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COVID-19 susceptibility and severity: Potential of *ACE1* I/D gene polymorphism (rs4646994) and *IFITM3* gene (rs12252) polymorphism among Myanmar people

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Abstract
Background: The COVID-19 pandemic caused by SARS-CoV-2 represents one of the most devastating global health crises. Among the various factors contributing to increased risk, host genomic variation is increasingly recognized as a critical determinant of susceptibility to infection and the diversity of clinical outcomes. Polymorphisms in the *ACE1* gene (rs4646994 I/D) and *IFITM3* gene (rs12252 T>C) are of particular interest as predictors of clinical phenotypes, as revealed by association studies exploring the genetic basis of COVID-19 manifestations.
Objective: To investigate the association of *ACE1* I/D and *IFITM3* T>C gene variants with susceptibility to and severity of SARS-CoV-2 infection among the Myanmar population.
Methods: A case-control study was conducted from 2021 to 2023, involving 150 COVID-19-positive patients and 150 COVID-19-negative controls from Yangon Division. Genomic DNA was extracted from whole blood using the salting-out method. Gene polymorphisms were identified using the PCR-RFLP technique. Data analysis was performed using SPSS version 20.2, with chi-square tests and one-way ANOVA applied as appropriate.
Results: The observed genotype frequencies conformed to Hardy-Weinberg equilibrium. The DD genotype and D allele of the *ACE1* gene were significantly more frequent in COVID-19 patients than in controls. Similarly, the mutant CC genotype and C allele of the *IFITM3* gene were significantly more prevalent among COVID-19 patients. Both *ACE1* (DD genotype and D allele) and *IFITM3* (CC genotype and C allele) polymorphisms were significantly associated with increased risk of severe COVID-19 infection.
Conclusions: Carriers of the DD genotype and D allele of the *ACE1* gene, as well as the CC genotype and C allele of the *IFITM3* gene, are more likely to exhibit increased susceptibility to and severity of COVID-19. These gene polymorphisms may influence both the incidence and clinical outcome of COVID-19 and could serve as predictive markers for disease risk and severity.

Keywords: SARS-CoV-2, COVID-19, *ACE1*, *IFITM3*

Introduction
The clinical presentation of SARS-CoV-2 infection ranges widely, from asymptomatic cases to severe illness and death. Several studies suggest that viral factors—including viral load and genomic mutations—may influence disease severity. In addition, the host's genetic background is thought to affect both the intensity of infection and clinical outcomes. Other host-related factors such as race, age, sex, immune status, and comorbidities like diabetes, hypertension, cardiovascular disease, chronic respiratory disorders, and cancer can also impact the course and manifestations of COVID-19. However, disparities in socioeconomic status do not fully account for the observed differences in infection outcomes, particularly the significant variation in mortality rates among certain ethnic minorities [1]. Notably, the role of genetic polymorphisms—specifically single nucleotide polymorphisms (SNPs)—in modulating individual susceptibility to and severity of infectious diseases is well documented [2, 3].

The angiotensin-converting enzyme 1 (*ACE1*) insertion (I)/deletion (D) polymorphism (rs4646994), involving a 287-base pair Alu sequence in intron 16, accounts for much of the interindividual variability in circulating ACE1 activity and exhibits considerable geographic variation. Since the onset of the COVID-19 pandemic, considerable attention has been directed toward the potential impact of *ACE1* I/D polymorphisms on COVID-19 prevalence and outcomes. Early studies, such as that by Delanghe and colleagues, proposed that the D allele might be a confounding factor in the spread of COVID-19, suggesting that increased D allele frequency correlates with higher morbidity and mortality rates across 33 countries in Europe, North Africa, and the Middle East [4]. Yamamoto and co-workers further suggested that the D allele in the *ACE1* gene may contribute to increased susceptibility to SARS-CoV-2 infection and exacerbation of symptoms, including pneumonia [5].

