ISSN: 2755-0125

Journal of Virology Research & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Impact of ACE2 and TMPRSS2 Activity on Clinical Manifestations of COVID-19 in Pointe-Noire, Congo

Rebecca Frédérique Dussaud[1,3], Luc Magloire Anicet Boumba[1,2,3*], Landry Martial Miguel[1], Parode Ragive Takale[1,9], Charley Elenga-Bongo[1,4], Freddy Saturnin Pouki[1,5-7], Aladin Atandi Batchy[1,6,7], Colombe Sagesse Luzayisu[1,3], Donatien Moukassa [1,3] and Ange Antoine Abena [1,8]

[1]Faculty of Health Sciences, Marien Ngouabi University, BP: 69 Brazzaville, Congo

[2]Pointe-Noire Research Zone, National Institute for Health Science Research (IRSSA), Congo

[3]Microbiology and Molecular Biology Laboratory, Loandjili General Hospital, Pointe-Noire, Congo

[4]Adolph Sicé General Hospital, Pointe-Noire, Congo

[5]Private Clinic Louise Michel, Pointe-Noire, Congo

[6]Tié Tié Referral Hospital, Pointe-Noire, Congo

[7]Guénin Medical Clinic, Pointe-Noire, Congo

[8]Denis Sassou Nguesso University, Brazzaville, Congo

ABSTRACT

Introduction: The COVID-19 pandemic caused by SARS-CoV-2 exhibits marked clinical heterogeneity, ranging from asymptomatic cases to severe complications. Viral entry depends on ACE2 and TMPRSS2 proteins, whose activity may influence disease progression.

Objective: To evaluate the association between ACE2 and TMPRSS2 activity and the severity of COVID-19 clinical manifestations.

Methods: A cross-sectional descriptive study included 170 RT-PCR confirmed SARS-CoV-2 patients. Demographic (age, sex) and clinical (symptom) data were extracted from medical records. ACE2 and TMPRSS2 protein activity was measured using immunoenzymatic assays from blood samples. Patients were stratified into moderate and severe forms according to standardized clinical criteria.

Results: The average age was 31.7 ± 4.4 years (range 24–68), with a male predominance (78%). Predominant symptoms in severe forms included fever (54.6%), cough (55.6%), and ageusia (56%). A significant correlation was found between ACE2 activity and severe disease forms ($p < 0.001$). TMPRSS2 activity was also associated with severity, though less prominently ($p = 0.029$).

Conclusion: These findings suggest that ACE2 and TMPRSS2 activity may serve as predictive biomarkers of COVID-19 severity. Quantifying these markers could enable early patient stratification and optimized therapeutic strategies. Prospective studies are needed to validate their clinical utility.

***Corresponding author**

Prof. Luc Magloire Anicet Boumba, Hospital-University Biologist, Marien Ngouabi University, Republic of the Congo.

Received: April 25, 2025; **Accepted:** April 28, 2025; **Published:** May 05, 2025

Keywords: ACE2, TMPRSS2, SARS-CoV-2, Clinical Severity, COVID-19

Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, emerged as a global pandemic after its appearance in China at the end of 2019. On January 30, 2020, the WHO declared this outbreak a public health emergency of international concern. As the third highly pathogenic coronavirus of the 21st century after SARS-CoV (2002) and MERS-CoV (2012), SARS-CoV-2 had resulted in over 768 million confirmed cases and 6.9 million deaths worldwide by June 18, 2023 [1].

In Congo, the first case was reported on March 14, 2020 (MSP-SITREP No. 233, 2022). As of December 22, 2024, more than 25,234 cases were recorded, including 24,845 recoveries and 389 deaths (case fatality rate: 1.54%) according to the WHO (2025). Clinical severity ranges from asymptomatic forms to fatal complications, influenced by biological and genetic factors [2].

SARS-CoV-2 enters human cells via ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane serine protease 2) receptors, which are expressed in the respiratory tract, blood vessels, and heart [3]. Overexpression of ACE2 increases susceptibility to lung injury, while high levels of TMPRSS2 promote accelerated viral replication [4,5]. However, few studies

have explored these markers in resource-limited settings.

This study aimed to assess the impact of blood activities of ACE2 and TMPRSS2 on the severity of COVID-19 in Pointe-Noire, Republic of the Congo.

Materials and Methods

Study Population

A descriptive cross-sectional study was carried out on COVID-19 patients followed at the Loandjili and Adolphe Sicé General Hospitals in Pointe-Noire.

Clinical Data Collection

Demographic (age, sex) and clinical data were extracted from medical records, with a focus on symptom severity (WHO classification).

