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Longitudinal analysis of Covid-19 infection trends and in-hospital mortality across six pandemic waves in Tunisia

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Abstract

Background The global impact of the COVID-19 pandemic was remarkably diverse, unfolding with multiple waves that have touched countries and continents in distinctive ways, leading to varying rates of mortality. The objectives of this study were to examine the characteristics and in-hospital fatality rates of COVID-19 patients hospitalized in the Monastir governorate over two years, with an overall analysis and a wave-specific breakdown throughout the pandemic's progression.

Methods We carried out a two-year longitudinal study, enrolling all COVID-19-infected patients admitted to both public and private health facilities in the governorate of Monastir from March 2020 to March 2022. The study covered six complete infection waves. Patients were followed from their first day of admission to their outcome in hospital. The data were collected using a questionnaire manually completed by well-trained residents. The data were globally analyzed across all hospitalized patients and then compared based on the different waves.

Results Overall, 5176 were hospitalized. The cumulative in-hospital case fatality rate (CFR) over the study period was 21.4%. After the first wave (W1), the in-hospital CFR followed a gradual increase, reaching its peak at 27.5% during W4 (*alpha variant*). Later, it decreased to 21.8% during W5 (*delta variant*), and further declined to 19.5% during W6, associated with the *Omicron variant* (overall $p<0.001$). W5 exhibited the highest proportions of infections, hospitalizations, and in-hospital deaths. W6 featured a low hospitalization rate of 2.8% and a decline in severe cases. Nevertheless, there was a significant surge in hospitalizations among both the pediatric (≤ 18 years) and geriatric (≥ 75 years) populations, with a pronounced impact on the elderly with chronic conditions. This surge resulted in an increase in fatalities among the elderly. The length of stay (LoS) decreased throughout the course of the pandemic, declining from 13 days [10;14] in W1 to 4 days [2;9] in W6 with almost half of them had a LoS less than seven days (55.6%).

Conclusion This study underscores the critical interplay of variant-specific disease severity, patient demographics, and evolving healthcare responses in managing COVID-19's impact on hospital outcomes.

Keywords SARS-Cov-2, Mortality, Hospital, Trends, Tunisia

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Text box 1. Contributions to the literature

• This study provides a comprehensive, wave-specific analysis of in-hospital COVID-19 mortality trends, contributing to explain how the pandemic evolved in healthcare settings with limited resources.

• By detailing variant-specific impacts on hospitalization rates, severity, and length of stay, particularly among vulnerable age groups, this research adds critical insight into the interplay between patient demographics and COVID-19 outcomes over time.

• The findings highlight the importance of adaptive healthcare responses and offer a valuable reference for public health strategies, supporting improved preparedness and management of future pandemic waves in similar regions.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in 2019–2020 led to the globally pervasive Coronavirus Disease 2019 (COVID-19). The rapid global transmission of SARS-CoV-2 has placed a substantial burden on healthcare systems, straining the entire medical infrastructure [1]. The impact of COVID-19 extends beyond the substantial loss of lives, encompassing significant damages to healthcare and education systems, as well as economies worldwide [2]. The SARS-CoV-2 has undergone a series of mutations over time, leading to the emergence of multiple genetic variants exhibiting increased viral transmissibility, virulence, and a potential for reduced efficacy of vaccines or immunity. These variants were responsible for the evolution of the pandemic in successive waves, each characterized by specific epidemiological profiles [3]. The global impact of the COVID-19 pandemic was remarkably diverse, unfolding with multiple waves that have touched countries and continents in distinctive ways, leading to varying rates of mortality [2, 4]. At the onset of the pandemic, Africa faced a comparatively lower impact than Asia, Europe, the United States, and Iran. Nevertheless, the epidemiological landscape swiftly transformed, resulting in a rapid spread of the pandemic across almost the entire continent. Notably, countries such as South Africa, Egypt, Morocco, and Algeria experienced a significant impact [5]. As the pandemic concluded, Europe emerged with the highest COVID-19 fatality rate among regions (1.9%), followed by the Eastern Mediterranean (1.8%) and the Americas (1.6%) [4]. This variability can be attributed to a multitude of factors beyond the circulating viral variants, including population demographics, clinical characteristics, health infrastructures, the effectiveness of preventive measures implemented, along with people's adherence and vaccination coverage rates [6]. The exchange between countries has played an important role in the introduction of new lineages, facilitating their rapid dissemination across borders. Tunisia, like nations worldwide, has witnessed the successive emergence of different waves, mirroring the global trajectory of COVID-19 infections. Thanks to stringent measures implemented early on, primarily through general lockdowns and border closures, the first wave was characterized by a low incidence of cases, hospitalizations, and deaths [7]. Subsequently, the country has experienced five waves of COVID-19 cases and associated deaths [8]. On the African continent, Tunisia ranks among the countries with the highest number of deaths since the beginning of the pandemic. From March 19, 2020 to November 13, 2022, Tunisia has reported 29,266 deaths due to COVID-19, reflecting a crude mortality rate (CMR) of 247.9 per 100,000 inhabitants [9]. The Tunisian vaccination program commenced in March 2021, later than the global launch in December 2020 [10]. By April 2022, 54% of the population had received two vaccine doses, and 10% received a third dose. While nearly 60% in certain urban areas had received three doses, this figure did not exceed 4.5% in many rural regions [11].

Despite the abundance of information published since the onset of the crisis concerning hospital situations and mortality worldwide, limited studies have attempted to analyze the course of epidemiological features among COVID-19 hospitalized patients throughout all waves of the pandemic and make comparisons between these waves. To the best of our knowledge, this study is the first in our country to compare the six consecutive waves of the pandemic, with a specific focus on in-hospital fatality rates and survival rates, providing a comprehensive overview within the specific context of Tunisia.

The objective of this study was to describe the sociodemographic details, clinical characteristics, and in-hospital fatality among hospitalized COVID-19 patients in the Monastir governorate from March 2020 to March 2022, encompassing both an overall perspective and specific details across different waves of the pandemic.

Methods

Study design

A two-year prospective cohort study was carried out, enrolling all COVID-19-infected patients admitted to both public and private health facilities in the governorate of Monastir from March 2020 to March 2022. The study covered six infection waves. Patients were followed from their first day of admission to their final outcome in hospital.

