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Coronavirus Pandemic

Prevalence of comorbid asthma in Tunisian patients with COVID-19: clinical features and outcomes

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has resulted in around 1 million COVID-19 infection cases and over 29,000 deaths in Tunisia thus far. There is great variability in the prevalence of asthma among patients with COVID-19, but the impact of asthma on patients with COVID-19 is not clear. We sought to describe the clinical features of Tunisian patients with COVID-19 and to compare asthmatic and non-asthmatic patients.

Methodology: This retrospective study included 675 Tunisian patients who were hospitalized with COVID-19. Clinical characteristics were collected from medical records. Bivariate analyses and multivariate regression models were used to assess the associations between asthma and the risk of severe symptoms, including death/recovery.

Results: The prevalence of asthma in the sample was 14.5%. The results show that asthmatic patients with COVID-19 have significantly less severe symptoms and better outcomes than non-asthmatic patients.

Conclusions: Asthma was not found to be associated with higher severity or worse prognosis among patients with COVID-19 in Tunisia.

Key words: COVID-19; asthma; severity; comorbidity.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been rapidly spreading to countries and overwhelming healthcare systems throughout the world [1]. COVID-19 was first diagnosed in Wuhan [2], and the first confirmed case in Tunisia was reported in March 2020 [3]. On 8 May 2020, the total number of confirmed cases of COVID-19 was 1030 [5]. On September 2021 the COVID-19 pandemic has resulted in over one million cases and more than 29,000 deaths in Tunisia.

Coronaviruses are respiratory viruses and have been implicated in both upper respiratory tract infections and asthma exacerbations [6]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections can involve comorbidities such as cardiovascular disease, obesity, certain malignancies, and diabetes [7]. Data regarding the prevalence of the disease in asthmatic patients are lacking [8], but some potential protective mechanisms against SARS-CoV-2 in such patients have been hypothesized.

Mendes *et al.* reviewed all the studies on COVID-19 published since its emergence and showed that asthma was described as a premorbid condition in only 1.6% of all patients. This rate is far less than expected considering the global prevalence of asthma [9].

Furthermore, this could suggest that having asthma as a premorbid condition either represents no risk for COVID-19 or could be a protective factor. This study showed that the prevalence of asthma in patients with COVID-19 varies across the globe, ranging from 21% in Australia to less than 2% in China, Kazakhstan, and Vietnam [10].

However, two studies in Strasbourg and the Seattle region reported that 14% of patients had pre-existing asthma as a comorbidity [10]. These differing rates of comorbid asthma in patients with COVID-19 among studies may be due to the overall differences in prevalence of asthma in the populations considered [11]. This study agrees with the current literature in suggesting that asthma is not a risk factor for COVID-19 [12]. Thus, understanding the impact of preexisting asthma on the course and outcome of COVID-19 in Tunisia could provide new data and insights. The aim of this research is to investigate the clinical characteristics of hospitalized patients with COVID-19 and to reveal the relationship between SARS-CoV-2 infection, clinical manifestations, and asthma pathology.

Methodology

Identification of patients with COVID-19

This retrospective cohort study was conducted across four hospitals in different regions of Tunisia (Gabes, Sfax, Kairouan, and Monastir) between August 2020 and February 2021. A total of 675 patients with confirmed COVID-19 infection were included. A confirmed case of COVID-19 was defined by a positive reverse transcription polymerase chain reaction (RT-PCR) result from a specimen collected on a nasopharyngeal swab or endotracheal aspirate sample in intubated patients [13]. All demographic information and clinical characteristics (including medical history, comorbidities, and symptoms) of the patients were obtained and recorded in a database. The date of disease onset, hospital admission date, and the severity of COVID-19 were also recorded. All patients provided oral consent to use their medical records for this publication. Ethical approval for the research project was also obtained from the Ethics Committee of the CHU Habib Bourguiba Sfax (Tunisian Ministry of Health).