Conversely, Zheng and Cao, in a recent review, proposed that the absence of the *ACE1* D/D genotype may offer protection against severe lung injury in COVID-19 patients [6]. However, these findings were primarily based on epidemiological analyses of public databases reporting allele frequencies and regional COVID-19 outcomes. Emerging evidence highlights the contribution of the renin-angiotensin system to the pathogenesis of COVID-19. While the *ACE1* I/D polymorphism has been identified as a potential risk factor for COVID-19, its role remains controversial and warrants further investigation.

Another gene of interest is IFITM3 (Interferon-induced transmembrane protein 3), which plays a crucial role in the immune response by restricting the replication of many viruses. Multiple studies have shown that IFITM3 and its orthologs can inhibit a broad spectrum of viruses, including enveloped RNA viruses from nine viral families, as well as non-enveloped RNA viruses and DNA viruses. These include dengue virus, West Nile virus, Ebola virus, SARS-CoV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) [7-13].

Among *IFITM3* polymorphisms, the most studied variant is rs12252, a non-synonymous SNP located in the first exon. The substitution of the major allele (T) with the minor allele (C) has been predicted to result in altered mRNA splicing, producing an N-terminally truncated IFITM3 protein with a 21-amino-acid deletion. This truncated form may impair the protein's antiviral function. The CC and TC genotypes of *IFITM3* (rs12252) are more prevalent in East Asian populations compared to Europeans. Importantly, the C allele has been associated with rapid progression of acute HIV infection [15], increased severity of influenza [16], and more recently, severe COVID-19 outcomes [17].

Given the variation in COVID-19 disease severity among individuals, host genomic differences likely play a key role in disease susceptibility and progression. Identifying these genetic markers is essential for predicting risk, improving clinical management, and guiding vaccine development. In particular, the *ACE1* I/D polymorphism (rs4646994) and the *IFITM3* (rs12252) variant may contribute to both increased susceptibility and severity of COVID-19.

Therefore, these polymorphisms could serve as part of a genetic risk stratification panel to identify individuals at high or low risk of severe COVID-19, enabling more targeted surveillance and management strategies. Accordingly, this study aimed to investigate the association between the *ACE1* I/D (rs4646994) polymorphism and *IFITM3* rs12252 variant with individual susceptibility to and severity of SARS-CoV-2 infection in the Myanmar population.

Materials and Methods

This case-control study was conducted from 2021 to 2023 in accordance with the ethical principles outlined in the Declaration of Helsinki for biomedical research involving human subjects. The study was approved by the Institutional Human Research Ethics Committee of the Defence Services Medical Academy. A total of 150 confirmed COVID-19 patients and 150 healthy controls, verified as COVID-19 negative by laboratory testing, were included in the study.

Written informed consent was obtained from all participants prior to sample collection. Medical history was recorded using a standardized proforma. Subsequently, 3 mL of venous blood was collected from each participant into an EDTA tube under standard infection prevention and control protocols, including proper hand hygiene, environmental disinfection, and the use of personal protective equipment (PPE).

Patients were classified into three groups—mild, moderate, and severe/critical COVID-19 cases—based on the World Health Organization (WHO) criteria for COVID-19 severity classification (Table 1).

Table 1: WHO Classification of COVID-19 Severity [18]

COVID-19	Mild disease	Moderate disease (Pneumonia)	Severe disease (Severe Pneumonia)
Clinical Signs	Without evidence of viral pneumonia or hypoxia	Clinical signs of pneumonia ▪ fever ▪ cough ▪ dyspnea ▪ fast breathing ▪ no signs of severe pneumonia	Clinical signs of pneumonia ▪ fever ▪ cough ▪ dyspnea ▪ fast breathing ▪ severe respiratory distress
SpO_2 in room air	≥ 90%	≤ 90%	≤ 90%
Respiratory Rate (breaths/min)	< 30	< 30	≥ 30

Genomic DNA was extracted from whole blood samples using the salting-out method. DNA quality and concentration were assessed using agarose gel electrophoresis (AGE) and a Nanodrop spectrophotometer (BioSpec-nano, Shimadzu, Japan).

