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Frequency and Predictors of COVID-19 Worsening Among Patients Initially Managed on An Outpatient Basis: An Observational Study in Sfax Governorate; Tunisia

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Introduction

The COVID-19 pandemic is a crisis of mismatch between resources and infection burden. It has caused high utilization of healthcare resources including hospitalization [1]. In Tunisia, Since the discovery of the index case of COVID-19 in Marsh 2020, the spread of the virus has expanded exponentially due to community-based human-to-human transmission. The impact of the pandemic has put the spotlight on serious problems that the Tunisian healthcare system suffers from including strained health institution. COVID-19 symptoms are variable ranging from no symptom to severe symptoms and need hospitalization [2]. Factors other than severity of symptoms could increase the risk of hospitalization and mortality. Indeed, elderly people and those with underlying health conditions are at higher risk of COVID-19 hospitalization, and even death [3,4]. Nevertheless, other studies show controversial results [5,6]. Some of the worsening of the disease occurs early, but the vast majority of respiratory distress tables are observed late [7]. Thus, patients who initially had been managed on an outpatient basis may require late hospitalization or may even die. However, studies about COVID-19 ambulatory patients are under-described in the literature and the majority of studies on COVID 19 related hospitalization and death have been based on hospital samples. Knowledge of factors associated with the COVID-19 hospitalization and death is critical in implementing preventive measures and minimizing direct medical and indirect costs of COVID-19. In this regard, this study aimed to determine the factors associated with the worsening of COVID-19 among patients who at first had been managed on an outpatient basis.

Methods

Study Desing and Setting

We conducted an observational study in the month of junaury 2021 using telephone interview method in Sfax governorate. The governorate of Sfax, the second largest city in Tunisia by its economic importance, is located in the southern coastal of Tunisia. It had a population of 983,300 according to the last Tunisian census of 2016.

The Target Population

The Inclusion Criteria

The study participants were the exhaustive list of patients tested positive for SARS-COV 2 in Sfax in month of october 2020 and who at first had been managed on an outpatient basis. These patients were recorded in the regional COVID-19 registry collected by the Regional Health Directorate. We called all these patients, or their relatives in case of death.

The Non-Inclusion Criteria

We did not include patients who were supposed to be hospitalized when the diagnosis of COVID-19 was made but they refused to do so; those who refused to participate in the study; and those who missed our call.

The Exclusion Criteria

Minors (those who have not achieved the age of 18 were excluded from the study).

Collection Techniques and Tools

Three clinical researchers called patients and filled the telephonic survey. Patient demographics and baseline clinical characteristics were recorded, including age, sex, profession, tobacco use , Body mass index (BMI), regular physical activities, personal history, the notion of bed rest during the COVID-19 infection, COVID-19 clinical presentation, computerized tomography (CT) scan finding , the anticoagulation drug therapy received by the patients , the Antiplatelet use and the evolution: The event defining the aggravation was: hospitalization or death

Case Definition

--We classified the clinical presentation according to the NIH

guidelines: Asymptomatic or Pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virologic test but who have no symptoms that are consistent with COVID-19 [8]. Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging. Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥94% on room air at sea level. Severe Illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency>30 breaths/min, or lung infiltrates >50%. -BMI was classified according to the proposed criteria of World Health Organization (WHO), underweight < 18.5, normal = 18.5-24.5, overweight = 25.0-29.9, and obese ≥30.00. -We defined regular physical activities by walk, jogging for at least 30 min, 3 days a week [9,10]. -Regarding profession the term blue collar was frequently used to describe working-class jobs that require manual labour. These jobs are often both physically and psychologically demanding and have been linked with various adverse health outcome, while the term white-collar workers was frequently used to describe working-class jobs with a superior educational level and high compensation level [11,12].

Ethical and Administrative Considerations

In order to protect all participants, ethical measures have been taken. Individual informed consent was taken from each respondent. We explained to them the objective of this survey and also the interest of their participation. A prior approval of the protocol of the study was obtained from the Regional Ethics Committee, CPP SUD (reference: 0293/2021).