Data collection and identification of asthma among patients with COVID-19

Data were collected by reviewing the medical records of patients with COVID-19 admitted to the hospitals in Sfax (n = 25), Kairouan-Monastir (n = 22), and Gabes (n = 628). The clinical characteristics recorded were age, gender, presence of three major COVID-19 symptoms (cough, fever, and dyspnea), medical history, and the following outcomes: the duration in days of stay in the hospital and/or the intensive care unit (ICU) if relevant and the final outcome of the disease (deceased or not). The data collected from RT-PCR and scanner analysis were used to confirm patients with COVID-19 (N = 675). The patients were stratified based on the presence (N = 99) or absence (N = 576) of asthma as assessed by the international classification of disease ninth revision (ICD-9) and ICD-10 codes. In the case of patients with asthma, a manual chart review was performed to document prescriptions of inhaled corticosteroids (ICS) and/or systemic corticosteroids at the time of the diagnosis for COVID-19 or hospitalization.

Statistical analysis

Statistical analyses were performed with the R language. Descriptive statistics were computed for all variables. Categorical data are presented as numbers (%), and continuous data are presented as the mean ± standard deviation or as the median (interquartile range of 25-75th percentiles) as appropriate. The association between pairs of variables was tested using a Chi square and Fisher exact test (FET) tests for pairs of qualitative (binary) variables and by an independent-sample t-test between quantitative and categorical variables. Pearson correlation was also used to assess the relationships between pairs of continuous variables. Multivariate binary logistic regression was used to assess which clinical variables can explain the disease outcome (death), and adjusted odds ratios (ORs) were obtained with their 95% confidence intervals. All p values below 0.05 were considered as statistically significant.

Results

Demographics and clinical characteristics

The sample contained 675 patients who were diagnosed with COVID-19 and admitted to the hospital, including 358 men and 317 women. 99 patients were asthmatic (14.6%) and 64 were obese (9.7%) (body mass index (BMI) ≥ 30). The degree of obesity was classified into 3 groups (I, II, III) according to the adult BMI ranges: obese I: BMI 30–34.9, obese II: BMI 35–39.9, and obese III: BMI ≥ 40.

The median age was 65 years (IQR = 21) and ranged from 16 to 101 years (Table 1).

The average age was significantly different between asthmatic and non-asthmatic patients (p = 0.0007) and between obese and non-obese patients (p = 0.046), but

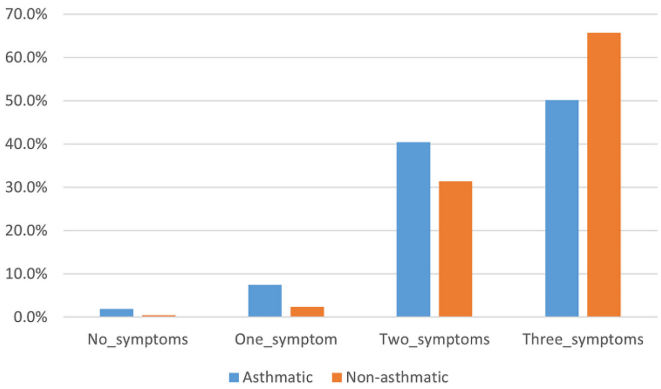
not between males and females ($p = 0.43$) according to an independent-sample t-test. About half (48.5%) of asthmatic patients were men (53.6% of men were non-asthmatic). There was no significant difference in gender frequency between asthmatic and non-asthmatic patients (Chi squared test, $p = 0.37$, FET $p = 0.33$), but there were significantly more obese patients in the asthmatic group (15.7% vs. 8.3%, $p = 0.005$, FET $p = 0.0054$). In our sample, 10 patients had no symptoms (1.5%), 559 had cough (82.7%), 489 had fever (72.3%), 610 had dyspnea (90.2%), 371 had all three symptoms together (54.9%), and 254 had two symptoms only (37.6%) (Table 1).

Most of the patients' hospital stays ranged from 1 to 28 days with an average of 6 days. 60.2% of patients stayed less than 1 week, while only 8.6% of them stayed for more than 2 weeks. Among the 641 hospitalized patients, 142 spent only 1 day in the ICU, and 13 spent between 2 and 17 days there. The total death rates were 31.2% and 23% of the patients who spent at least 1 night in the ICU. Most of those who stayed in the ICU for only 1 day died on that day (94.4%), indicating that these people were received in a status of severe respiratory distress. There were only two patients (15.4%) who died among the 13 who spent two days or more in the ICU.