One-way ANOVA was used to evaluate differences in continuous variables with a 95% confidence interval. The chi-square (χ^2) test was applied to assess differences in genotype and allele frequencies for the ACE1 I/D and IFITM3 (rs12252) polymorphisms, as well as to evaluate deviations from Hardy-Weinberg equilibrium (HWE). Allelic and genotypic frequencies were calculated using the direct gene counting method. Associations between gene polymorphisms and disease phenotypes were determined using Fisher's exact test. All statistical analyses were performed using SPSS version 20.2.

Results

Table 2: Demographic data of the study population

Variables	COVID-19 (n = 150)	Control (n = 150)	Statistics	
			χ^2	p-value
Age (years)				
≤ 50	48	53	0.3732	0.541
>50	102	97		
Sex				
Male	88	102	2.8134	0.093
Female	62	48		

Table 2 shows the demographic data of the study population. The COVID-19 positive patients and COVID-19 negative controls were not significantly different between the two groups of age (≤ 50 years vs. >50 years) and that of different sexes (male vs. female) respectively.

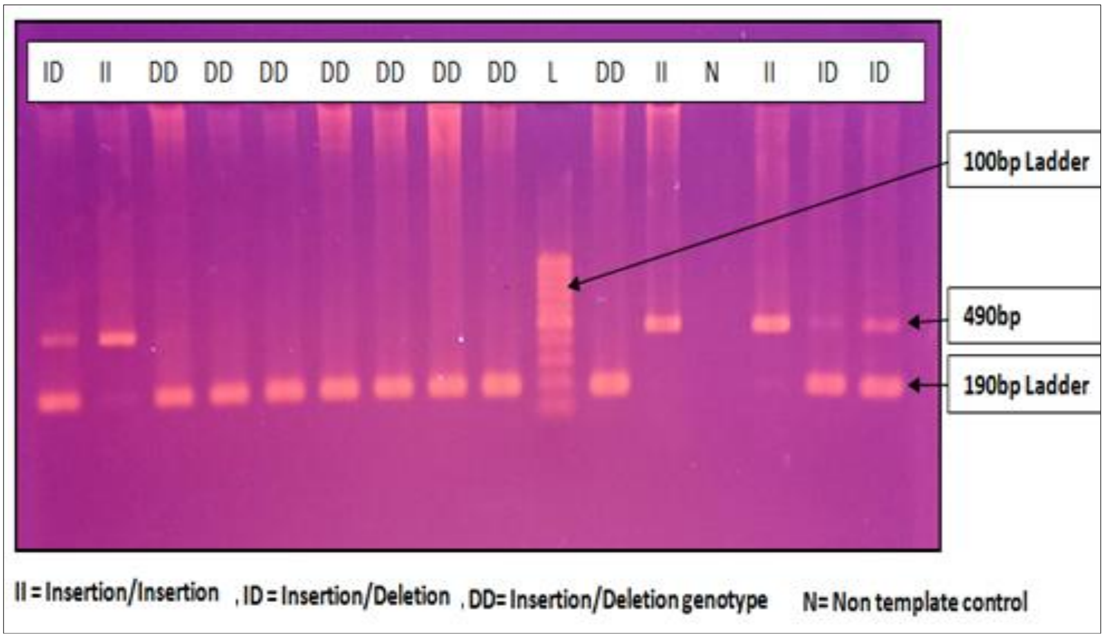

Fig 1: *ACE1* gene I/D polymorphism products by 2% agarose gel electrophoresis

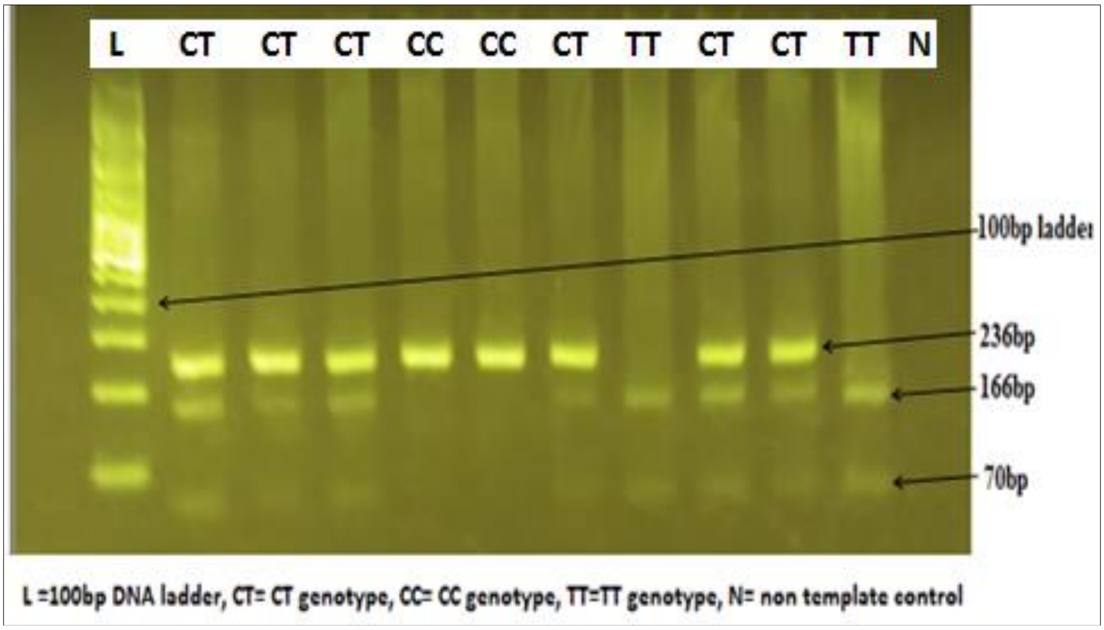

Fig 2: *IFITM3* gene (rs12252) polymorphism products by 2% agarose gel electrophoresis

Figures (1) and (2) shows the electrophoresis pattern of 2% agarose gel electrophoresis for *ACE1* gene I/D polymorphism and *IFITM3* gene (rs12252) polymorphism products respectively.