Study setting

The Monastir governorate, situated in the central-eastern part of Tunisia, is a city known for its industrial and tourist activities [12]. During the study period, the governorate had one tertiary care university hospital with two units (Fattouma Bourguiba University Hospital—FBUH A and B), 12 regional and district hospitals, 88 primary health care centers and some private clinics. The facilities actively involved in the treatment of COVID-19 patients were FBUH A and B, two regional hospitals in the delegations of Moknine and Ksar Hellal, two district hospitals in Tbolba and Jammel, and two private clinics. The FBUH is a tertiary care center that serves as a referral hospital for the surrounding regions. It was the only facility equipped to handle severe cases requiring admission to intensive care units. Furthermore, the hospital underwent a reorganization to effectively respond to the pandemic. Multiple departments were dedicated to receiving COVID-19 patients.

Study population

The analysis considered all hospitalized cases of SARS-CoV-2 infection admitted between March 2020 and March 2022 in the governorate of Monastir. All patients admitted with laboratory-confirmed SARS-CoV-2 infection at public and private healthcare facilities in the Monastir governorate over 24 months (March 2020 to March 2022) and meeting the inclusion criteria were included in this study. Therefore, sample size calculations were not employed. The diagnosis of positive cases was based on real-time reverse transcriptase polymerase chain reaction (RT-PCR) and/or a positive rapid test from a naso- or oropharyngeal swab and/or a thoracic computed tomography scan showing lung lesions suggestive of COVID-19 pneumonia. Hospitalization was due either to COVID-19 itself or to a nosocomial COVID-19 infection acquired during the hospital stay, both requiring specific management. For the nosocomial group, the admission date was defined as the date of diagnosis. To account for possible reinfections and rehospitalizations, patients were recorded multiple times if readmitted for distinct infectious episodes.

Individuals who were not residents of Monastir, as well as those of foreign nationality who were hospitalized in this region, were also included.

Patients with symptoms suggestive of COVID-19 but with negative biological results and no confirmatory imaging were not included. Additionally, asymptomatic patients who incidentally tested positive for COVID-19 upon admission for unrelated reasons and did not require targeted.

Data collection

The data collection ranged from March 2020 to June 2022, involving two distinct steps: follow-up and verification.

Follow-up step (March 2020 to March 2022)

In September 2020, the registry for all hospitalized COVID-19 patients was established at FBUH. This registry was an Excel database containing epidemiological data, including gender, date of birth, residence, nationality, diagnostic confirmation (TDR-Ag and/or PCR and/or thoracic CT scan), admission date, discharge date, and outcome (death or hospital discharge). Well-trained resident doctors conducted almost daily visits to all specialized COVID-19 units, as resources allowed. They completed surveys for COVID-19 patients who met the criteria, gathering information from medical records or through direct interviews with the patient or their attending physician. Patients were followed until death or discharge from the hospital. If patients were transferred to another department, their follow-up continued in the new department. Finally, all the collected data were continuously stored in the registry.

For other healthcare facilities within the governorate, a standardized Excel database developed by the Department of Preventive Medicine and Epidemiology at FBUH in Monastir was introduced. This database included variables such as gender, date of birth, admission date, discharge date, outcome (death or hospital discharge), comorbidities, and functional symptoms. The relevant departments were required to enter the information of all confirmed COVID-19 hospitalized patients into this database.

Verification step (April to June 2022)

This step was implemented to complete any missing data, if available. A second data check was conducted by reviewing all available paper or computerized medical records of COVID-hospitalized patients at FBUH. Phone calls were also conducted to verify certain variables, particularly those related to the evolution of the disease after hospital discharge. The data were collected using a questionnaire (proposed by the Ministry of Health) manually completed by well-trained residents. Subsequently, the information gathered through the questionnaires was entered into an Excel© database and cross-referenced with registry data to fill in any missing information. Finally, a double data verification process was carried out by a second investigator.

The collected data included the patient's date of birth, sex, occupation, residence, nationality, comorbidities (including diabetes, lung diseases, heart diseases, renal diseases, immune system diseases, and liver diseases), vaccination status, date of admission, reason for admission, time between symptom onset and hospital admission, diagnostic confirmation (TDR-Ag and/or PCR and/or thoracic CT scan), all developed symptoms, type of supportive oxygen therapy upon hospital admission and/or during the hospital stay, drugs used to treat COVID-19, and hospitalization outcome (death, discharge, or transfer to other facilities).

Definition of variables

Person characteristics

Variables related to the in hospital stay such as inpatient outcome (discharge, transfer, or death) admission to intensive care unit (ICU) and length of stay (LoS).

Demographic parameters (age and gender), comorbidities and functional symptoms were also collected.

The severity level was classified into three categories [13, 14]. Mild cases were patients who do not require additional oxygen or intensive care. Moderate cases were patients with breathing difficulties or mild pneumonia and requiring supplementary oxygen during admission outside the intensive care unit. Severe cases were patients admitted to intensive care, exhibiting acute respiratory distress syndrome (ARDS), requiring intubation, suffering from multisystem organ failure or who have died.

Time characteristics

To identify the different waves, we established the epidemic curve during the study period, and we identified six distinct periods coinciding with increased COVID-19 cases and hospitalizations in Tunisia.

The initial wave, spanning from March 15, 2020, to June 19, 2020, saw the prevalence of wild strains. Following a brief interlude, the second wave surged from July 5, 2020, to December 14, 2020, dominated by the continued prevalence of wild strains. Subsequently, the third wave occurred from December 15, 2020, to March 25, 2021, with wild strains persisting as the predominant variant until January 2021. The fourth wave, spanning from March 26, 2021, to May 18, 2021, marked the emergence of the Alpha variant in April 2021. The fifth wave, spanning from May 19, 2021, to October 21, 2021, was characterized by the dominance of the Delta variant, peaking in July 2021. Finally, the sixth wave unfolded from December 31, 2021, to March 31, 2022, with the Omicron variant emerging as the dominant strain in February 2022.

Data analysis

The data were initially entered into an Excel database. After verification and data cleaning, they were transferred to the Statistical Package for the Social Sciences (SPSS) version 20.0 for data analysis. These data were globally analyzed across all patients and then compared based on the different waves.

Categorical variables were presented with frequencies and percentages, and continuous variables were described using means with standard deviations (SD) or medians with interquartile ranges [Q25-Q75], depending on the normality distribution of the variable. The normality distribution was evaluated through the Kolmogorov–Smirnov test. The Chi-square and Fisher exact tests were used for percentage comparisons, while the T-student test was employed for mean comparisons, and the Mann–Whitney and Kruskall-Wallis tests were used for median comparisons. Admission outcomes were reported in terms of frequencies and percentages. Epidemic curves were generated to illustrate the weekly incidence rates of overall confirmed cases, hospitalizations, and in-hospital fatalities, covering the period from March 15th, 2020 (week 2020–12) to March 31st, 2022 (week 2022–14).