Bivariate correlation of asthmatic status with clinical features and death

Table 1 shows that the symptoms were significantly more prevalent in non-asthmatic patients, except for dyspnea, which seemed to have a similar rate in the two groups of patients. However, when we compared the frequency of patients with the three symptoms together (which can be considered as very severe cases), the frequency is significantly higher in non-asthmatic patients than in asthmatics (56.8% vs. 44.4%, $p = 0.006$, FET $p = 0.028$). Based on the occurrence of these three symptoms, we defined 4 severity classes as follows: 0: no symptoms, 1: only one symptom, 2: only two symptoms, and 3: three symptoms. We found a significant association between severity and asthmatic status ($\chi^2 = 17.4$, df = 3, $p = 0.00057$, FET $p = 0.0038$), with asthmatics having less severe symptoms (Figure 1).

Figure 1. Severity of symptoms in asthmatic and non-asthmatic patients.



10 patients had no symptoms of COVID-19, 559 had cough, 489 had fever, 610 had dyspnea, 371 had all three symptoms, and 254 had only two symptoms. We defined four severity classes as follows: 0: no symptoms, 1: only one symptom, 2: only two symptoms, 3: three symptoms. We found a significant association between severity and asthmatic status ($\chi 2 = 17.4$, df = 3, p = 0.00057) with asthmatic patients having less severe symptoms.

None of the correlations between age, duration of hospitalization, and duration of ICU stay were significant in the general sample or the two asthmatic groups, except the correlation between age and duration of ICU stay in the non-asthmatic group, which was highly significant but weak ($r = 0.20$, $p = 0.0000015$). The rate of admission to the ICU was not significantly different between asthmatics and non-asthmatics ($p =$

Table 1. Demographic and clinical characteristics of Tunisian patients with COVID-19 and stratified by asthma status.

Variables	Mean ± SD or % of cases	Asthmatic	Non-asthmatic	*p* value
Age (n = 674)	64.5 ± 15.4	59.2 ± 16.3	65.4 ± 15.0	**0.0007*** **
Asthma (n = 674)	9.7%			
Obesity (n = 662)	14.9%	15.7%	8.3%	**0.005*** **
Gender (n = 675)	53% (male)	48.5%	53.9%	0.37
Cough	82.7%	84.3%	72.7%	**0.007*** **
Fever	72.4%	74.3%	61.6%	**0.013***
Dyspnea	90.2%	92.0%	89.9%	0.85
ICU (Yes/No) (n = 675)	23%	25.2%	22.7%	0.65
Duration in the intensive care unit (ICU)	0.35 ± 1.2	0.22 ± 0.42	1.1 ± 2.85	**0.027***
Hospitalization (Yes/No)	95.0%	89.9%	95.8%	**0.025***
Duration in hospital	6.3 ± 4.9	6.2 ± 5.3	7.1 ± 4.9	0.09
Death (n = 675)	31.1%	22.2%	32.7%	**0.049***

ICU: intensive care unit. Data are expressed as numbers (n) and percentages (%), and values in bold indicate statistical significance. **p* value indicated is for the comparison between asthma and non-asthma groups using Chi-squared test. Mortality data in this cohort were determined up to August 2020.

0.65, FET $p = 0.60$), but the duration was longer for asthmatic patients ($p = 0.027$). The hospitalization rate was higher among non-asthmatic patients, while there was no difference between the two groups in the average duration of hospitalization (Table 1). The death rates were slightly but significantly higher among non-asthmatic patients than asthmatic patients (32.7% vs. 22.2%, $p = 0.049$, FET $p = 0.045$), suggesting that asthmatics are at lower risk of death from COVID-19, although it might depend on the severity of the disease at admission, as will be seen in multivariate analyses.