Biological Investigation

Laboratory analyses were carried out at the Laboratoire d'Analyses Biomédicales HDL of the Polyclinique Fondation Marie Madeleine Gombes in Pointe noire.

Samples

- **Blood:** After consent, a 5 mL venous sample was taken from the elbow in a dry tube without anticoagulant.
- **Nasopharyngeal:** A Citoswab swab (CITOTEST, China) was inserted deep into the nasopharynx to collect secretions, preserved in viral transport medium (VTM).

Serum Biomarker Assay

ACE2: Quantified by ELISA (Kit PRS-01837hu, Nanjing Pars Biochem) with spectrophotometric detection at 450 nm.

Interpretation

- Not expressed: < 25.3 µg/L
- Expressed: 25.3-50.6 µg/L
- Overexpressed: > 50.6 µg/L

TMPRSS2: Assayed by sandwich ELISA (Invitrogen Kit EEL046).

Interpretation

- **Not expressed:** < 0.83 ng/mL
- **Expressed:** 0.83-3.7 ng/mL
- **Overexpressed:** > 3.7 ng/Ml

Molecular Analysis

RNA Extraction

RNA from nasopharyngeal samples was purified using Total RNA Purification Insert PI12200-37 (Norgen Biotek, Canada).

Quantitative RT-PCR

Amplification of the SARS-CoV-2 E and RdRp genes was performed using the Covid-19 TaqMan RT-PCR Kit (Norgen Biotek) following the manufacturer's instructions.

- Reaction mix: 10 µL Master Mix, 1.5 µL primers/probes, 3.5 µL nuclease-free water, 5 µL RNA.
- Thermal parameters
- Reverse transcription: 50°C, 20 min
- Initial denaturation: 95°C, 3 min
- 45 cycles: 95 °C (15 s), 58 °C (30 s).
- Detection: Fluorochromes FAM (E gene) and HEX (internal control).

Statistical Analysis

Statistical analysis has enabled us to classify the study variables into:

- Categorical variables: Numbers (percentages), χ^2 test.
- Quantitative variables: Means ± standard deviation.

SPSS v26.0, IBMa software was used for statistical analysis, with a Significance threshold of $p < 0.05$.

Ethical Considerations

The study was approved by the Health Research Ethics Committee of the Marie Madeleine Gombes Foundation (n°152/CERS/FMMG-2021/PNR), in accordance with the Declaration of Helsinki.

Results

Sociodemographic Characteristics

The study population consisted of 170 COVID-positive subjects, 78% male and 22% female. The sex ratio (M/F) was 3.6 (Figure 1). The mean age was 31.7± 4.4 years, with extremes ranging from 24 to 68 years.

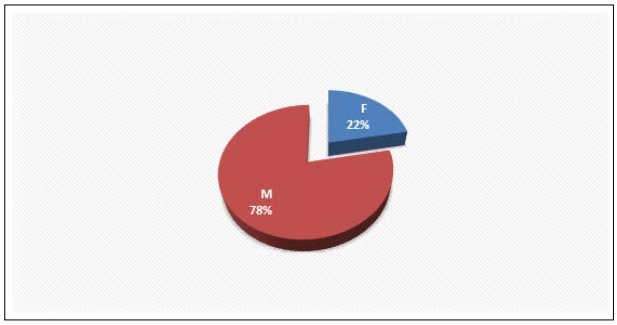

Figure 1: Distribution of Study Population by Gender

Clinical Features

Table I shows the clinical manifestations of our study population. Fever, rate and agueusia were the most common signs in weaning forms of the disease.

Table I: Clinical Characteristics

Characteristic	symptoms		
	Moderate N = 92	severe N = 78	p
FATIGUA			<0.001
No	29 (56%)	23 (44%)	
Yes	63 (53%)	55 (47%)	
AGUEUSY			<0.001
No	42 (74%)	15 (26%)	
Yes	50 (44%)	63 (56%)	
ANOSMIA			<0.001
No	73 (54%)	61 (46%)	
Yes	19 (53%)	17 (47%)	
COUGH			0.012
No	64 (59.8%)	43 (40.2%)	
Yes	28 (44.4%)	35 (55.6%)	
FEVER			0.025
No	52 (63.4%)	30 (36.6%)	
Yes	40 (45.4%)	48 (54.6%)	

Expression of CEA2 According to Severity

Our results show that CEA2 is over-expressed in 56% of patients with severe disease, versus 30% with moderate disease (Table II).

