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Impact of Polymorphism in Transmembrane Serine Protease 2 Gene on Disease Outcome in COVID-19 Patients

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A B S T R A C T

Severity of corona virus disease-2019 (COVID-19) infection varied widely among patients. Thus, many studies were performed to clarify the disease immune-pathological aspects, different genetic, epidemiological, clinical and radiological characters for delineation of the exact factors responsible for disease severity. Transmembrane serine protease 2 (TMPRSS2) plays an important role in viral entry into host cell. Thus, this study aimed to assess polymorphism in TMPRSS2 gene and its impact on disease outcome in COVID-19 patients. This prospective study included 91 patients divided into four groups according to disease severity defined by world health organization (WHO). No significant association was detected between TMPRSS2 rs12329760 genotypes or alleles and severity of disease.

Introduction

At the end of 2019, a number of pneumonic patients emerged in Wuhan, China caused by the novel severe acute respiratory syndrome coronavirus-2 “SARS-COV-2” and the disease was defined as corona virus disease-2019 “COVID-19” by WHO (Peeri *et al.*, 2020).

Severity of infection in the era of COVID-19 varied widely among different patients. Thus, many studies were performed to clarify the disease immune-pathological aspects, different genetic, epidemiological, clinical and radiological characters for delineation of the exact factors responsible for disease severity, which may be reflected on the preventive and therapeutic approaches (Péterfi *et al.*, 2022; Statsenko *et al.*, 2022).

SARS-CoV-2 can infect host cells via binding to the angiotensin-converting enzyme 2 (ACE2) receptor which is widely distributed but largely expressed in endothelial cells (Hoffmann *et al.*, 2020). This is followed by cleavage of hemagglutinin protein by

the transmembrane serine protease 2 (TMPRSS2) allowing viral fusion to cell membrane and cell entry (Hoffmann *et al.,* 2020 and Zhou *et al.,* 2020).

TMPRSS2 is a host protease composed of transmembrane helix, small cytoplasmic segment and extracellular portion, the latter is composed of three domains: the low-density lipoprotein (LDL) receptor like domain, the scavenger receptor cysteine-rich domain (SRCR) domain and the peptidase domain (Lucas *et al.,* 2014).

This study aimed to evaluate the role of rs12329760 polymorphism in the transmembrane serine protease 2 gene and its impact on disease outcome in COVID-19 patients.

Patient and methods

This prospective study was carried out for two year from December 2020 to December 2022 and included 91 patients divided into four groups:

Group (A): mild cases (symptomatic cases with no evidence of pneumonia).
Group (B): moderate cases (signs of pneumonia with oxygen saturation ≥ 90% on room air).
Group (C): severe cases (pneumonia with oxygen saturation < 90% on room air or respiratory rate > 30 breaths/min.
Group (D): critical cases developing acute respiratory distress syndrome (ARDS).
Patient classification according to severity is based on world health organization (WHO) guidelines (WHO, 2020).

Genotyping procedure steps

DNA extraction: using the QIAamp DNA blood mini kit (provided by QIAGEN cat. No.K0781, USA) for DNA extraction from whole blood.

Analysis of the genetic polymorphism of TMPRSS2 (rs12329760) using TaqMan assays for analyzing genetic variation. This polymorphism causes the replacement of valine to methionine in the TMPRSS2 protein at position 160 (Schönfelder *et al.,* 2021).

Detection of allele: The genotyping assay determines the presence or absence of SNP based on the change in fluorescence of the dyes associated with the probes.

Statistical analysis

The collected data was revised, coded, tabulated using Statistical package for Social Science (SPSS version 25.0). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Results and Discussion

The number of cases with CC genotype of rs12329760 in mild, moderate, severe, and critical conditions were 9(47.8 %), 10(43.5%), 13(52.0%) and 15 (62.5%) respectively.

While the number of cases with CT genotype were 10 (52.2%), 13 (56.5%), 12 (48.0%) and 9 (37.5%) respectively.

There was no association between rs12329760 genotypes and alleles with COVID-19 severity grades.

No significant association was found between rs12329760 genotypes with clinical manifestations, need for assisted ventilation, CRP or d-dimer positivity nor radiological findings.

TMPRSS2 plays a pivotal role in viral infection through bond cleavage between viral S protein and ACE2 receptor on target cell, with subsequent activation of S protein (Rabi *et al.,* 2020).

Therefore, many studies evaluated the role of TMPRSS2 polymorphism as a major determinant of viral infection and hence disease outcome. Moreover, camostat -a potent protease inhibitor- has been studied as a potential therapy against SARS-

COV-2 providing shorter disease course and ameliorated symptoms (Chupp *et al.,* 2022). The role of endogenous protease inhibitors have also been evaluated in COVID-19 patients, alpha-1 antitrypsin has been found to be protective against disease severity with more serious disease course occurring in patients with alpha one antitrypsin deficiency. Such finding may explain the surge of severe cases occurred in parts of Italy with high prevalence of alpha one antitrypsin deficiency (Bai *et al.,* 2023).

