Prehospital Particularities of Covid-19 infection and factors associated with its severity during the omicron variant wave (East-center of Tunisia)

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Abstract

Background: The Omicron variant of SARS-CoV-2, characterized by high transmissibility and partial immune evasion, led to significant waves of COVID-19 globally. This study aimed to evaluate the epidemiological and clinical characteristics of COVID-19 cases during the Omicron wave in Tunisia, focusing on severity predictors.

Methods: A prospective study was conducted from January 1st to February 28th, 2022, in the EMS03. Data were collected through patient records and follow-up interviews. COVID-19 severity was classified as mild, moderate, or severe per WHO guidelines. Predictors of severity were identified through univariate and multivariate analyses.

Results: Among 2,948 calls received, 420 confirmed COVID-19 cases were analyzed. The mean age was 48 years (±21.62), with 51% female. Comorbidities were present in 42.1% of cases, and 69.6% were vaccinated against COVID-19. The most reported symptoms were cough (67.5%), myalgia (61.2%), and fever (57.4%). Severe COVID-19 infection presentation was observed in 19.5% of cases, with 28.3% requiring hospitalization, 9.3% needing ICU care, and a mortality rate of 15.5%. Predictors of severity included advanced age, male sex, comorbidities, low education level, and lack of vaccination. Vaccinated individuals exhibited reduced severity, but severity was not significantly associated with the number of doses or type of vaccine.

Conclusion: The Omicron wave presented predominantly symptomatic cases with milder disease severity compared to earlier variants. However, age, comorbidities, and vaccination status significantly influenced outcomes. Enhanced vaccination coverage remains critical in mitigating severe COVID-19.

Keywords: Omicron variant, COVID-19 severity, predictors, Tunisia, vaccination, epidemiology

INTRODUCTION

In December 2019, an unexplained pneumonia outbreak was reported in Wuhan, Hubei Province, China[1]. A new coronavirus, "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) was identified, and the World Health Organization (WHO) named this infection coronavirus disease 2019 (COVID-19)[1].

Given the rapid spread of SARS-CoV2 worldwide, the WHO declared a Public Health Emergency of International Concern on 30 January 2020 and named the outbreak a pandemic on 11 March 2020[2].

In these late years, serial mutants of SARS-CoV-2 have triggered several waves of COVID-19 epidemics. To date, the WHO has identified five mutants characterized as specific Variants of Interest (VOIs) and Variants of Concern (VOCs), including alpha, beta, gamma, delta, and omicron [3,4].

In November 2021, South Africa experienced a rapid spread of SARS-CoV-2 fueling the fourth wave of COVID-19. The B.1.1.529 variant (Omicron) was first detected in samples collected in Botswana on November 11th and in South Africa on November 14th, and the WHO declared a VOC shortly thereafter[5]. Since then, Omicron has spread rapidly worldwide and was detected in Tunisia on 3 December 2021. It was brought from Istanbul by a 23-year-old Congolese tourist [6].

It was demonstrated that the Omicron has significantly higher rates of mutations, compared to previous SARS-CoV-2 variants (particularly in the S-gene, encoding the spike protein) [7,8]. These changes affected the virus's properties leading him to a higher potential of transmissibility [7].

Although full vaccination leads to a series of antibody productions, partial immune evasion has also been noticed with Omicron[9]. However, a marked reduction in hospitalization and mortality rates was reported in various studies [7,8].

In this context, we conducted our study with the aim of identifying the epidemiological and clinical characteristics of COVID-19 during the Omicron wave in the territory of the emergency medical service of the east center of Tunisia (EMS 03), and to study the severity of this variant and its associated factors.

METHODS

Study design and setting: A prospective study was conducted in the territory of EMS03 during the Omicron wave, dating from January 1st to February 28th, 2022.