We calculated the following indicators:

In-hospital Case mortality rate (CMR) (%) is defined as the percentage of people who have died from COVID-19, divided by the total population, during a specific time period**.** It is calculated as follows [15]:

$$\text{In}-\text{hospitalCMR} = \{\text{Number of COVID} - 19\ \text{deaths}\}/\{\text{Total population during a specific time period}\}^{*}100$$

In-hospital Case fatality rate (CFR) (%) is defined as the number of people passed away by COVID-19 in hospital divided by the total number of hospitalized cases in a given time. it is calculated as follows [16]:

$$\text{In}-\text{hospital CFR} = \{\text{Number of COVID} - 19\ \text{in} - \text{hospital deaths}\}/\{\text{Number of hospitalized COVID} - 19\text{cases during a specific time period}\}^{*}100$$

Hospitalization rate (%) is defined as the ratio of people hospitalized for COVID-19 to the total number of confirmed cases within a given time. It is calculated as follows [17]:

$$\text{Hospitalizationrate} = \{\text{Number of COVID} - 19\ \text{hospitalizations}\}/\{\text{Number of COVID} - 19\ \text{cases during as pecific time period}\}^{*}100$$

Ethical considerations

The study was approved by the Ethics Committee of the Faculty of Medicine of Monastir (reference number: IORG 0009738N200 OMB 0990–0279). Strict confidentiality and anonymity were maintained. The anonymous exploration of personal data within the context of the COVID-19 epidemic was authorized by the National Data Protection Authority.

Results

Epidemic description

During study period in the Monastir governorate, we noted 58,862 confirmed cases, 5,176 hospitalizations (8.8%) and 1,109 in-hospital COVID-19 related deaths (21.4%), corresponding to a mean of 494.6 infections per week and 43.5 hospitalizations per week respectively. The global incidence rate was 4,854 infections per 100,000 people/year. The global hospitalization rate was 427 hospitalizations per 100,000 people/year. The global in-hospital case mortality rate was 9.1 deaths per 100,000 people/year.

1. **Epidemic description according to time characteristics**

   Of the 5,176 COVID-19 inpatients, 7 (0.1%) were admitted during W1, 863 (16.7%) during W2, 1104 (21.3%) during W3, 570 (11%) during W4, 2129 (41.1%) during W5, and 503 (9.7%) during W6.

   The epidemic curves revealed five peaks among the infected, hospitalized, and deceased cases from June 2020 to March 2022, aligning with the last five waves. During the initial period spanning from March to June 2020, which we identify as the first wave in our study, there was no clearly defined peak observed.

   The highest number of infections, hospitalizations, and in-hospital deaths were recorded during W5, accounting for 21,285 (36.2%), 2,129 (41.1%), and 466 (42%), respectively. The hospitalization rate exceeded 10% during the first five waves, reaching its peak in W4 at 14.9%, and decreasing to 2.8% during W6. During the first two waves, the in-hospital case fatality rate (CFR) was around 14%. It increased significantly to 23.8% in W3 and to 27.5% in W4. As the pandemic evolved, the in-hospital CFR gradually decreased to 21.8% in W5 and 19.5% in W6 (overall $p < 0.001$) (Table 1, Fig. 1).

2. **Epidemic description according to person characteristics**

   a **Sociodemographic characteristics**

   The sex ratio of infection cases was 0.74 ($p < 0.001$). The mean age was 39.4 ± 17.7 and the 19–45 age group totaled 30,705 cases (53.2%). The sex ratio of hospitalized cases was 1.15. The mean age was 59.9 ± 17.3 and the 61–75 age group totaled 1764 cases (34.7%). The sex ratio of in-hospital deaths was 1.38 ($p < 0.05$). The mean age was 67.1 ± 14.5 and the 61–75 age group totaled 449 deaths (41.5%). Seven children out of the 84 hospitalized pediatric patients died. The highest hospitalization rate was detected among the 61–75 age group (31.1%), and the highest in hospital CFR was observed among those aged over 75 (34.9%) (See Table 2).

   b **Clinical characteristics**

   The ICU admission rate was 15.7% for hospitalized patients and 30.6% for those who died in the hospital. Out of the 685 patients admitted to the ICU, 304 died, resulting in a CFR in the

Table 1 COVID-19 cases, hospitalizations, and deaths in Monastir, Tunisia, March 2020-March 2022: Overall and across pandemic waves

	Infections N (%)	Hospitalizations N (%)	In-hospital deaths N (%)	Hospitalization rate (%)	In-hospital CFR (%)◊
Waves					
W1	49 (0.1)	7 (0.1)	1	14.3	14.3
W2	6450 (11)	863 (16.7)	124 (11.2)	13.4	14.4
W3	9387 (15.9)	1104 (21.3)	263 (23.7)	11.8	23.8
W4	3835 (6.5)	570 (11)	157 (14.2)	14.9	27.5
W5	21,285 (36.2)	2129 (41.1)	466 (42)	10	21.9
W6	17,855 (30.3)	503 (9.7)	98 (8.8)$	2.8	19.5$
Overall	58,861 (100)	5176 (100)	1109 (100)	8.8	21.4