The Results Analysis Plan

Statistical analysis was performed using IBM SPSS.25 Software. Categorical variables were expressed as numbers and percentages. The Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and non-Gaussian continuous variables were expressed as medians and interquartile ranges (Q1-Q3). The predictive threshold of hospitalisation and mortality was determined using the ROC Curve. The study of the associations between variables was done by hypothesis tests. The association between two qualitative variables was made by the Pearson "Chi2" test when the conditions were verified otherwise the exact Fisher test was a remedy. The study of factors associated with hospitalization and death was done by calculating the crude Odds Ratio (OR) in univariate analysis and adjusted Odds Ratio (AOR) after a multivariate analysis by binary logistic regression. An error risk of 20% was used to include indicator variables in the multivariate analysis. For all tests performed, the significance threshold was set at 5%. The variables in the final model were manually selected using a step-by-step top-down procedure. Indeed, at each step of the main factor removal process, the variable with the largest "small p" is rejected from the model, if this "small p" is greater than 5%. The model quality was verified by the Hosmer–Lemeshow goodness-of-fit.

Results

Among 2165 patients who tested positive during the study period and who responded to our call, 76 patients needed serious clinical attention and were hospitalized immediately. Thus, Our study was carried out on 2089 subjects. The median age of participants was 40 years (Q1-Q3=7-55 years) . One thousand two hundred thirty four (59.1%) were female. The sex ratio (M / F) was equal to 0.69. Overall , 672 participant (32.2%) were unemployed or retired and 562 (26.9%) were White-Collar workers. Overall , 405 participants were obese (16.4%). Among participants, 1097 (52.5%) didn't have regular physical activities in the last 6 months. Two hundred fifty participants (12%) were smokers. History of cardiovascular diseases was noted in 379 cases (18.1%). The most frequent cardiovascular diseases was hypertension (262 cases ;12.5%). History of respiratory illness was noted in 118 cases (5.6%) . The most common endocrine disorders was diabetes (194 cases ;9.3%) . Among the study population, 29 participants (1.4 %) had the history of thromboembolic disease ; 6 participants (0.3%) had stroke history and 15 participants (0.7%) had renal failure history . Overall , 21 participants (1%) had a personal history of cancer , among them 8 (0.4%) had an active cancer. The notion of bed rest during the COVID-19 infection was noted in 254 cases (12.2%). The clinical presentation of COVID-19 was moderate in 254 patients (12.2%), mild in 1623 patients (77.7%), and asymptomatic in 212 patients (10.1%). CT scan was performed in 267 patients (12.7%) and showed COVID-19 signs in 178 patients (8.5%). Among the study population, 499 participants (23.9%) received anticoagulation drug therapy and 103 participants (4.9%) received Platelet Aggregation Inhibitor. Regarding the evolution : 145 patients (6.9%) required hospitalization and 19 participants (0.9%) have died. (Table 1). The most frequent cause of death was the respiratory distress syndrome (68.4%). The study of the area under the curve (AUC) ROC studying the association between age and hospitalisation showed that the AUC was significantly different of 0.5 (0.76, IC95% [0.7- 0.8], p<0.001). The determination of the predictive threshold of hospitalisation revealed a threshold of 60 years (Figure 1). In univariate analysis (Table 2) , general factors associated with hospitalization were tobacco use (OR=0.4 [0.2-0.8] ; p=0.013) , obesity (OR=1.6 [1.1-2.4] ; p=0.01) , age (OR=6.1 [4.3-8.7] ; p<10-3), male gender (OR=2 [1.4-2.8] ; p<10-3) and regular physical activities (OR=0.6 [0.4-0.8] ; p=0.004). Medical antecedents associated with hospitalization were cardiovascular disease (OR=1.9 [1.3-2.8] ; p<0.001), history of thromboembolic disease (OR=2.8 [1.07-7.8] ; p<0.001), bed rest (OR=13.3 [8.1-23] ; p<0.001) , hypertension (OR=2.3 [1.5-3.4]; p<0.001) , ischemic cardiac diseases (OR=3.4 [1.4-8] ; p=0.002) , heart Failure (OR=2 [1.2-3.4] ; 0.003), dyslipidemia (OR=2.4 [1.3-4] ; p<0.001) and renal failure (OR=4.9 [1.5-15] ; p=0.017). Clinical presentation of COVID-19 at the time of diagnosis (OR= 3.9 [2.5-5.9]; p<0.001) and Ct scan signs (OR=3.1 [1.7-4] ; p<0.001) were also associated with hospitalization. Regarding mortality , the study of the area under the curve (AUC) ROC studying the association between age and death showed that the AUC was significantly different of 0.5 (0.91, IC95% [0.85- 0.97], p<0.001). The determination of the predictive threshold of death revealed a threshold of 60 years (Figure 2). In univariate analysis, general factors associated with death were age (OR=27.9 [8-69]; p<0.001), male gender (OR=5.4 [1.8-16]; p<0.001) and regular physical activities (OR=0.1 [0.03-0.5]; p<0.001. Medical antecedents associated with death were cardiovascular disease (OR=2.1 [1.7-5.5]; p=0.037), history of thromboembolic disease (OR=8.9 [1.9-40]; p<0.001) and bed rest (OR=10 [4-25]; p<0.001) . Clinical presentation of COVID-19 at the time of diagnosis (OR= 10 [4-25] ;p<0.001) and Ct scan signs (OR=8.1 [3.2-20.4]; p<0.001) were also associated with death. In multivariate analysis , Independent factors associated with hospitalization were age (>60 years) (AOR=2.4 [1.5-3,8]; p<0.001), male gender (AOR=2.1 [1.3-3.2]; p=0.002), physical activities (AOR=0.6 [0.3-0.9] ;p=0.041) , bed rest (AOR= 18.2 [11.4-29] ;p<0.001) and CT signs of COVID-19 (AOR=5.9 [3.6-9.5]; P<0.001). Independent factors associated with death were age