Table 3: *ACE1* I/D and *IFITM3* (rs12252) polymorphisms in the study population

Variables	COVID-19 (n = 150)	Control (n = 150)	Statistics	
			χ^2	*p-value*
***ACE1* gene I/D Polymorphism**				
Genotypes				
II	30	38	13.54	0.001
ID	41	64		
DD	79	48		
Alleles				
I	101	140	10.54	0.001
D	199	160		
***IFITM3* gene (rs12252) Polymorphism**				
Genotypes				
TT	30	49	7.48	0.023
CT	67	64		
CC	53	37		
Alleles				
T	127	176	16.008	0.000
C	173	124		

The genotype and allele frequency distribution of *ACE1* and *IFITM3* gene polymorphism are presented in table 3. As shown, for the *ACE1* gene, the individuals with DD and ID genotypes were more susceptible to COVID-19 disease compared to the II genotype. The GG genotype of *IFITM3* (rs12252) polymorphisms was associated with susceptibility to COVID-19 infection. Both of these results were statistically significant ($p < 0.05$).

Table 4: Association of *ACE1* I/D and *IFITM3* (rs12252) polymorphisms and Severity of COVID-19 disease in the study population

Variables	Mild (n = 69)	Moderate (n = 40)	Severe (n = 41)	Statistics	
				χ^2	*p-value*
***ACE1* gene I/D Polymorphism**					
Genotypes					
II	18	6	6	5.22	0.264
ID	21	11	9		
DD	30	23	26		
Alleles					
I	57	23	21	10.54	0.03
D	81	57	61		
***IFITM3* gene (rs12252) Polymorphism**					
Genotypes					
TT	19	5	6	5.58	0.23
CT	30	17	15		
CC	20	18	20		
Alleles					
T	68	27	27	5.90	0.052
C	70	53	55		

Table 5: Association of *ACE1* I/D and *IFITM3* (rs12252) polymorphisms and Severity of COVID-19 disease in the study population (Recessive model)