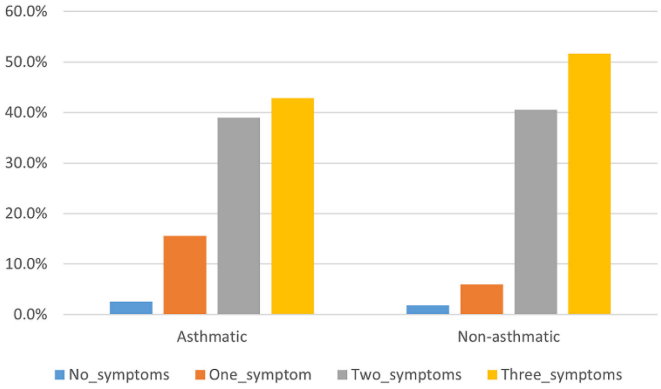
Multivariate analyses

In order to identify the most predictive factor of the final outcome of COVID-19 (death), we used binary logistic regression with death as a dependent variable and all other variables as explanatory variables, including asthmatic status. Table 2 shows that only four variables were significantly associated with death: age ($p = 0.00007$), fever ($p = 0.031$), the ICU admission (yes/no) ($p = 2.10\text{-}16$), and duration of hospitalization ($p = 0.035$). The odds ratio (OR) adjusted for gender and asthmatic status in Table 2 show that admission to the ICU was the most predictive variable with an OR of 2.11 (95% CI: 1.99-2.25). This means that those who are admitted to the ICU are twice as likely to die than those who are not. Also, age was the second most significant risk factor with an increased risk of 0.5% for each year of age.

The severity scale defined earlier was highly associated with death ($p = 0.009$; OR = 1.05; 95% CI: 1.01-1.09), showing that patients who had more severe symptoms were more likely to die. This was true in the general population and for both asthmatic and non-asthmatic patients, as can be seen in Figure 2. It is worth noting that there was no significant difference in death between asthmatic and non-asthmatic groups when adjusting for confounding factors such as age, gender, and clinical features. Even if we consider the subsample with the highest severity class (n = 371; 44 asthmatics and 327 non-asthmatic), there is still no significant difference in death rate between asthmatic and non-asthmatic patients in the multivariate logistic regression analysis ($p = 0.94$).

In order to see which variables are associated with asthmatic status in a multivariate setting, we considered it as a dependent variable in a logistic regression. The significantly associated variables were age ($p = 0.004$), obesity ($p = 0.007$), and the severity of symptoms ($p = 0.006$). The negative regression coefficient of severity shows that asthmatic patients have lower severity on average than non-asthmatic patients, as already reported in the bivariate analyses (Figure 1).

Figure 2. Death rate in asthmatic and non-asthmatic patients according to severity of symptoms.



The death rates were slightly but significantly higher in non-asthmatic patients compared to asthmatic patients (32.7% vs. 22.2%, p = 0.049), suggesting that asthmatic patients are at lower risk of death from COVID-19. When we considered the severity scale as defined in the text and Figure 1, we found that it is highly associated with death (p = 0.009; odds ratio (OR) = 1.05; 95% CI 1.01-1.09), showing that patients who had more severe symptoms were more likely to die.

Table 2. Identification of the most predictive factor of the final outcome of COVID-19 using multivariate analyses.

Variables	Beta	*p* value	OR [95% CI]
Gender	-0.042	0.094	**0.958 [0.912, 1.007]**
Age	**0.005**	**3.10^{-9}**	**1.005 [1.003, 1.006]**
Obesity	**-0.024**	**0.577**	**0.976 [0.897, 1.062]**
Cough	0.026	0.423	**1.027 [0.961, 1.097]**
Dyspnea	0.044	0.306	**1.045 [0.959, 1.140]**
Fever	**0.060**	**0.0311**	**1.062 [1.005, 1.122]**
ICU admission	**0.748**	**2.10^{-16}**	**2.114 [1.989, 2.247]**
Duration of hospitalization	**0.005**	**0.034**	**1.005 [1.000, 1.010]**
Asthmatic status	0.006	0.854	**1.006 [0.934,1.084]**

ICU: intensive care unit. Data are expressed as adjusted odds ratio (OR), percentages (%), and confidence interval (CI). Values in bold indicate statistical significance. Statistics were analyzed using Chi-squared test.