(>60 years) (AOR=12.3 [3.4-44.6]; p<0.001), male gender (AOR=4.8 [1.5-15.1]; p=0.007), physical activities (AOR=0.1 [0.036-0.7]; p=0.018) and bed rest (AOR= 4.6 [1.7-12.3] ;p=0.002) (Table 3) .

Table 1: General and clinical characteristics of the study population

	Number	Percentage (%)
Age (median (Q1-Q3))	40 years (Q1-Q3=7-55 years)	
Gender		
Male	855	40.9
Female	1243	59.1
Professional category		
unemployed or retired	672	32.1
White collar/Students	706	33.8
Bleu collar/ Healthcareworkers	711	34.1
Obeses	405	
Tobacco use	250	12
Regular physical activities		
Cardivascular diseases	379	18.1
Hypertension	262	12.5
Ischemic Cardiac diseases	35	1.7
Heart Failure	167	8
Respiratory illness	118	5.6
Diabetes	194	9.3
Dyslepidemia	110	5.3
Other endocrine disorders	70	3.4
Thromboembolic disease	29	1.4
Stroke History	6	0.3
Renal failure history	15	0.7
Cancer History	21	1
Actif cancer	8	0.4
Cancer in remission	13	0.6
Bed rest during the COVID-19 infection	254	12.2
Clinical presentation of COVID-19 at the time of diagnosis		
Asymptomatic	212	10.1
Mild	1623	77.7
Moderate	254	12.2
CT scan		
Non performed	1822	87.2
Normal	89	4.3
Covid-19 signs	178	8.5
Anticoagulation therapy	499	23.9
Antiplatelet use	103	4.9
Evolution		
Hospitalization	145	6.9
Death	19	0.9
Causes of death (n=19)		
respiratory distress syndrome	13	68.4
Thromboembolic event	4	21
Other causes	2	10.6

CT : computerized tomography

Table 2: Univariate analysis: Factors associated with COVID-19 hospitalization and death