Table II: ACE2 Expression According to Severity

Characteristic	Gravity		
	Moderate N = 92	Severe N = 78	p
ACE2S2			<0,001
Not expressed	36 (39%)	7 (9,0%)	
Expressed	28 (30%)	27 (35%)	
Over expressed	28 (30%)	44 (56%)	

TMPRSS2 Expression According to Severity

Our results show that TMPRSS2 is over-expressed in 47% of cases in patients with the severe form of the disease, versus 34% in the moderate form (Table III).

Table III: TMPRSS2 Expression According to Severity

Characteristic	Gravité		
	Moderate N = 92	Severe N = 78	p
			0,029
TMPRSS2			
Not expressed	43 (47%)	21 (27%)	
Expressed	18 (20%)	20 (26%)	
Over expressed	31 (34%)	37 (47%)	

Discussion

Epidemiological Context and Molecular Mechanisms

The COVID-19 pandemic, caused by SARS-CoV-2, has revealed significant clinical and biological disparities among infected populations. In Pointe-Noire (Republic of the Congo), this crisis highlighted the importance of molecular determinants of infection, particularly the ACE2 receptor and the TMPRSS2 protease, which are crucial for viral entry. Our study aimed to evaluate their activity in modulating disease severity.

Sociodemographic Characteristics of Patients

Sociodemographic analysis revealed a male predominance (78% of cases, M/F sex ratio = 3.6), consistent with national and international trends [6,7]. This disparity may be attributed to increased ACE2 expression in men and hormonal factors: androgens, which are higher in males, regulate TMPRSS2 expression [8,9]. Additionally, the mean patient age (31.7 ± 4.4 years) contrasts with earlier studies indicating increased vulnerability among older adults, suggesting an age-specific epidemiological dynamic in this young population.

Clinical Manifestations According to Severity

Symptom assessment revealed distinct profiles between moderate and severe forms:

- Fatigue: A universal symptom, independent of disease severity, confirming the findings of [10].
- Ageusia: Significantly more prevalent in severe forms ($p < 0.001$), who associated it with milder cases. This discrepancy may reflect genotypic or methodological variations [11].
- Anosmia: Observed across all forms, with a predominance reported in mild cases [12].
- Cough and fever: More frequent in severe cases ($p = 0.017$ and $p = 0.031$), likely linked to pulmonary lesions and systemic hyperinflammation [13,14].

Role of ACE2 and TMPRSS2 in Pathogenicity

While ACE2 expression was detected in both groups, its plasma activity was significantly higher in severe patients. This may indicate enhanced membrane shedding, releasing the enzyme into circulation [15]. Paradoxically, reduced pulmonary ACE2 activity could exacerbate local inflammation, as suggested by [16]. These findings align with, who emphasized that ACE2 is not the sole determinant of severity but interacts with immunological and inflammatory factors [17].

A progressive overexpression of TMPRSS2 was noted, increasing from 64% in moderate cases to 84.6% in severe cases. This upregulation correlates with accelerated viral replication, intensifying tissue damage [18]. Findings by Ziegler et al. support this correlation, although individual variations (comorbidities, age) influence its impact [19].

Synthesis of Proposed Mechanisms

Moderate forms are characterized by effective immune regulation and uniform ACE2/TMPRSS2 expression, limiting viral progression. Conversely, severe forms combine inflammatory dysregulation, receptor overexpression facilitating viral entry, and aggravating comorbidities [20]. These observations underscore the multifactorial role of the host in disease pathogenesis [21].

Conclusion

Our study demonstrates that plasma activity of ACE2 and TMPRSS2 is significantly increased in severe cases of COVID-19 [22]. These proteins emerge as promising biomarkers for predicting disease severity and guiding therapeutic strategies [23-25]. However, their application requires prospective validation, incorporating genetic, immunological, and environmental parameters to refine their predictive value across diverse populations [26-29].

References

1. Ayoub SE, Shaker OG, Masoud M, Essam A. Hassan, Eman M. Ezzat, Mona I. Ahmed, et al. (2024) Altered serum expression of lncRNA CASC2 and miRNA-21-5p in patients with COVID-19. Hum Genomics 18: 1-11.
2. De Greef J, Pothen, L, Yildiz H, Poncin W, Reychler G, et al. (2020) COVID-19: Infection par le virus SARS-CoV-2. Louvain Médical 139: 290-301.
3. Firlej V, Majidipur A, Berry F, Soyeux P, Destouches D, et al. (2021) Régulation de TMPRSS2 par la voie des androgènes et implications dans l'infection SARS-CoV-2 Prog Urol 31: 783.
4. Ziegler CGK, Samuel J Allon, Sarah K Nyquist, Ian M Mbano, Vincent N Miao, et al. (2020) SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 181:1016-1035.
5. Yan R, Zhang Y, Li Y, Xia L, Guo Y, et al. (2020) Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 367: 1444-1448.
6. Freddy Saturnin Pouki, Luc Magloire Anicet Boumba, Parode Ragive Takale, Rebecca Frédérique Dussaud, Charley Elenga-Bongo, et al. (2024) Biological Factors Associated with Poor Prognosis in Type 2 Diabetic Patients with COVID-19 in Pointe Noire. Sch Acad. J Biosci 12: 115-120.
7. Boumba Anicet Luc Magloire, Aubièrge Victoire Kimpamboundi-Matondo, Parfait Christy Nganga, Colombe Sagesse Luzayisu, Ragive Parode Takale, et al. (2022) Sars-Cov-2 and COVID-19: Epidemiological, Diagnostic, and Therapeutic Aspects in Pointe-Noire, Republic of the Congo. Journal of Virology Research & Reports 3: 1-6.

8. Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, et al. (2014) The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 4: 1310-1325.
9. Setlur SR, Mertz KD, Hoshida Y, Demichelis F, Lupien M, et al. (2008) Estrogen-dependent signaling in a molecularly distinct subclassof aggressive prostate cancer. J Natl Cancer Inst 100: 815-825.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 395: 497-506.
11. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, et al. (2020) Self-reported Olfactory and Taste Disorders in Patients with Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. Clin Infect Dis 71: 889-890.
12. Mao L, Jin H, Wang M, Hu Y, Chen S, et al. (2020) Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 77: 683-690.
13. Yang X, Yu Y, Xu J, Huaqing Shu, Jia'an Xia, et al. (2020) Clinical course and outcomes of critically ill patients with SARSCoV-2 pneumonia in Wuhan, China: a singlecentered, retrospective, observational study. Lancet Respir Med 8: 475-481.
14. Wang D, Hu B, Hu C (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323: 1061-1069.
15. Vaduganathan M, Vardeny O, Michel T, Thomas Michel, John JV McMurray, et al. (2020) Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 382: 1653-1659.
16. Dirk van Lier, Matthijs Kox, Karine Santos, Hans van der Hoeven, Janesh Pillay, et al. (2021) See Less. Increased angiotensin 2-converting enzyme activity in the blood of critically ill patients with COVID-19 ERJ 7: 00848-2020.
17. Zhou F, Yu T, Du R, Guohui Fan, Ying Liu, et al. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 95: 1054-1062.
18. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. (2020) SRAS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 181: 271-280.
19. Bertram S, Heurich A, Lavender H, Gierer S, Danisch S, et al. (2012) Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. PLoS One 7: e35876.
20. Cheng Z, Zhou J, To KK, Chu H, Li C, et al. (2015) Identification of TMPRSS2 as a susceptibility gene for severe 2009 pandemic A (H1N1 influenza and A(H7N9) influenza. J Infect Dis 212: 1214 21.
21. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, et al. (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 7: 11.
22. Kuba K, Imai Y, Rao S, Gao H, Guo F, et al. (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirusinduced lung injury. Nat Med 11: 875-879.
23. MSP: Ministry of Health and Population. Report on the disease situation in Coronavirus COVID-19. Republic of the Congo. SITREP. 233; 2022. https://www.afro.who.int/sites/default/files/2022-03/SITREP_N_233-COVID-19-CONGO_DU_29_MARS%202022-%20VF-1.pdf.
24. Pettersson A, Lis RT, Meisner A, Flavin R, Stack EC, et al. (2013) Modification of the association between obesity and lethal prostate cancer by TMPRSS2: ERG. J Natl Cancer Inst 105: 1881-1890.
25. Penney KL, Pettersson A, Shui IM, Graff RE, Kraft P, et al. (2016) Association of prostate cancer risk variants with TMPRSS2: ERG status: evidence for distinct molecular subtypes. Cancer Epidemiol Biomarkers Prev 25: 745-749.
26. Poaty H, Poaty GE, NDziessi G, Ngakeni EG, Makouka TD, et al. (2021) Diabetes and COVID-19 in Congolese patients. Afr Health Sci 21: 1100-1106.
27. Samavati L, Uhal BD (2020) ACE2, much more than just a SARS-CoV-2 receptor. Front Cell Infect Microbiol 10: 317.
28. Shirbhate E, Pandey J, Patel VK, Kamal M, Jawaid T, et al. (2021) Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention. Pharmacol Rep 73: 1539-1550.
29. Yunita R, Wahyuni AS, Sinaga BY, Yamamoto Z, Soebandrio A, et al. (2024) Role of ACE2 and TMPRSS2 polymorphisms on COVID-19 outcome and disease severity in adult patients: A prospective cohort study in a tertiary hospital, Indonesia. Narra J 4: e919.