$ p-value < 0.001

◊ case fatality rate

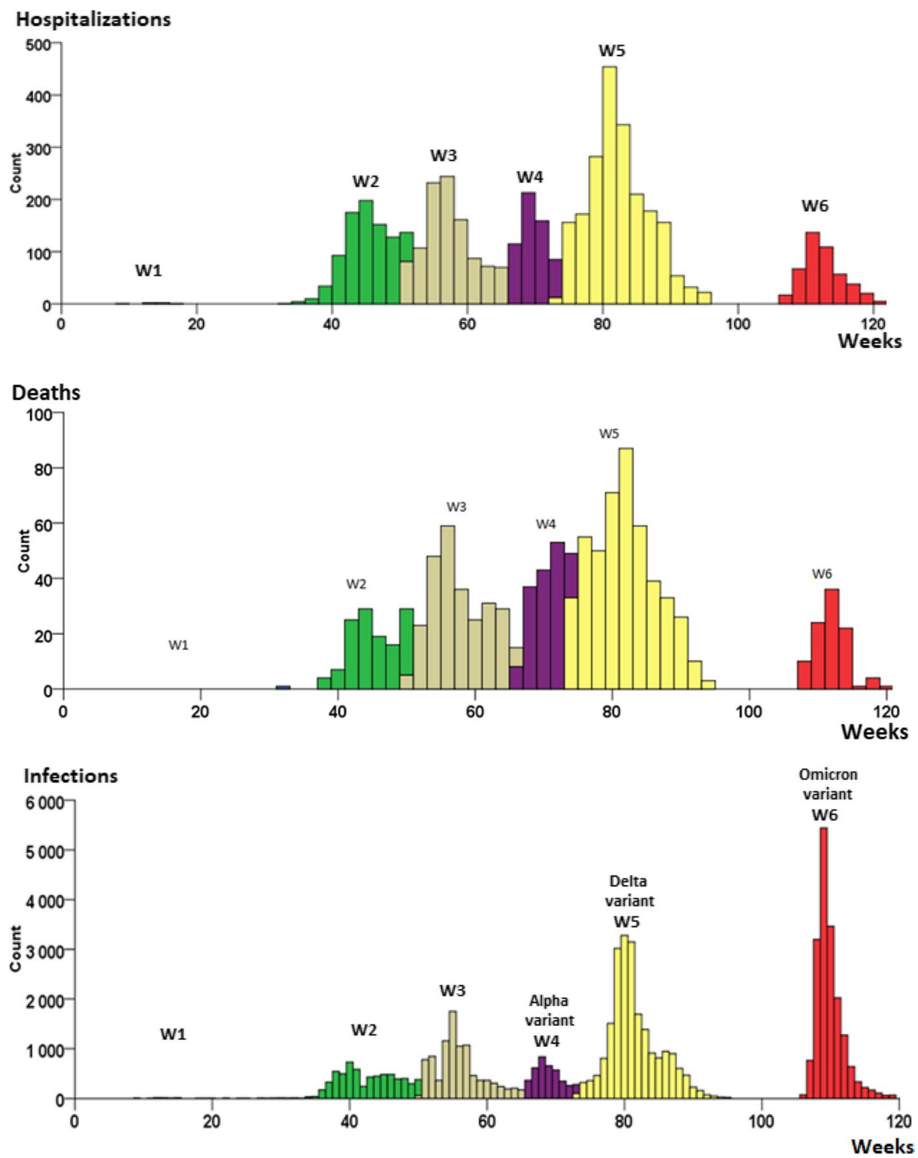

Fig. 1 Distribution of COVID-19 Infections, Hospitalizations and In-hospital Deaths across different waves in Monastir region (Tunisia), March2020-March2022

ICU of 44.4%. Overall, 1,486 (40.1%) were classified as mild cases, 879 (23.7%) as moderate cases and 1,341 (36.2%) as severe cases. Among 3645 patients admitted to hospital, 1,660 (46.6%) had one or more comorbidities. Among 888 patients who died in hospital, 427 (48.1%) had co-morbidities. The three most common comorbidities in both groups were hypertension, diabetes, and cardiovascular diseases. The three most common symptoms among hospitalized and in-hospital deceased individuals were as follows respectively: respiratory signs, particularly dyspnea, fever, and asthenia. Among 1815 hospitalized COVID-19 women, 115 (6.3%) were pregnant. Among 391 died women 45 (11.5%) were pregnant. The in-hospital CFR during pregnancy was 39.1% (Table 4).

c **Length of hospital stay**

The median length of hospital stay (LoS) was 6 days [95% CI: 2–11], with significant variation across waves ($p<0.001$). It decreased throughout the pandemic, from 13 days in Wave 1 to 4 days in Wave 6. The LoS for deceased patients was similar, at 6 days [95% CI: 2–13], also showing

Table 2 Distribution of COVID-19 infections, hospitalizations, and deaths by age and gender in Monastir region, March2020-March2022

	Infections	Hospitalizations	In-hospital Deaths*	Hospitalization rate (%)	In-hospital CFR (%)
N (overall)	58,862	5176	1109	8.8	21.4
Gender, n (%)					
Male	25,011 (42.5)	2767 (53.5)	643 (58.0)	11.1	23.2
Female	33,816 (57.5)	2408 (46.5) *	465 (42.0) *	7.1	19.3
Age (years), mean ± SD					
	39.4 ± 17.7	59.9 ± 17.3	67.1 ± 14.5	-	-
Age group, n (%)					
0–18 year	6363 (11)	84 (1.7)	7 (0.6)	1.3	8.3
19–45 year	30,705 (53.2)	910 (17.9)	85 (7.8)	3.0	9.3
46–60 year	11,892 (20.6)	1373 (27)	213 (19.6)	11.5	15.5
61–75 year	5628 (9.7)	1764 (34.7)	449 (41.4)	31.3	25.5
> 75 year	3160 (5.5)	949 (18.7) *	331 (30.5) *	30.0	34.9

SD standard deviation

* 0.001 < p-value < 0.05 (Chi-square test)

significant differences across waves ($p < 0.001$). The median ICU stay was 12 days [95% CI: 6–18] for hospitalized patients and 10 days [95% CI: 5–17] for those who died, with a decline over time, reaching 8.5 days in Wave 6. In Wave 1, two patients were admitted to the ICU: one stayed 4 days and was discharged, while the other stayed 67 days before dying. The median time from symptom onset to hospitalization was 7 days [95% CI: 4–10], with significant differences across waves. The shortest time was in Wave 6, at 5.5 days [95% CI: 2–9]. Nearly half of hospitalizations (55.6%) had a LoS of less than 7 days, followed by 28.4% staying 7–14 days, and 16% staying more than 14 days. Most patients stayed less than 7 days across all waves, except in Wave 1, where there were more varied stays (Fig. 2).

During the first wave, there were 49 infected individuals, the lowest across all waves, with men making up 53.1% (26 cases). In subsequent waves, women showed the highest infection rates, peaking in Wave 4 at 59.7%. The 19–45 age group had the most infections overall, especially in Wave 5, where it reached 57.6%. The highest total infections was recorded in Wave 5.

Hospitalizations were limited in the first wave, with only seven cases (four women and three people aged 19–45). In the last five waves, men had higher hospitalization rates, peaking in Wave 3 at 58.3%. Most hospitalizations were among patients aged 61–75, peaking in Wave 3 at 43%. In Wave 6, hospitalizations notably increased for those over 75, reaching 35.6% (Table 3). Throughout all waves, most in-hospital deaths occurred among men, with a peak in Wave 3 at 62.7%, primarily affecting those aged 61–75 or older, depending on the wave. In Wave 5, mortality rates rose, especially for young adults (19–45) and middle-aged adults (46–60), at 11.4% and 26.6%, respectively. In Wave 6, mortality significantly increased among those over 75, with 56.4% of deaths in this age group (See Table 3).