The EMS03 manages pre-hospital medical emergencies occurring in its territory; in four governorates (Sousse, Kairouan, Monastir, and Mahdia). The EMS includes: (1) A medical regulation unit that ensures the appropriate medical response to any urgent call for care. During COVID-19, a sub-unit was created to receive calls for polymerase chain Reaction

(PCR) testing. PCR tests were carried out the day after to drivers or passengers in the EMS parking lot through the window of their car (Driving test). (2) A mobile resuscitation unit controlled by the regulation. It provides urgent medical interventions.

Study population: All subjects contacting the EMS 03 during the study period were included. Then, patients with a negative PCR and/or chest CT scan were excluded from the study analysis.

Study process and data collection:

-In the first step, we collected the patients' files during the study period.

-In a second step, we selected patients suspected of being infected by SARS-Cov-2; having contact with an infected subject, or presenting symptoms suggestive of a COVID-19 infection, and excluded subjects with no suspected COVID-19 infection.

-In the third step, we excluded subjects confirmed as not COVID-19-infected.

Data were collected via admission records for hospitalized subjects and by phone calls for subjects who did a Driving Test or those left at home after a medical intervention.

- First, we collected information concerning the patient's history and the clinical presentation from the intervention sheets and the digital regulation platform (SI-SAMU software).

Then, we followed up with the patients and collected information about the outcomes.

Measures: Sociodemographic features, medical history**,** and clinical presentation were assessed using a validated questionnaire (Supplementary material). The collected information included age, sex, area of residence, governorate, education level, healthcare profession, smoking, height, weight, comorbidities, vaccination status**,** and symptoms. A clinical examination and chest CT scan were performed to assess the severity. The COVID-19 infection was confirmed by Rapid antigen testing a PCR test**,** or a Chest CT scan.

The severity of COVID-19 infection was classified as mild, moderate, or severe; according to the WHO classification[10,11].

Statistical analysis: We used the Kolmogrov-Smirnov (KS) test to check the normality of the quantitative variables. Continuous variables with a normal distribution were expressed as mean and standard deviation (SD). Variables with asymmetric distribution were presented as the median and the interquartile range (IQR). Categorial variables were expressed as frequency rates and percentages. To assess the severity predictors of COVID-19 infection severity we, used the chi-square test or Fisher's exact test for qualitative variables and Student's test or Mann-Whitney's U test for quantitative variables. The variables were included at the 20% threshold in the multivariate analysis, to identify the determinants of severity. A multivariate analysis using the binary logistic regression models was performed to determine the independent factors related to COVID-19 severity. A p-value less than 0.05 was considered statistically significant.

RESULTS

We enrolled 2,948 calls, of which 1,448 were suspected of being COVID-19-infected. Only 420 patients were confirmed to have a COVID-19 infection (Figure 1). The mean age was 48±21.62 years with extremes ranging between 8 and 103 years. More than half (51%) were female. Almost half of the patients had a higher education level (49.6%) (Table 1). Only 3.8% were healthcare professionals. The proportion of patients with comorbidities was 42.1%. A history of COVID-19 infection was reported in 9.8% of cases. More than two-thirds of patients (69.6%) were vaccinated against COVID-19.

Most of the patients were symptomatic (99.3%). The major symptoms were cough (67.5%), myalgia (61.2%), fever/chills (57.4%), and fatigue (54%). No patient reported ageusia and only 1.9% presented anosmia (Table 2).

Infection was classified as severe in 19.5% of cases. Among the 420 patients, 28.3% required hospitalization (in an intensive care unit (ICU) in 9.3% of cases). Only 33.1% of the subjects needed oxygen. 3.3 % of subjects were intubated. The mortality rate was at 15.5%.

The COVID-19 infection severity predictors were as the age ($p \leq 10^{-3}$) (patients aged over 60 presented more severe forms); male sex (25.9% vs 13.6%; p=0.002); low education level ($p \leq 10^{-3}$); comorbidities (44.4% vs 13.6%, $p \leq 10^{-3}$). Patients vaccinated against COVID-19 developed a less severe presentation than unvaccinated ones (14.7% vs 31.9%; (p≤10-3).