Variables	Mild (n = 69)	Moderate + Severe (n = 81)	Statistics		
			χ^2	OR (95%CI)	p-value
***ACE1* gene I/D Polymorphism**					
Genotypes					
II + ID	39	32	2.070	1.99 (1.03-3.82)	0.038
DD	30	49			
Alleles					
I	57	44	2.57	1.88 (1.16-3.06)	0.010
D	81	118			
***IFITM3* gene (rs12252) Polymorphism**					
Genotypes					
TT + CT	49	43	2.08	2.07 (1.04-4.10)	0.037
CC	20	38			
Alleles					
T	68	54	2.41	1.76 (1.11-2.80)	0.016
C	70	108			

The different severity and odd ratio of risk factors in genotype and allele frequencies distribution of *ACE1* and *IFITM3* gene polymorphisms were described in tables 4 and 5. The DD genotype and D allele of *ACE1* gene were significantly associated with an increased risk of severe COVID-19 disease (OR = 1.99, 95% CI = 1.03-3.82, p = 0.038; OR = 1.88, 95% CI = 1.16-3.06, p = 0.010). Also, the *IFITM3* gene (Mutant CC genotype and C allele) polymorphisms were significantly associated with an increased risk of severe COVID-19 disease (OR = 2.07, 95% CI = 1.04-4.10, p = 0.037; OR = 1.76, 95% CI = 1.11-2.80, p = 0.016).

Discussion

The novel coronavirus disease 2019 (COVID-19) poses a global threat due to its fluctuating incidence and lethality. The relationship between genetic polymorphisms and COVID-19 remains inconsistent across studies. Therefore, this study aimed to investigate the associations between genetic variants, particularly *ACE1* and *IFITM3*, and the susceptibility to and severity of COVID-19.

Regarding *ACE1* I/D polymorphism, our study demonstrated that carriers of the DD genotype and the D allele were significantly more susceptible to COVID-19 compared to those with the II genotype and the I allele. Furthermore, among COVID-19 patients, the DD genotype and D allele were also significantly associated with increased disease severity.

Although genetic studies on COVID-19 remain limited, research on other viral diseases has previously identified relevant genetic associations. A meta-analysis by Teodoro J. Oscanoa *et al.* (2021) [19] on *ACE1* I/D polymorphism and COVID-19 severity in hospitalized patients reported that individuals with the DD genotype had a 47% higher risk of severe disease compared to those with the II or ID genotypes (IRR = 1.47; 95% CI = 1.15-1.89; p = 0.002), with low heterogeneity (I^2 = 9.4%). A protective effect was observed in the II vs. DD + ID model (IRR = 0.72; 95% CI = 0.54-0.97; p = 0.028; I^2 = 0%), while the DD vs. II + ID model yielded an IRR of 1.48 (95% CI = 1.10-1.97; p = 0.009) [19].

Similarly, a systematic review and meta-analysis by Valentina Pecoraro *et al.* (2023) evaluating *ACE1*, *ACE2*, *IFITM3*, *TMPRSS2*, and *TNF-α* gene polymorphisms in relation to COVID-19 susceptibility and severity found no significant associations for *ACE1*, *ACE2*, *TMPRSS2*, and *TNF-α* gene variants with infection status across 35 studies. However, for disease severity, their analysis of 15 studies (involving 1223 patients with severe disease) showed that the DD genotype of *ACE1* (rs4646994/rs1799752) was associated with an increased risk of severe disease (OR = 1.61; 95% CI = 1.21-2.14; p = 0.001), although with high heterogeneity (I^2 = 60%). Significant associations were found in dominant (OR = 1.50), homozygous (OR = 1.53), and additive (OR = 1.40) models, but not in the recessive model [20]. These findings are consistent with our results.

The renin-angiotensin-aldosterone system (RAAS) is a key signaling pathway that regulates vascular function, systemic and local blood flow, blood pressure, and sodium balance. When sodium concentration is low in the renal tubules, the macula densa signals for the release of renin from the kidneys. Renin converts angiotensinogen into angiotensin I, which is further converted into angiotensin II (Ang II) by the angiotensin-converting enzyme (ACE), mainly in the lungs. Ang II then stimulates aldosterone secretion from the adrenal cortex [21, 22].