Hypertension, diabetes, and cardiovascular disease were the most common comorbidities across all waves. Wave 6 saw a significant rise in deaths among vulnerable groups, particularly those over 75 (59.6%) and those with at least one comorbidity, especially three or more (42.6%). Respiratory symptoms, fever, and fatigue were consistently the most common symptoms. Digestive symptoms ranked fourth in waves 5 and 6, while rheumatological symptoms held that position in waves 2, 3, and 4. ENT symptoms were the least frequent, peaking at 7.6% in wave 2. Oxygen support was provided to 68.8% of hospitalized patients and 76.1% of those who died, with 5.8% of all hospitalized patients needing invasive mechanical ventilation, rising to 18.5% among deaths. Common treatments included C3G antibiotics (34.7%), low-molecular-weight heparin, and corticosteroids. Vitamins C (35.6%), D (12.1%), and zinc (10.6%) were used less frequently. In Wave 1, two patients were admitted to the ICU, with one death. Wave 4 had the highest severity rate at 42.3%, while Wave 6 had the lowest at 32.1%. ICU admissions peaked in Wave 2 at 20.8% and were highest among those who died, reaching up to 47.9% in Wave 6. Wave 5 recorded the most severe cases (539), ICU admissions (237), and ICU deaths (95) (Tables 4 and 5).

Table 3 Distribution of COVID-19 infections, hospitalizations, and deaths, by age and gender across pandemic waves in Monastir region, March2020-March2022

Infections	W1 (N = 49)	W2 (N = 6450)	W3 (N = 9387)	W4 (N = 3835)	W5 (N = 21,285)	W6 (N = 17,855)	*p**
N							
Gender							
Male	26 (53.1)	2697 (41.8)	3854 (41.1)	1545 (40.3)	9477 (44.5)	7412 (41.5)	$< 10^{-3}$
Female	23 (46.9)	3753 (58.2)	5529 (58.9)	2289 (59.7)	11,786 (55.4)	10,436 (58.4)	
Age (years), mean ± SD*	41.7 ± 15.4	43.1 ± 17.9	44.5 ± 17.7	45.2 ± 17.5	38.2 ± 16.7	35.7 ± 17.8	0.019
Age, N (%)							
0–18	0	364 (6)	433 (4.7)	167 (4.4)	2088 (10.1)	3311 (18.6)	NA
19–45	31 (63.3)	3098 (50.7)	4647 (50.1)	1847 (48.5)	11,906 (57.6)	9176 (51.5)	
46–60	9 (18.4)	1392 (22.8)	2198 (23.7)	977 (25.6)	4175 (20.2)	3141 (17.6)	
61–75	9 (18.4)	850 (13.9)	1388 (15)	626 (16.4)	1600 (7.7)	1155 (6.5)	
> 75	0	412 (6.7)	608 (6.6)	194 (5.1)	901 (4.4)	1045 (5.9)	
Hospitalizations	**W1 (N =** 7)	**W2 (N =** 863)	**W3 (N =** 1104)	**W4 (N = 570)**	**W5 (N = 2129)**	**W6 (N = 503)**	**p***
Gender							
Male	3 (42.9)	471 (54.6)	643 (58.3)	309 (54.2)	1066 (50.1)	275 (54.7)	$< 10^{-3}$
Female	4 (57.1)	392 (45.4)	460 (41.7)	261 (45.8)	1063 (49.9)	228 (45.3)	
Age (years), mean ± SD*	50.4 ± 22.5	62.3 ± 15.7	64.6 ± 14.5	62.4 ± 15.0	55.1 ± 17.4	63.5 ± 21.8	0.11
Age, N (%)							
0–18	0	5 (0.6)	8 (0.8)	0	39 (1.8)	32 (6.6)	**$< 10^{-3}$**
19–45	3 (42.9)	120 (14)	98 (9.2)	83 (14.8)	561 (26.6)	45 (9.3)	
46–60	1 (14.3)	219 (25.6)	258 (24.3)	156 (27.9)	657 (31.1)	82 (16.9)	
61–75	2 (28.6)	334 (39.1)	457 (43)	218 (38.9)	599 (28.4)	154 (31.7)	
> 75	1 (14.3)	177 (20.7)	241 (22.7)	103 (18.4)	254 (12)	173 (35.6)	
Deaths	**W1 (N = 1)**	**W2 (N = 124)**	**W3 (N = 263)**	**W4 (N = 157)**	**W5 (N = 465)**	**W6 (N = 98)**	**p***
Gender							
Male	1 (100)	72 (58.1)	165 (62.7)	84 (53.5)	262 (56.3)	59 (60.2)	0.34
Female	0	52 (41.9)	98 (37.3)	73 (46.5)	203 (43.7)	39 (39.8)	
Age (years), mean ± SD*	-	69.5 ± 15.3	70.2 ± 11.9	65.8 ± 15.3	63.8 ± 14.7	74.2 ± 12.3	0.018
Age, N (%)							
0–18	0	3 (2.4)	2 (0.8)	0	2 (0.4)	0	$< 10^{-3}$
19–45	0	6 (4.8)	5 (2.0)	19 (12.5)	53 (11.4)	2 (2.1)	
46–60	0	18 (14.5)	38 (15.3)	26 (17.1)	123 (26.5)	8 (8.5)	
61–75	0	48 (38.7)	117 (47.0)	68 (44.7)	185 (39.8)	31 (33.0)	
> 75	1 (100)	49 (39.5)	87 (34.9)	39 (25.7)	102 (21.9)	53 (56.4)	

SD: standard deviation, *W* wave

* *p*-value for chi-square test

Discussion

To our knowledge, this longitudinal study is the first in our country to systematically compare the six consecutive pandemic waves, with a specific focus on in-hospital fatality rates, providing a comprehensive understanding within the Tunisian context. The study included all COVID-19-infected patients admitted to both public and private health facilities in the Monastir governorate from March 2020 to March 2022, covering six infection waves. The in-hospital case fatality rate fluctuated across the six waves, aligning with global trends and highlighting the dynamic nature of the pandemic. The initial wave, marked by a prompt response and effective preventive measures, successfully contained the virus. However, subsequent waves, influenced by factors such as border reopening and the relaxation of preventive measures, presented new challenges. The fourth wave, driven by the Alpha variant, saw the highest in-hospital CFR, peaking at 27.5%, due to the variant's characteristics, strain on the healthcare system, and pandemic fatigue. The fifth

Table 4 Distribution of COVID-19 hospitalizations and in-hospital deaths by severity level, comorbidities, symptoms, oxygen support, and pharmacological treatments