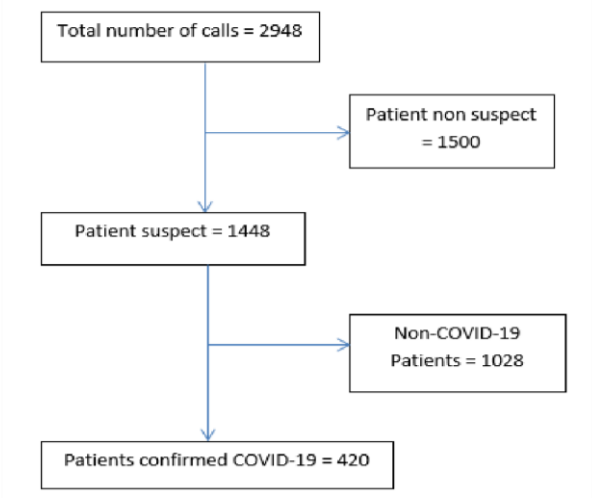

Figure 1. Flow chart of study population

On the other hand, we did not find an association between the severity and the number of doses (p=0.128), nor with the type of vaccine (p=0.054). Thus, influenza vaccination has no association with the presentation severity (p=0.351).

Clinical symptoms that were associated with a severe COVID-19 infection were cough (p=0.026), dyspnea($p \leq 10^{-3}$), sore throat($p \leq 10^{-3}$), and chest pain(p=0.042).

We did not find an association between severity and the healthcare profession (p=0.297)

The independent predictors of a severe presentation of the COVID-19 infection were the history of coronary artery disease, cancer, or auto-immune disease, and the presence of cough as an initial symptom. The presence of sore throat and vaccination were associated with a significant decrease in the severe presentation of COVID-19 infection.

Table 1: Participants' characteristics at baseline

Socio-demographiccharacteristics		n(%)
Age groups	< 19 years	34(8.4)
	20 - 59 yearsold	242(57.6)
	>60 yearsold	143(34)
Type	male	206(49)
	female	214(51)
Governorate of origin	Sousse	307(73.1)
	Monastir	57(13.6)
	Mahdia	51(12,1)
	Kairouan	5(1.2)
residence	Urban	328(81.4)
	Rural	75(18.6)
Level of study	Illiterate	60(14.9)
	Primary	42(10.4)
	Secondary	101(25.1)
	Superior	200(49.6)
Healthprofessional	no	381(96.2)
	yes	15(3.8)
smoking	no	316 (76.7)
	yes	96(23.3)
obesity	no	316 (89.3)
	yes	38 (10.7)
Flu vaccine	no	376 (98.4)
	yes	6 (1.6)
COVID vaccine	no	116 (30.4)
	yes	266 (69.6)
Number of doses	1	47 (17,8)
	2	178 (67.4)
	3	38 (14.4)
	4	1 (0.4)
type of vaccine	Inactivated (sinopharm-sinovac)	41(16.2)
	viral vector(sputnink-astrazenika-janssen)	53 (20.9)
	RNA (moderna-pfizer)	159 (62.8)
Comorbidities		177(42.1)
CVD		84 (20.0)
Diabetes		81(19.3)
HTN		68(16.2)
Coronaryarterydisease		14(3.3)
CRI /asthma		39(9.3)
Renalinsufficiency		13(3.1)
Systemicdiseases		7(1.7)
Neoplasia		9(2.3)
atopy		7(1.9)
PreviousCOVID-19		35 (9.8)

DISCUSSION

In our study, most of the patients were symptomatic (99.3%). This is consistent with results found in a study conducted in Norway reporting a rate of symptomatic subjects of 98.7% (91% having at least 3 symptoms) [12]. In another study conducted in Japan, the rate of symptomatic subjects was 91.1%[13]. It was similar in France with a rate of 89% [14]. However, in Korea, the rate of asymptomatic subjects reached almost half of cases with a rate of 47.5% [15].