The primary RAAS axis—ACE/Ang II/AT1R—plays a dual role: binding to AT1 receptors promotes vasoconstriction, inflammation, oxidative stress, and fibrosis, whereas AT2 receptor binding counters these effects. Chronic RAAS activation exacerbates Ang II/AT1-mediated effects, including fibrosis, apoptosis, ADH and aldosterone release, and water and sodium retention [21, 22].

The spike protein of SARS-CoV-2 interacts with ACE2, competing with Ang II for binding. This interaction downregulates ACE2 expression, disrupting the ACE/ACE2 balance and promoting pathological activation of the ACE/Ang II/AT1R axis. As a result, Ang II-mediated vasoconstriction increases, while protective Ang (1-7)-mediated vasodilation decreases [21, 22]. This imbalance contributes to COVID-19 progression, particularly in patients with comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease [23].

With regard to the *IFITM3* gene, our study found that individuals carrying the CC genotype and C allele of the *IFITM3* (rs12252) polymorphism were significantly more susceptible to COVID-19 and more likely to develop severe disease compared to those with the TT genotype and T allele.

The meta-analysis by Pecoraro *et al.* (2023) also investigated *IFITM3* (rs12252), evaluating susceptibility in three studies comprising 1034 COVID-19-positive patients and 875 controls. They found significant associations for the C allele in both the recessive (OR = 5.67; 95% CI = 1.01-31.77; p = 0.05; I^2 = 0%) and heterozygous (CT) models (OR = 1.64; 95% CI = 1.15-2.33; p = 0.007; I^2 = 0%) [20]. Regarding disease severity, four studies (332 severe vs. 782 non-severe cases) identified a significant association in the C recessive model (OR = 2.26; 95% CI = 1.05-4.89; p = 0.04; I^2 = 0%). No significant associations were found in other genetic models. These findings support the results of our present study [20].

Interferon-induced transmembrane protein 3 (IFITM3) is a restriction factor involved in antiviral defense. It limits viral entry by altering membrane properties and intracellular trafficking. IFITM3 is known to inhibit cellular entry of multiple viruses, including influenza A, HIV, vesicular stomatitis virus, and SARS-CoV [8]. Studies suggest that IFITM3 may reduce membrane fluidity, interfere with viral fusion, trap viruses in endosomes, and accelerate endosome-lysosome trafficking, thus preventing viral replication [24-26]. It can also interact with viral proteins such as the HIV-1 envelope, inhibiting their processing and preventing fusion with host cell membranes [10].

In virology, it is well established that host genetic background significantly influences susceptibility to viral infections. Genetic variations can affect viral recognition, immune system activation, and infection outcomes. Host polymorphisms involved in innate immunity may impact both susceptibility to and prognosis of COVID-19. Evidence suggests that these genetic factors contribute to inter-individual variability in immune responses.

The clinical course of SARS-CoV-2 infection varies widely, from asymptomatic cases to severe illness and death. The factors influencing this variability remain under investigation. Several studies indicate that both viral factors (e.g., viral load, mutations) and host factors (e.g., age, gender, immune status, comorbidities such as diabetes, hypertension, and cancer) may influence disease severity and outcome. Unfortunately, our current study did not include these variables. Future studies should incorporate these factors to better understand their roles in COVID-19 susceptibility and progression. Identifying the determinants of SARS-CoV-2 virulence will aid in the development of targeted treatment strategies and improved infection control measures.

Conclusion

Carriers of the DD genotype and D allele of the *ACE1* gene, as well as the CC genotype and C allele of the *IFITM3* gene polymorphisms, were more likely to be susceptible to and at greater risk of developing severe COVID-19 than other genotypes. These gene polymorphisms influence both the incidence and clinical outcomes of COVID-19 and may serve as predictive markers for disease risk and severity. Further studies involving more diverse ethnic populations and individuals with different underlying health conditions are necessary to fully establish the association between host genetic background and the pathogenesis of viral infection.

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