This study had evaluated polymorphism of the TMPRSS2 rs12329760 in Egyptian population and revealed no association between rs12329760 genotypes or alleles with COVID-19 severity grades in consistency with results obtained among German, Indonesian and Chinese patients (Schönfelder *et al.,* 2021 and Wulandari *et al.,* 2021).

This may be explained by the fact that such polymorphism affects SRCR-like domain and has no impact on the catalytic capacity of the enzyme (Izmailova *et al.,* 2023). Different studies evaluating this missense mutation in diverse population groups showed marked discrepancy in their results; some studies revealed significant association between T allele and disease severity (Rokni *et al.,* 2022 and Yaghoobi *et al.,* 2023). Whereas other studies revealed contrary association between T allele and reduced disease severity and incidence of infection (Ravikanth *et al.,* 2021 and David *et al.,* 2022).

Table.1 Association of rs12329760 genotypes and alleles with studied groups.

rs12329760		Mild (n=19)	Moderate (n=23)	Severe (n=25)	Critical (n=24)	p	OR (95% CI)
Genotypes	**CC**	9 (47.8%)	10 (43.5%)	13 (52%)	15(62.5%)	0.242	0.767 (0.493-11.95)
	CT	10(52.2%)	13 (56.5%)	12 (48%)	9 (37.5%)		
Alleles	**C**	28(73.9%)	33 (71.7%)	38 (76%)	39(81.3%)	0.367	0.868 (0.638-1.181)
	T	10(26.1%)	13 (28.3%)	12 (24%)	9 (18.7%)		

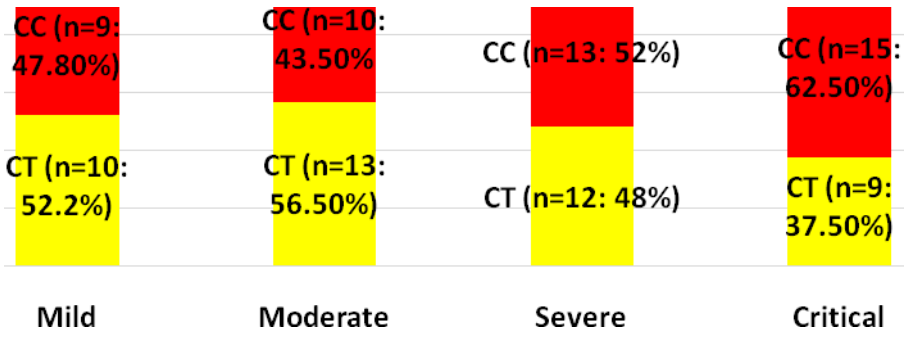
OR, odds ratio; CI, confidence interval. Ordinal regression analysis was used.

Table.2 Association of rs12329760 genotypes with other parameters (clinical, need for assisted ventilation, biochemical and radiological findings)

	CC **n=47 n (%)**	CT **n=44 n (%)**	p	OR (95% CI)
Cough	30 (63.8%)	29 (65.9%)	0.836	1.058(0.623-1.796)
Fever	32 (68.1%)	22 (50.0%)	0.080	0.625(0.369-1.057)
Dyspnea	29 (61.7%)	23 (52.3%)	0.364	0.786(0.468-1.322)
MV	7 (14.9%)	5 (11.4%)	0.619	0.847(0.44-1.631)
CPAP	6 (12.8%)	3 (6.8%)	0.343	0.703(0.34-1.456)
Positive CRP	36 (76.6%)	36 (81.8%)	0.540	1.201(0.669-2.155)
Positive D-dimer	5 (10.6%)	6 (13.6%)	0.661	1.161(0.595-2.263)
GGOs	38 (80.9%)	34 (77.3%)	0.675	0.883(0.493-1.58)
Consolidation	25 (53.2%)	18 (40.9%)	0.241	0.733(0.437-1.231)

MV: mechanical ventilation, CPAP: continuous positive airway pressure, CRP: C reactive protein, GGOs: ground glass opacities, OR, odds ratio; CI, confidence interval.

Fig.1 Association of rs12329760 genotypes with studied groups



Such discrepancy may be due to diverse racial backgrounds of targeted patients in these studies, a study evaluating TMPRSS2 in Egyptian population revealed no association between such polymorphism and disease severity in consistent with our results (Alaa *et al.*, 2023). Also, other hidden genetic factors may influence the action of TMPRSS2 on COVID-19 infection (Gupta *et al.*, 2022).

One of the limitations of our study is being single centered with relatively small sample size. Thus, we suggest further studies with larger sample size and more diverse population groups. Also, evaluating the impact of other possible polymorphism in TMPRSS2 and ACE2 genes may elucidate in part the dilemma of variable disease course and unpredictable outcome in COVID-19 patients.

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