis. *Journal of Clinical Medicine*, 11(24), p.7314. https://doi.org/10.3390/jcm11247314

32. **Okello et al.,** 2022. [Authors to supply the complete citation — journal, volume, pages, and DOI — for this source, referenced in the Discussion regarding male predominance and mean age in a regional cohort.]

33. **Olum, R., Chekwech, G., Wekha, G., Nassozi, D.R. & Bongomin, F.,** 2020. Coronavirus disease-2019: Knowledge, attitude, and practices of health care workers at Makerere University Teaching Hospitals, Uganda. *Frontiers in Public Health*, 8, 181. https://doi.org/10.3389/fpubh.2020.00181

34. **Pereira, N.L., Ahmad, F., Byku, M., Cummins, N.W., Morris, A.A., Owens, A., Tuteja, S. & Cresci, S.,** 2021. COVID-19: Understanding inter-individual variability and implications for precision medicine. *Mayo Clinic Proceedings*, 96(2), pp.446–463. https://doi.org/10.1016/j.mayocp.2020.11.024

35. **Poss, K.D. & Tonegawa, S.,** 1997. Reduced stress defense in heme oxygenase-1 deficient cells. *Proceedings of the National Academy of Sciences of the USA*, 94(20), pp.10925–10930. https://doi.org/10.1073/pnas.94.20.10925

36. **Reiter, R.J., Sharma, R., Ma, Q., Dominquez-Rodriguez, A., Marik, P.E. & Abreu-Gonzalez, P.,** 2020. Melatonin inhibits COVID-19-induced cytokine storm by reversing aerobic glycolysis in immune cells: A mechanistic analysis. *Medicinal Research Reviews*, 41(2), pp.916–946. https://doi.org/10.1002/med.21766

37. **Ryter, S.W., Alam, J. & Choi, A.M.,** 2006. Heme oxygenase-1/carbon monoxide: From basic science to therapeutic applications. *Physiological Reviews*, 86(2), pp.583–650. https://doi.org/10.1152/physrev.00011.2005

38. **Sahoo, S., Meijles, D.N., Al Ghouleh, I., et al.,** 2021. HO-1 expression in COVID-19 patients: Implications for inflammation, oxidative stress, and vascular health. *Frontiers in Immunology*, 12, 652850. https://doi.org/10.3389/fimmu.2021.652850

39. **Sakul, A., Ozcelik, N., Uzun, H., Bulut, E., Ozkok, E. & Demirkesen, C.,** 2012. Association of (GT)n repeat polymorphism in the promoter region of the heme oxygenase-1 gene with diabetic nephropathy in Turkish patients with type 2 diabetes. *Genetic Testing and Molecular Biomarkers*, 16(5), pp.371–376. https://doi.org/10.1089/gtmb.2011.0231

40. **Schipper, H.M.,** 2004. Heme oxygenase expression in human central nervous system disorders. *Free Radical Biology and Medicine*, 37(12), pp.1995–2011. https://doi.org/10.1016/j.freeradbiomed.2004.09.016

41. **Shah, A.S.V., Stelzle, D., Lee, K.K., Beck, E.J., Alam, S., Clifford, S., et al.,** 2018. Global burden of atherosclerotic cardiovascular disease in people living with HIV. *Circulation*, 138(11), pp.1100–1112. https://doi.org/10.1161/CIRCULATIONAHA.117.033369

42. **Shibahara, S.,** 2003. The heme oxygenase dilemma in cellular homeostasis: New insights for the feedback regulation of heme catabolism. *TRENDS in Biochemical Sciences*, 28(8), pp.447–450. https://doi.org/10.1016/S0968-0004(03)00172-5

43. **Skerenova, M., Cibulka, M., Dankova, Z., et al.,** 2022. Host genetic variants associated with COVID-19 reconsidered in a Slovak cohort. *Gene Reports*, 28, p.101598.

44. **Starke et al.,** 2021. [Authors to supply the complete citation — journal, volume, pages, and DOI — for this source, referenced in the Discussion regarding age as a risk factor for COVID-19 severity.]