Discussion

To our knowledge, this is the first comprehensive and large cohort study on Tunisian patients with COVID-19 and comorbid asthma. In our study, 675 patients were diagnosed with COVID-19, and 99 of them were asthmatic (14.6%). The prevalence of asthma in the sample is similar to that reported in the UK (14-17.9%) [14]. This contrasts with the lower prevalence of asthma reported in China and Italy (about 6.6%) [15,16]. In addition, other cohorts have reported a higher prevalence of patients with asthma in Germany (25%) [17]. This variability in asthma prevalence among patients with COVID-19 in different countries might be explained by differences in the frequency of asthma in the general population or methods of ascertainment.

In our cohort, most patients were middle-aged or older, and the male-to-female ratio was almost 1:1 (358 men and 317 women). This is lower than what has been observed in patients with SARS coronavirus infections, which had a predominance of females (61.0%) [18], but it is similar to the rate reported by Wang *et al.* (54.3%) [19]. In our cohort, about half (48.5%) of asthmatic patients were men (53.6% of whom were non-asthmatic), and there was no significant difference in gender frequency between asthmatic and non-asthmatic patients (Chi-squared test, $p = 0.37$). The median age of all Tunisian patients was 65 years (IQR = 21) (Table 1), which is close to the data reported by Wang *et al.* (56.0 years) [19] and Chen *et al*. (55.5 years) [20], but older than the sample studied by Huang *et al.* (49.0 years) [21].

In general, older people (> 50 years) are more susceptible to COVID-19 and more likely to experience more severe symptoms than younger patients (< 50 years). Using an independent-sample t-test, we found that the average age in our cohort was significantly different between asthmatic and non-asthmatic patients and between obese and non-obese patients, but not between males and females. Among 99 asthmatic patients, 64 were obese (9.7%). Asthmatic patients were more often obese than non-asthmatic patients in our cohort. Worldwide, a high prevalence of obesity was previously reported in COVID-19 cohorts and non-COVID-19 asthma cohorts, and obesity may lead to severe exacerbations [22].

Concerning symptoms of COVID-19 in our sample, 10 patients had no symptoms (1.5%), 559 had cough (82.7%), 489 had fever (72.3%), and 610 had dyspnea (90.2%) (Table 1). Furthermore, 371 had all three of these symptoms together (54.9%), while 254 had two symptoms only (37.6%). We did not find other chronic comorbidities like hypertension, diabetes mellitus, and cardiovascular diseases, which are the most common underlying diseases [21,22].

Table 1 shows that symptoms were significantly more prevalent in non-asthmatic patients except for dyspnea, which seemed to be similar in the two groups of patients. The frequency of patients with all three symptoms together was significantly higher among non-asthmatic patients. Using bivariate correlation, we found a significant association between severity and asthmatic status, with asthmatic patients tending to have less severe symptoms. In addition, we observed that the death rates were slightly but significantly higher in non-asthmatic patients compared to asthmatic patients (32.7% vs. 22.2%), suggesting that asthmatic patients are at a lower risk of death by COVID-19.

Mortality data were reported by four studies [23-25]. A meta-analysis of data from 744 asthmatic patients and 8,151 non-asthmatic patients indicated that the presence of asthma had no significant effect on mortality (OR = 0.96; 95% CI 0.70-1.30; $I^2 = 0\%$; $p = 0.79$) [26]. Also, the rate of admission to the ICU was not significantly different between asthmatic patients and non-asthmatic patients, but the duration was longer for asthmatic patients. The hospitalization rate was higher in non-asthmatic patients, while there was no difference between the two groups in average duration of hospitalization.

Our results are consistent with the study by Choi *et al*., who showed that the duration and prevalence of admission were not significantly different between the two groups [27]. However, in contrast to our findings, they reported higher mortality rates in patients with COVID-19 who had underlying asthma (7.8%) compared to non-asthmatic patients (2.8%; $p < 0.001$), but the severity of asthma showed no significant association with mortality in both univariate and multivariate analyses [28].