	H[a]	D[b]
Severity: n (%)	***N*=3706**	***N*=1109**
Mild cases	1486 (40.1)	0
Moderate cases	879 (23.7)	0
Severe cases	1341 (36.2)	1109 (100)
Comorbidities: n (%)	***N*=3645**	***N*=888**
Hypertension	943 (25.9)	250 (28.2)
Diabetes	868 (23.8)	213 (24.0)
Cardio-vascular disease	412 (11.3)	117 (13.2)
Chronic lung disease	269 (7.4)	63 (6.9)
Dyslipidemia	180 (4.9)	56 (6.3)
Chronic renal disease	134 (3.8)	31 (3.5)
Oncological disease	37 (1)	18 (2.0)
Immune system disease	30 (0.8)	7 (0.8)
No. of comorbidities: n (%)	***N*=3645**	***N*=888**
0	1947 (53.4)	461 (51.9)
1	664 (18.2)	155 (17.5)
2	498 (13.7)	135 (15.2)
> =3	498 (13.7)	137 (15.4)
COVID 19 Signs: n (%)	***N*=3645**	***N*=888**
Respiratory signs	2521 (69.1)	679 (76.4)
Fever	1436 (39.4)	300 (33.8)
Asthenia	904 (24.8)	237 (26.7)
Digestive signs	405 (11.1)	70 (7.9)
Rheumatological Signs	390 (10.7)	86 (9.7)
Neurological and psychological signs	290 (8.0)	98 (11.0)
ENT signs	166 (4.6)	46 (5.2)
Women: n (%)	***N*=1815**	***N*=391**
Pregnant	115 (6.3%)	45 (11.5%)
Maximum level of O2 support: n (%)	***N*=3721**	***N*=898**
No oxygen support	1161 (31.2)	215 (23.9)
Nasal cannula	1920 (51.6)	366 (40.8)
Reservoir mask	12 (0.3)	0
Non-invasive ventilation	159 (4.3)	87 (9.7)
Nasal High flow oxygen	198 (5.3)	55 (6.1)
CPAP	56 (1.5)	9 (1.0)
Invasive ventilation	215 (5.8)	166 (18.5)
Pharmacological treatment: n (%)	***N*=1393**	***N*=393**
Antibiotics	1231 (88.4)	312 (79.4)
Heparin	1115 (80)	313 (79.6)
Corticoids	1051 (75.4)	315 (80.0)
Vitamin C	496 (35.6)	53 (13.5)
Vitamin D	168 (12.1)	39 (9.9)
Zinc	148 (10.6)	3 (0.8)

ENT Ears, nose, and throat

[a] Hospitalizations

[b] In-Hospital Deaths

wave, driven by the Delta variant, experienced the highest numbers of infections, hospitalizations, and in-hospital deaths, reflecting the complex interaction of variant aggressiveness, delayed vaccination, and relaxed measures. The final wave demonstrated lower hospitalization and mortality rates, likely influenced by the less virulent nature of the *Omicron* variant, along with increased vaccination coverage and community immunity.

Our study revealed a male predominance among hospitalizations and in-hospital deaths. These observations align with previous findings in both national and international literature, suggesting that men are more prone to developing severe forms of the disease and require hospitalization due to COVID-19 [18–26]. A national longitudinal study covering all COVID-19-related deaths in Tunisia between March 2020 and February 2021, totaling 8051 deaths, reported a sex ratio (M/F) of 1.8 [27]. Besides, a metanalysis (MA) incorporated data from 43 studies spanning 12 countries indicated a male predominance among hospitalized patients in all countries studied, with Europe reporting the highest percentage of males (69.6%), followed by North America (58.2%), and Asia (54.5%) [28]. These disparities based on gender could be attributed to biological sex distinctions, including sex-based variations in immune responses, hormonal influences and genetic polymorphism. It is crucial to recognize that gender differences in health behaviors, such as smoking, and the presence of pre-existing conditions, such as diabetes and hypertension, can also significantly contribute to these disparities [20, 29, 30].

In terms of age, the elderly demonstrated the highest rates of hospitalization and in hospital death. The thorough national study on all Covid-19-related fatalities in Tunisia from March 2020 to November 2022 disclosed a median age of 72 years, ranging from 0 days (newborns) to 112 years [31]. This difference underscores the variation in population distribution among the country's governorates. Besides, an umbrella review comprising 120 systematic reviews revealed a consistent, linear relationship between age and the risk of disease severity [32]. Thus, it is well established in the literature that the elderly are more vulnerable to the COVID-19 pandemic [33, 34]. Concerning the pediatric population (18 and under), our study revealed significantly lower hospitalization and in-hospital case fatality rates compared to other age groups at 1.3% and 8.3% respectively. Our CFR among children is lower than the rates reported in the United States [35, 36], Mexico [37], India [38], Indonesia [39], and Iran (13%) [40]. These differences may be explained by variables such as predominant virus driving the outbreak at the time of reporting, social restriction measures enforced, prevalence of comorbidities, socioeconomic issues, health infrastructure, or even ethnicity

Table 5 Distribution of COVID-19 hospitalizations and in-hospital deaths according to ICU admission and level of severity across pandemic waves in Monastir region, March2020-March2022

	W1		**W2**		**W3**		**W4**		**W5**		**W6**	
	H○	**D●**	**H**	**D**	**H**	**D**	**H**	**D**	**H**	**D**	**H**	**D**
ICU admission	n = 7	n = 1	n = 664	n = 102	n = 961	n = 237	n = 488	n = 144	n = 1777	n = 416	n = 454	n = 94
n (%)	2 (28.6)	1 (100)	138 (20.8)	35 (34.3)	148 (15.4)	80 (33.8)	77 (15.8)	48 (33.3)	237 (13.3)	95 (22.8)	83 (18.3)$	45 (47.9)$
Severity	n = 7		n = 552		n = 812		n = 404		n = 1535		n = 396	
Mild n (%)	1 (14.3)	-	212 (38.4)	-	330 (40.6)	-	178 (44.1)	-	664 (43.3)	-	101 (25.5)$	-
Moderate n (%)	4 (57.1)	-	136 (24.6)	-	184 (22.7)	-	55 (13.6)	-	332 (21.6)	-	168 (42.4)$	-
Severe n (%)	2 (28.6)	-	204 (37)	-	298 (36.7)	-	171 (42.3)	-	539 (35.1)	-	127 (32.1)*	-

○ Hospitalizations

● In-Hospital Deaths

* 0.001 < *p*-value < 0.05 (chi-square test for comparison between waves)

$ *p*-value < 0.001 (chi-square test for comparison between waves)