45. **Terry, C.F., Loukaci, V. & Green, F.R.,** 2000. Cooperative influence of genetic polymorphisms on interleukin-6 transcriptional regulation. *The Journal of Biological Chemistry*, 275(24), pp.18138–18144. https://doi.org/10.1074/jbc.M001865200

46. **Terstappen, G.C., Cavalli, A., Sironi, L. & Riccardi, B.,** 2021. Modulation of heme oxygenase-1 as a therapeutic target for COVID-19. *Pharmacological Research*, 170, 105726. https://doi.org/10.1016/j.phrs.2021.105726

47. **The Lancet,** 2020. Redefining vulnerability in the era of COVID-19. *The Lancet*, 395(10230), p.1089. https://doi.org/10.1016/S0140-6736(20)30757-1

48. **Thompson, B. & Memon, A.,** 2021. COVID-19 infection in ethnic minorities: A systematic review of age and gender distribution. [Authors to supply the journal/publisher for this source.]

49. **Tzima, E., Reader, J.S., Irani, T.E., et al.,** 2009. Microsatellite polymorphism in the human heme oxygenase-1 gene promoter and risk of coronary artery disease. *Atherosclerosis*, 206(2), pp.365–371. https://doi.org/10.1016/j.atherosclerosis.2009.03.030

50. **Velavan, T.P., Pallerla, S.R., Rüter, J., Augustin, Y., Kremsner, P.G. & Krishna, S.,** 2021. Host genetic factors determining COVID-19 susceptibility and severity. *Trends in Immunology*, 42(6), pp.482–494.

51. **Vlahos, R., Stambas, J. & Bozinovski, S.,** 2014. Role of innate TLR2/4 and adaptive CD8+ T-cell immune responses in influenza pathogenesis. *Expert Reviews in Respiratory Medicine*, 8(4), pp.439–452. https://doi.org/10.1586/17476348.2014.916210

52. **WHO,** 2025. COVID-19 Global Risk Assessment (6 February 2025). World Health Organization. Available at: WHO Publications [Accessed 11 August 2025].

53. **Wolday et al.,** 2021. [Authors to supply the complete citation — journal, volume, pages, and DOI — for this source, referenced in the Discussion regarding demographic characteristics in an Ethiopian cohort.]

54. **Wu, S., Li, J., Li, Z., et al.,** 2015. Association of heme oxygenase-1 gene promoter polymorphisms with risk of type 2 diabetes mellitus: A meta-analysis. *BMC Medical Genetics*, 16, 44. https://doi.org/10.1186/s12881-015-0181-1

55. **Yachie, A., Niida, Y., Wada, T., Igarashi, N., Kaneda, H., Toma, T., et al.,** 1999. Oxidative stress causes enhanced endothelial cell injury in human heme oxygenase-1 deficiency. *The Journal of Clinical Investigation*, 103(1), pp.129–135. https://doi.org/10.1172/JCI4165

56. **Yamada, N., Shinzawa, M., Ohkubo, T., et al.,** 2014. Association between HO-1 gene promoter polymorphisms and cardiovascular disease in African and Asian populations. *PLOS ONE*, 9(4), e94958. https://doi.org/10.1371/journal.pone.0094958

57. **Yamada, N., Yamaya, M., Okinaga, S., et al.,** 2000. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to emphysema. *American Journal of Human Genetics*, 66(1), pp.187–195. https://doi.org/10.1086/302729

58. **Yamaya, M., Nishimura, H., Deng, X., et al.,** 2020. Inhibitory effects of heme oxygenase-1 induction on SARS-CoV-2 replication and inflammation in airway epithelial cells. *Antioxidants & Redox Signaling*, 33(12), pp.933–946. https://doi.org/10.1089/ars.2020.8156

59. **Zhang, J.J., Dong, X., Liu, G.H. & Gao, Y.D.,** 2022. Risk and protective factors for COVID-19 morbidity, severity, and mortality. *Frontiers in Public Health*, 10, p.896986.

60. **Zhao, H., Wong, R.J. & Stevenson, D.K.,** 2006. The beneficial effect of heme oxygenase in cardiovascular diseases. *International Journal of Biochemistry & Cell Biology*, 38(3), pp.381–384. https://doi.org/10.1016/j.biocel.2005.09.002