Our patients mainly reported respiratory and general symptoms. Cough was the most common symptom (67.5%) followed by myalgia (61.2%), fever (57.4%), and fatigue (54%). These results are consistent with the literature. However, regarding upper respiratory symptoms, 26.7 % of patients had rhinorrhea and 23% had a sore throat which is not congruent with the literature showing a high prevalence of these symptoms among patients with Omicron.

A study conducted in the United States of America (USA) including 43 subjects infected with Omicron showed that cough and fatigue were the most reported signs (89% and 65% respectively). However, fever was present in 14% of cases [16]. A Norwegian study found that cough (83%), followed by rhinorrhea or nasal obstruction (78%), fatigue/asthenia (74%), sore throat (72%), headache (68%), and fever (54%) were the most common reported signs by patients with Omicron [12]. A Canadian study on 1,063 cases of Omicron found that rhinorrhea (73%), cough (65%), and headache (54%) were the most common symptoms [17]. A study in India on 1175 cases of Omicron reported that patients complained mostly of fever (43%), followed by soreness (23%), rhinorrhea (22%), and cough (21%) [18]. A study conducted in the United Kingdom (UK), including only vaccinated individuals who were infected with Omicron, found that rhinorrhea (77%), headache

Table 2: symptoms of covid-19 reported by the study population in Tunisia during Omicron wave from January 01 to February 28, 2022

Symptoms	n(%)
Cough	283 (67.5)
Arthromyalgia	257 (61.2)
Fever /chills	241 (57.4)
Fatigue	227 (54.0)
Headache	162 (38.6)
Dyspnea	162 (38.6)
Rhinorrhea	112 (26.7)
Sore throat	96 (23.0)
Vomiting/Nausea	22 (5.2)
Chest pain	21 (5.0)
Palpitation	16 (3.8)
Abdominal pain	13 (3.1)
Diarrhea	16 (3.8)
Anosmia	8 (1.9)
Agueusia	0 (0.0)
By system	
General signs	371 (89.0)
Respiratorysigns	320 (76.7)
ENT signs	170 (40.7)
Cardiovascularsigns	33 (8.1)
Digestive signs	42 (10.0)
severity	
hospitalization	
no	301(71.7)
yes	119(28.3)
Hospitalizationdepartment	
Medical Service	79(66.4)
Intensive care unit	40(33.6)
Oxygenation/ventilation	
no	281(66.9)
yes	139(33.1)
Oxygenation / Ventilation means	
LN	30(21.6)
MHC	42(30.2)
optiflow	9(6.5)
CPAP	13(9.3)
NIV	31(22.3)
Intubation	14(10.1)
Evolution	
survivors	337(84.5)
Deaths	62(15.5)

(75%), sore throat (71%) and sneezing (63%) were the most common symptoms [19].

Several studies compared the symptoms of Omicron and different variants and found a significant rise in upper respiratory symptoms, especially sore throats. For instance, one of these studies conducted in the US found significantly higher rates of sore throats during the Omicron wave than during the pre-delta period (29.6%, $P < 0.001$) and Delta (29.1%, $P < 0.001$) [20]. This is consistent with another study conducted in the UK [21]. However, sore throat was also common in symptomatic cases with negative PCR, suggesting that sore throats may not be a specific predictor of Omicron. Besides, symptoms reported during COVID-19 are like signs found in any infection by other respiratory viruses such as (influenza A and B, respiratory syncytial virus, adenovirus, parainfluenza, rhinovirus, and human metapneumovirus. As we did not perform sequencing to determine the variant, we can't conclude that the symptoms reported in our study are caused exclusively by Omicron alone. The non-predominance of upper respiratory signs can be explained by the coexistence of other variants of SARS-CoV-2 such as Delta during the study period.