Factors	Hospitalization (n=145)			Death (n=19)		
	N (%)	OR [95% CI]	p	N (%)	OR [95% CI]	p
Age						
> 60 years (N=348)	73 (21)	6.1 [4.3-8.7]	$<10^{-3}$	16 (4.6)	27.9 [8-69]	$<10^{-3}$
≤ 60 years (N=1741)	72 (4.1)	1		3 (0.2)	1	
Gender						
Male (N=850)	83 (9.7%)	2 [1.4-2.8]	$<10^{-3}$	15 (1.8%)	5.4 [1.8-16]	$<10^{-3}$
Female (N=1234)	62 (5%)	1		4 (0.3%)	1	
Professional category						
Unemployed or retired (N=672)	59 (8.8%)	-	0.32	7 (1%)	-	0.65
White-Collar workers/ students (N=706)	34 (4.8%)			5 (0.4%)		
Bleu-Collar workers/ Healtcareworkrs (N=711)	52 (7.3%)			3 (0.9%)		
Tobacco use						
Yes (N=250)	8 (3.2%)	0.4 [0.2-0.8]	0.013	3 (1.2%)	1.3 [0.4-4.7]	0.606
No (N=1834)	137 (7.4%)	1		16 (0.9%)	1	
Obesity						
Yes (N=405)	40 (9.9%)	1.6 [1.1-2.4]	0.01	3 (0.7%)	0.7 [0.2-2.6]	0.9*
No (N=1679)	105 (6.2%)	1		16 (1%)	1	
Regular physical activities						
Yes (N=987)	52 (5.2%)	0.6 [0.4-0.8]	0.004	2 (0.2%)	0.1 [0.03-0.5]	<10-3
No (N=1097)	93 (8.5%)	1		17 (1.5%)	1	
Cardiovascular diseases						
Yes (N=379)	42 (11.1%)	1.9 [1.3-2.8]	$<10^{-3}$	6 (2.1%)	2.1 [1.7-5.5]	0.037
No (N=1705)	103 (6%)	1		13 (0.7%)	1	
Hypertension						
Yes (N=262)	34 (13%)	2.3 [1.5-3.4]	$<10^{-3}$	4 (1.5%)	1.8 [0.6-5.6]	0.26
No (N=1822)	111 (6.1%)	1		15 (0.8%)	1	
Ischemic Cardiac diseases						
Yes (N=35)	7 (20%)	3.4 [1.4-8]	0.002	1 (2.9%)	3.3 [0.4-25]	0.22
No (N=2049)	138 (6.7%)	1		18 (0.9)	1	
Heart Failure						
Yes (N=167)	21 (12.6%)	2 [1.2-3.4]	0.003	2 (1.2%)	1.3 [4.3-8.7]	0.683
No (N=1917)	124 (6.5%)	1		17 (0.9%)	1	
History of respiratory illness						
Yes (N=118)	12 (10.2%)	1.4 [0.7-2.6]	0.155	2 (1.7%)	0.9 [0.8-1.01]	0.29*
No (N=1966)	133 (6.7%)	1		17 (0.9%)	1	
Diabetes						
Yes (N=194)	37 (19.1%)	3.8 [2.5-5.8]	$<10^{-3}$	4 (2.1%)	2.6 [0.6-8]	0.076
No (N=1890)	108 (5.7%)	1		15 (0.8%)	1	
Dyslepidemia						
Yes (N=110)	16 (14.5%)	2.4 [1.3-4]	$<10^{-3}$	2 (1.8%)	2.1 [0.8-8]	0.264
No (N=1974)	129 (6.5%)	1	-	17 (0.8%)	1	

Other endocrine disorders						
Yes (N=70)	9 (12.9%)	1.7 [0.8-3.7]	0.055	2 (2.9%)	0.8 [0.9-1.01]	0.131*
No (N=2014)	136 (6.7%)	1		17 (0.8%)	1	
History of thromboembolic disease						
Yes (N=29)	5 (17.2%)	2.8 [1.07-7.8]	0.046	2 (6.9%)	8.9 [1.9-40]	<10-3
No (N=2055)	140 (6.8%)	1		17 (0.8%)	1	
Renal failure						
Yes (N=15)	4 (26.7%)	4.9 [1.5-15]	0.017	1 (6.7%)	8.1 [0.9-65]	0.126*
No (N=2069)	141 (6.8%)	1		18 (0.9%)	1	
Bed rest during the COVID-19 infection						
Yes (N=254)	110 (43.3%)	13.3 [8.1-23]	$<10^{-3}$	11 (4.3%)	10 [4-25]	<10-3
No (N=1830)	35 (1.9%)	1		8 (0.4%)	1	
Active cancer/in remission cancer						
Yes (N=29)	1 (4.8%)	0.6 [0.8-5]	0.9*	1 (4.8%)	0.99 [0.98-1.1]	0.17*
No (N=2055)	144 (7%)	1		18 (0.9%)	1	
Clinical presentation of COVID-19 at the time of diagnosis						
Mild/Moderate	143 (45.3%)	3.9 [2.5-5.9]	$<10^{-3}$	16 (4.6%)	10 [4-25]	10-3
Asymptomatic	2 (0.9%)	1		3 (1.4%)	1	
CT scan- finding						
Covid19 signs	80 (44.9%)	3.1 [1.7-4]	$<10^{-3}$	8 (4.5%)	8.1 [3.2-20.4]	<10-3
Normal/non performed	65 (3.4%)	1		11 (0.6%)	1	
anticoagulation therapy						
Yes	115 (23%)	1.2 [1.1-1.3]	$<10^{-3}$	10 (2%)	3.5 [1.4-8.8]	0.006
No	30 (1.9%)	1		9 (0.6)	1	
Antiplatelet use						
Yes	**12 (11.7%)**	**1.8 [0.9-3.4]**	**0.054**	3 (2.9%)	3.6 [1.1-12]	0.028
No	133 (6.7%)	1		16 (0.8%)	1	