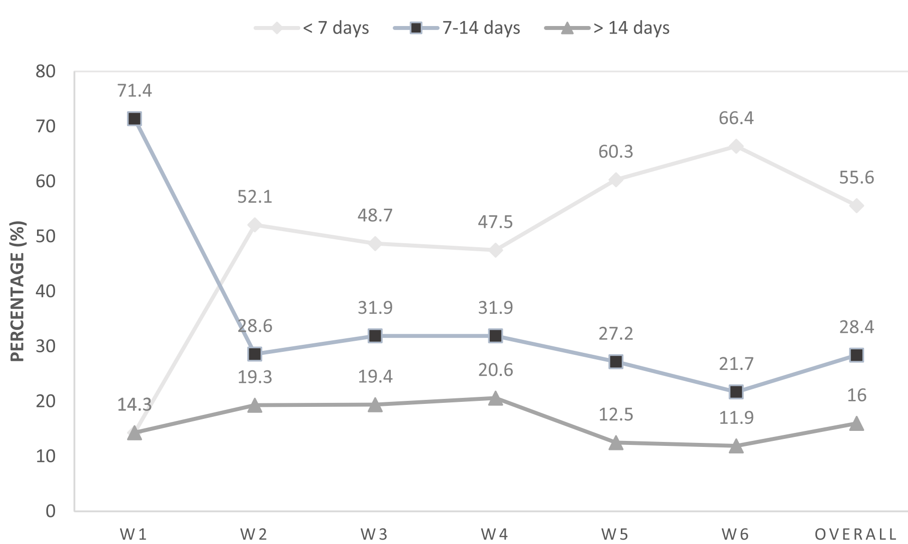

Fig. 2 Length of in-hospital stay (< 7 days, 7–14 days, > 14 days) for COVID-19 patients during successive pandemic waves in Monastir, Tunisia, March 2020-March 2022

as multisystem inflammatory syndrome has been more frequently reported in Hispanic children [41].

Additionally, in our study, we observed an increase in the number of infections and hospitalizations within this age cohort over the course of the pandemic, rising from 0% in W1 to 18.6% in W6 for infections, and from 0% in W1 to 6.6% in W6 for hospitalizations. The observed evolution among children during the pandemic aligns with findings in the literature and could be attributed to changes in prevention policies [42]. Initially, schools were closed, reducing contact among adolescents and youth and consequently decreasing the number of cases. However, with the reopening of schools, the relaxation of preventive measures and the implementation of a selective vaccination approach deliberately excluding children, the situation changed. Such strategies, adopted in various countries due to concerns over vaccine safety, resulted in limited vaccine coverage among children [42, 43].

Concerning the distribution of comorbidities, the three most prevalent comorbidities in our study among hospitalizations and deaths were hypertension (25.9% vs. 28.2%), diabetes (23.8% vs. 24.0%), and cardiovascular diseases (11.3% vs. 13.2%), observed both overall and across different waves. This aligns with findings from national and international studies [21, 28, 44–50]. Studies extensively demonstrated a robust correlation between the patient's medical condition and the severity of the infection [51].

Regarding symptoms, consistent with the literature, the majority (63.8%) of individuals experienced mild to moderate symptoms [52], a trend observed across different waves. Additionally, our findings align with previous studies, highlighting cardiorespiratory signs (69.1%) and fever (39.4%) as the most prevalent clinical signs [21, 53–56]. In an international study which included 60,109 symptomatic COVID-19 inpatients, the most frequently reported symptoms were fever, cough, and dyspnea [55].

In our study, we discussed symptoms in broad categories based on systems. During W6, we noticed a decline in the occurrence of respiratory symptoms, fever, weakness, neurological, and rheumatological symptoms. However, the signs related to ear, nose, and throat (ENT) stayed relatively unchanged. Similarly, various studies in the literature revealed a decrease in symptoms like cough, fever, shortness of breath, taste/smell loss, muscle pain, fatigue, and headache following the prevalence of the Omicron variant. However, a notable increase in the incidence of sore throat was specifically observed among the symptoms [57]. Studies showed that ageusia, anosmia and severe hypoxemia were less prevalent for Omicron than for the other variants, and cold-like symptoms were more indicative of Omicron compared to the earlier variants [58] [59].

According to our findings, the median LoS was 6 days [2–11]. The LoS in the ICU was twice the hospitalization duration at 12 days [6–18]. A systematic review of 52 studies, with 46 originating from China, revealed variations in the median LoS ranging from 4 to 53 days within China and 4 to 21 days outside of China. The decrease in the LoS over the course of the pandemic could be attributed to an enhanced understanding of the disease's pathophysiology, improved secondary care due to scientific advancements, and the exchange of information among different teams worldwide. Furthermore, the introduction of vaccination may have played a role in this improvement. Indeed, scientific literature reports that vaccinated individuals have a significantly shorter hospital stay (both with and without ICU admission) compared to those who are unvaccinated [60].

Concerning the evolution of in-hospital fatality across waves, the pandemic unfolded in six distinct waves in the region of Monastir during the study period, mirroring the overall pattern of the pandemic in Tunisia [61]. Despite fluctuations across waves, the in-hospital CFR consistently remained among the elevated figures globally [4].

The first wave had the lowest number of confirmed cases. Since January 22, 2020, Tunisia has implemented a series of stringent and proactive measures to curb the spread of the virus [62, 63]. As the virus began circulating within the country in early March 2020, authorities took swift and diverse actions to reduce COVID-19 transmission. Thanks to this wise and prompt strategy coupled with the Tunisian population's rigorous adherence to hygiene measures, the country was able to maintain an exceptionally low infection rate [61, 62]. As such, Tunisia's response to the COVID-19 pandemic during its first wave can offer valuable guidance for similar epidemic situations [63].

The second wave in our study saw a higher number of infections than the first wave (6,450 individuals), with an in-hospital CFR of 14.4%. According to the report by the National Observatory of New and Emerging Diseases (NONED), during this period, the Monastir governorate was classified as having a very high-risk level, with an incidence rate equal to or greater than 100 cases per 100,000 inhabitants, which explains the high hospitalization rate of 16.7% compared to the national Fig. (4.8%) [64].

The third wave exhibited a higher incidence of infections, hospitalizations, and in-hospital deaths, with a significant increase in the in-hospital CFR to 23.8%. This rise can be attributed to the occupancy of ICU beds and the emergence of the Alpha variant. The decrease in hospitalization rates during the third wave compared to the second in the Monastir region, coupled with the increase in the CFR, can be primarily attributed to the improvement in care provided by primary care physicians, thus contributing to the reduction of excessive hospitalizations. Additionally, subsequent adjustments to admission and discharge criteria were made to prioritize services for those who needed them the most [25].