None of our patients reported agueusia and only 1.9% reported anosmia. This is consistent with the literature which indicates a significant decrease in these signs among Omicron patients compared to other SARS-cov-2 variants [22][23]. This finding suggests that the site of the virus tropism may have changed between variants. This is further reinforced by the fact that the number of Omicron pneumonia is reduced compared to other variants [24,25]. Further reinforcing this hypothesis is that the incidence of sore throat has increased with Omicron, and it can be deduced that the viral replication site could be moved to the upper respiratory tract [19].

In our study, the prevalence of severe disease was 19.5%. Only 28.3% of patients required hospitalization. The hospitalization rate in a resuscitation unit was low (9.3%) and the death rate was 15.5%. Several studies found a significant decrease in severity and mortality with the new Omicron variant. Several cohort studies were conducted comparing the severity presentation of Omicron with other variants (namely the delta variant) and have demonstrated this result. In a study in South Africa, analyzing data from 11,000 patients with COVID-19, the authors found that the hospitalization rate of Omicron-infected patients was significantly lower than other variants. They also reported that the prevalence of severe forms was lower than delta-infected patients (OR 0.3, 0.2–0.5) [26]. A cohort study in Canada 11 622 Omicron cases paired with Delta cases noted that the hospitalization rate among Omicron cases was only 0.51% and the mortality rate was 0.03%, compared to 1.56% and 0.12% respectively for Delta cases. The risk of hospitalization or death among Omicron-infected subjects was 65% lower (relative risk,

RH = 0.35, 95% CI: 0.26, 0.46) than in the Delta-infected patients group. The risk of admission to an ICU or death was 83% lower (RH = 0.17, 95% CI: 0.08, 0.37) [27]. Another study in the UK showed that Omicron cases had a 59% lower risk of hospitalization than Delta and a 69% lower risk of death than Delta [28]. Another cohort study in Belgium found that the estimated risk of severe forms and admission to ICU was significantly lower in Omicron patients compared to Delta (RR = 0.63; 95% CI (0.30; 0.97) and RR = 0.56; 95% CI (0.14; 0.99), respectively), while no significant difference was found for mortality (RR = 0.78, 95% CI (0.28–1.29)[29].

Some studies tried to find an explanation for this decrease in mortality and severity with Omicron. They believe that cell-mediated immunity due to a previous natural COVID-19 infection or vaccination played an important role in decreasing the acuteness observed during the Omicron wave.

Studies showed that natural infection induces a diverse polyepitopical cell-mediated immune response that targets the spike protein (nucleocapsid protein and membrane protein) [30]. Therefore, cell-mediated immunity is likely more durable than humeral immunity, especially in small mutations affecting the spike protein [31], such as those seen in the Omicron variant. In addition, natural infection induces an immune response to memory T cells, including long-lived cytotoxic T cells (CD8+), which have a half-life of 125 to 255 days, ensuring longer-lasting immunity [32].

Although vaccination status appears to be well documented, in many cases, likely, previous infection by COVID-19 has not been documented and the rate of re-infection remains underestimated. If reinfections are less severe than primary infections, this fact could, in part, explain the reduced severity of the disease observed in patients infected with Omicron [33].

Although several studies suggest that Omicron is much less virulent than other variants, other studies taking into account the pre-existing immunity to COVID-19 (vaccination status and previous infection) assume the highest virulence of Omicron compared to other variants. Furthermore, Omicron has the ability to infect people with pre-existing immunity[9], thus protecting them from severe forms.

We found two studies comparing the intrinsic virulence of Omicron with the Delta, taking into account the immunizing effect of undocumented prior infections. Although these studies were conducted in regions where the prevalence of infected cases was different, after correction, each study showed that Omicron was approximately 75% as likely as Delta to cause hospitalization in subjects who were not immunized by either vaccination or previous SARS-CoV-2 infection [34,35]. This suggests that Omicron has similar intrinsic virulence with previous variants. With the available data, it is difficult to determine whether the low rate of

severe forms is related to the effect of pre-existing immunity to COVID-19 or the decrease in intrinsic virulence of Omicron. More comparative studies controlling pre-existing immunity, detection bias, care system capacity, and other factors are needed to conclude between these different assumptions.