Four variables were significantly associated with death in our study: age, fever, the ICU admission (yes/no), and duration of hospitalization. The ORs adjusted for gender and asthmatic status showed that admission to the ICU was the most predictive variable with an OR of 2.11, meaning that those who were admitted to the ICU were twice as likely to die than those who were not. Also, age was the second most significant risk factor with an increased risk of 0.5% for each year of age. This is consistent with all previous studies, which clearly showed that older people with COVID-19 are at higher risk of death [26].

Using multivariate and bivariate analyses, we found that the variables that significantly associated with

asthmatic status were age, obesity, and the severity of symptoms, with asthmatic patients having lower severity on average than non-asthmatic patients. Interestingly, patients with asthma and COVID-19 had an increased prevalence of multiple comorbidities compared to patients without asthma. In Tunisia, asthma does not seem to be a risk factor for patients with COVID-19.

It is now well recognized that older age, obesity, cardiovascular disease, and diabetes are risk factors of poor COVID-19 outcomes [2]. What is not yet clear is whether chronic respiratory diseases like asthma are among the risk factors as well. Li *et al.* evaluated 584 patients admitted to a hospital in Wuhan, China, and found that reports of pre-existing asthma were markedly lower (0.9%, n = 5) than in the general population (6.4%). Furthermore, Zhang *et al.* found a very low prevalence of 0.3% (n = 1) in their cohort of 290 COVID-positive patients [29].

Other studies worldwide have demonstrated an increased prevalence of asthma in COVID-19-positive individuals. These studies suggest that the lower prevalence of asthma reported in some studies could be attributed to underreporting, underdiagnosis, or poor recognition of chronic respiratory disease in patients with COVID-19 infection [30]. Zhu *et al.* found that once it was subcategorized, allergic asthma status was not significantly associated with severe COVID-19 symptoms [31].

Currently, there are conflicting hypotheses. Theoretically, asthmatic patients are thought to have increased susceptibility and severity to COVID-19 due to decreased anti-viral immune response and increased risk of viral induced exacerbation [32]. However, interestingly, it was hypothesized that type II inflammatory cytokines (IL-4, IL-5, and IL-13), accumulation of eosinophils, overproduction of mucus, and asthma treatment among asthma patients may be protective against COVID-19 [32]. SARS CoV-2 uses angiotensin converting enzyme 2 (ACE2) as its cellular receptor, similar to SARS and other seasonal coronaviruses [33]. Therefore, increased expression of ACE2 is suspected to increase susceptibility to COVID-19.

The respiratory epithelial cells in patients with asthma have decreased gene expression for ACE2 receptors, so they may be protective against COVID-19 infection [34]. Additionally, eosinophils could play a protective role against developing more severe clinical outcomes [34,35]. In addition, asthma-induced mucus plugging in the lower respiratory tract limits airflow, which could worsen the hypoxemia from diffuse alveolar damage caused by COVID-19 infection [35].

Conclusions

Our study is the first to address the influence of asthma on outcomes of patients with COVID-19 in Tunisia. Our data indicate that asthma is not associated with higher severity or worse prognosis of COVID-19 and that patients with asthma have a lower risk of death compared with patients without asthma. This suggests that asthma might be considered as a protective condition against SARS-COV-2 infection. The fact that asthmatic patients are under treatment for asthma might result in improved respiratory function that gives them better resistance to the respiratory distress cause by the SARS-CoV-2 virus. Such data were not available in our sample, and the possible interaction between medication and better outcomes of the disease needs further investigation.

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Authors' contributions

Imen Ben Rebeh, Marwa Ghariani, Riadh Ben Marzoug and Ahmed Rebai collected, analyzed the data and prepared the manuscript; Marwa Gargouri, Hela Gargouri, Nesrine Kallel, Sana Rouis, Wafa Marrakchi, Dhekra Chebil, Latifa Merzougui, Houda Ghorbel and Chakroun Mohamed contributed to the collection and curation of patient clinical information. Hassen Hadj Kacem, checked the data and edited the manuscript.

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