The fourth wave exhibited a lower total number of infections compared to W2 and W3, with a recorded count of 3,835 cases. However, there was a significant increase in the hospitalization rate, in-hospital CFR, and the percentage of severe cases in comparison to previous waves. Notably, there was a significant decrease in the percentages of hospitalized individuals and deaths within the older age groups compared to the third wave. On the other hand, the number of deaths increased among young people, particularly those aged between 19 and 45. The fourth wave coincided with the onset of the first phase of the national COVID vaccination program, which was launched in March 2021, which focused on healthcare workers and the elderly due to limited vaccine availability. This prioritization of vaccines could explain the reduction in hospitalization and lethality percentages among the elderly and its increase among younger individuals, a consequence of the vaccination's selection strategy. However, simultaneously, this wave was characterized by the emergence of the Alpha variant in Tunisia, which quickly became the most dominant variant [12], replacing the original Wuhan strain.

In Tunisia, the maximum peak was reached during W5, which began in July 2021 [25]. In May 2021, the *Delta variant* was initially identified in the country, leading to an uncontrolled spread across almost all regions throughout the summer of 2021 [7, 65]. The *Delta variant* proved to be the most lethal in terms of cumulative deaths in Tunisia, leading to an increase in hospitalizations and the demand for oxygen. Consequently, in July, Tunisia experienced the highest mortality rate in the Eastern Mediterranean region and on the African continent, recording 42.3 new deaths per 100,000 inhabitants due to Covid-19 [66]. On a global scale, despite vaccination programs and extensive vaccine coverage, *Delta variant* has rapidly spread, affecting the majority of territories and causing an increase in the number of cases, hospitalizations, ICU admissions and overall mortality, especially among the younger population [4]. This wave was a consequence of the relaxation of public health measures and inadequate control of preventive measures. On an individual scale, people experienced fatigue and a desire to return to their pre-pandemic habits, contributing to the resurgence of cases.

The sixth wave was characterized by the lowest hospitalization rate at 2.8% and a reduction in the number of severe cases despite the significant number of infected cases (17.855). Many studies corroborated our findings that confirmed *Omicron* cases had a lower hospitalization rate compared to other waves [18, 67–70]. In addition, the in-hospital CFR in the present study decreased compared to W3, W4, and W5, reaching 19.4%. This improvement aligns with a lower incidence of respiratory symptoms, fewer severe cases, and shorter hospitalization durations. Studies have consistently reported the milder nature of *Omicron* symptoms, including reduced rates of dyspnea, lower severity, fewer hospital admissions, and quicker recovery when compared to earlier variants, particularly the *Delta variant* [67, 71–73].

This improvement was likely influenced by factors such as increased vaccination coverage, and the less aggressive nature of the Omicron variant.

The global transformation in the SARS-CoV-2 infection profile and the attenuation of severity during W6 likely resulted from several factors. Firstly, the highly mutated Omicron variant, despite its increased transmissibility compared to previous variants, potentially exhibited reduced pathogenicity [74, 75]. The Omicron variant tended to replicate more in the upper respiratory tract than in the lungs, which may have reduced the risk of mortality [76, 77]. Secondly, the extensive vaccination coverage resulted in a high level of acquired immunity [78], due to the campaigns that began in March 2021, initially targeting high-risk populations, followed by mass vaccination that started in July 2021 [8].

Thirdly, there was a higher level of natural immunity due to previous infections. Additionally, a better understanding of the disease's pathophysiology, lower epidemic pressure, improvement in secondary care due to scientific advancements, and the exchange of information among different teams worldwide also played a crucial role in reducing the severity level [26].

This study was the first to comprehensively investigate hospital outcomes related to COVID-19, analyzing fatality rates across the six waves of the pandemic over a period of two years. The analysis involved a comparison of data over time (epidemic curve) and among the population based on socio-demographic and clinical characteristics. Secondly, it involved an extensive dataset of high-quality information gathered prospectively and subsequently verified through medical records. Thirdly, we closely followed all patients in the cohort until death or discharge. Ultimately, the exclusion of patients incidentally infected with *SARS-CoV-2* (asymptomatic or mildly symptomatic and without diagnostic confirmation) was implemented to maximize the certainty that mortality was directly attributed to COVID-19.

Limitations

While our discussion highlighted significant strengths, it is important to acknowledge certain limitations. In our study, the absence of detailed data on the direct cause of death may have led to a slight overestimation of in-hospital fatality rates. Establishing a direct causal link between death and COVID-19 was challenging, particularly in a hospital setting, due to the high prevalence of pre-existing health conditions. Additionally, our study focused on hospital deaths, excluding cases where patients were discharged but later passed away at home. This exclusion is consistent with the definition of in-hospital mortality. Furthermore, we did not include data on the vaccination status or previous COVID-19 infections of patients—key factors that likely influenced variations in mortality rates across different phases of the pandemic. To address this, we relied on national data regarding vaccination coverage in Tunisia. While some patient data was missing, the large sample size played a critical role in minimizing the risk of systematic bias when comparing different periods.

Conclusions

This localized insight into the pandemic's impact on Monastir has provided invaluable lessons for future pandemics. By meticulously examining demographic, clinical, and mortality aspects across multiple waves, we have unveiled nuanced dynamics that extend beyond general trends observed globally. This study highlights the crucial interaction between the severity of different COVID-19 variants, patient demographics, and the evolving healthcare responses in managing the impact of COVID-19 on hospital outcomes. Our research highlights also the need for continuous adaptation and targeted interventions to mitigate the impact of infectious diseases on public health. A proactive vaccination approach, aligned with evolving variants and epidemiological trends, is essential for building resilient public health systems. These systems can effectively address future pandemics by developing strategies tailored to regional contexts, thereby strengthening preparedness and response at both local and national levels. A key lesson from the pandemic is that global public health success depends on responding effectively and equitably to disease outbreaks.

Abbreviations

CFR	Case Fatality Rate
ICU	Intensive Care Unit
LoS	Length of Stay
MA	Metanalysis
W	Wave
WHO	World Health Organization

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Authors' contributions
MBF, AG, MK and ABS: conceptualization, formal analysis, methodology and writing—original draft. AG, WD, DBH, CB, IZ and AM: data collection and verification. NBA and SD: draft revision. MBF, IB, HA and ABS: supervision and substantively revised the draft.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was reviewed and approved by the institutional ethics committee of the Faculty of Medicine of Monastir. The researchers ensure that the study was conducted in compliance with principles of the Declaration of Helsinki.

Consent for publication
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Competing interests
The authors declare no competing interests.

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