Concerning associated factors for the severity of COVID-19 during the Omicron wave, we found in the univariate analysis a significant association between age and severity ($p<0.001$), however in multivariate analysis, this association has disappeared. A study on 25207 Chinese Omicron patients found that older subjects had a higher rate of severe forms than other age groups [[36]. Several other studies confirmed this association[37–40]. This can be explained by immune aging, which is responsible for developing weak immune responses to COVID-19 and inadequate immune responses to vaccination [41]. There is also a reduction in immunological memory associated with antibody loss, making elders more vulnerable to infection[41]. It is important to give more attention to older subjects with COVID-19 and to treat them earlier to prevent further deterioration.

In our study, males had a higher prevalence of severe forms. Several studies have shown an association between male sex and severity of infection by different SARS-CoV-2 variants such as Alpha, Gamma, and Delta [42–44]. Male patients may have a greater expression of the ACE2 enzyme, which is controlled by androgenic sex hormones, making this group of people more susceptible to infections and severe forms of SARS-CoV-2, knowing that this virus has great affinity to ACE2 receptors[42,45].

Our data showed a correlation between the risk of developing a severe form was associated with having at least one comorbidity (CVD, diabetes, HTN, coronary artery disease, system disease, COPD/asthma, and cancer). These pathologies were not independent predictors of severe presentation, this coincided with literature findings [36,44,46,47]. Diabetic patients have impaired phagocytic cells, making the treatment of infections ineffective [48]. Obesity, which is also among the severity predictors of influenza A (H1N1) infection [49], is associated with a decrease in functional capacity, expiratory reserve volume, and respiratory system compliance [50]. CVD and endocrine diseases may be responsible for changes in the expression of angiotensin-2 converting enzyme, which is the receptor where the spike protein of SARS-CoV-2 binds. This condition makes these subjects more susceptible to contracting COVID-19 and developing severe forms [45,51,52].

Regarding vaccination, we found in the univariate analysis that severity was significantly lower in vaccinated patients against COVID-19. However, no association was found after binary regression. Many studies have demonstrated the effectiveness of vaccination

against COVID-19. In fact, multiple doses provide additional protection against Omicron, inducing more effective immune responses against symptomatic infection and reducing the risk of hospitalization[53,54]. Considering the overall performance of the vaccination, some studies have reported that the efficacy of the vaccine is lower against Omicron compared to the other variants [55,56]. Additionally, Andrews et al. [57]analyzing South African, German, and British studies found a reduced neutralizing activity of vaccines against Omicron compared to that against Delta [57].

Strengths and limitations of the study

For logistical reasons, participants did not have a genotyping test to confirm infection with the Omicron variant. To genetically determine whether all cases were actually infected with the B.1.1.529 variant, additional laboratory testing is needed.

Our study only assessed clinical symptoms at the onset of the infection and did not track symptoms. Symptoms may superimpose after the swab test. To gain insight into the clinical presentation of this variant throughout the course of infection, more detailed data regarding clinical symptoms in the initial and later stages of infection are needed.

CONCLUSIONS

In 2021, the SARS-CoV-2 Delta variant was replaced by Omicron, which was classified as a VOC by the WHO [4]. Omicron appears to be different from previous variants; it is associated with an important ability of transmission, an ability to escape immune response, and it has a different clinical presentation, and a lower degree of severity [28].

Recognizing the factors associated with severity helps health actors to adopt strategies to deal with this variant. Staying alert to COVID-19 continuing vaccination efforts and adherence to prevention measures are needed to reduce the spread and impact of different variants. The public health system, and local, regional, and national authorities, must maintain the alert to detect, react, and adapt rapidly to the emergence of new variants.

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