*Fisher; OR: odds ratio; IC: confidence interval; CT: computerized tomography

Table 3: Multivariate analysis: Independent predictors factors of COVID-19 hospitalization and death

	Hospitalization		Death	
Characteristics	AOR [95% CI]	P	AOR [95% CI]	P
Age >60 years	2.4 [1.5-4.8]	$<10^{-3}$	12.3 [3.4-44.6]	<10-3
Male gender	2.1 [1.2-3.2]	0.002	4.8 [1.5-15.1]	0.007
Bed rest during the COVID-19 infection	18.2 [11.4-29]	$<10^{-3}$	4.6 [1.7-12.3]	0.002
Physical activities	0.6 [0.3-0.9]	0.041	0.1 [0.036-0.7]	0.018
Ct signs of covid 19	5.9 [3.6-9.5]	$<10^{-3}$	-	-

AOR= adjusted odds ratio; CI: Confidence Interval; CT: computerized tomography

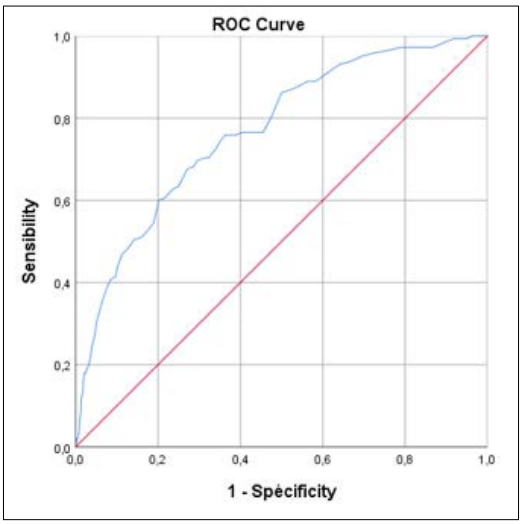

Figure 1: The Roc-Curve Studying the Association Between Age and Hospitalisation

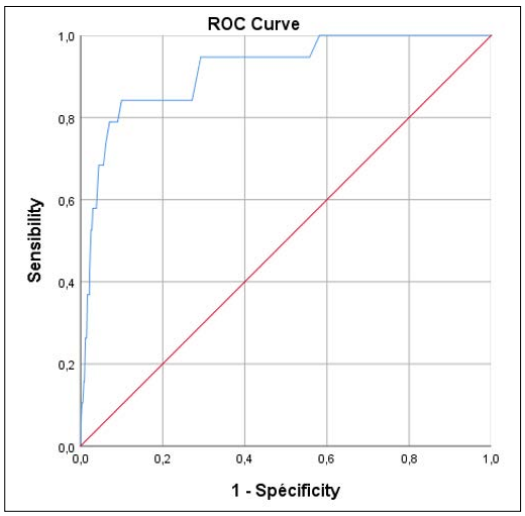

Figure 2: The ROC-curve studying the association between age and mortality

Discussion

To the best of our knowledge, this original study is the first survey illustrating the evolution of COVID-19- outpatient in our region. Starting from an exhaustive sample, this study gave an insight into the predisposing factors of COVID-19 hospitalization and death that have been reported in many published studies. The median age of participants was 40 years (Q1-Q3=30-55 years). It is a relatively young population compared to the age reported by several literature studies, may be because we did not include patients who were supposed to be hospitalized when the diagnosis of COVID-19 was made [13-15]. For gender, we noted female predominance (59.1%). Perhaps because women are being tested more than men, which can be explained by a higher level of concern about the pandemic. This is consistent with another study conducted in Germany but in disagreement with a nationwide Tunisian analysis which has shown no predominance of men or of women [16,17]. The most prevalent comorbidity was hypertension (12.5%), followed by diabetes (9.3%) as already found in Nationwide Analysis in China [15].

The clinical presentation of COVID-19 was mild in 77.7% which was supported by a Chinese report publishing [18]. Only 6.9% and 0.9% of participants were secondarily hospitalized and dead respectively. These results were lower than global hospitalization and mortality rates [17,19-22]. This difference could be explained by the non-inclusion of patients who were hospitalized when the diagnosis of COVID-19 was made. Moreover, studies about COVID-19 ambulatory patients are under-described in the literature, and that is why we conducted this observational study. We found acute respiratory failure and thromboembolic events were the most common causes of death. This result was in agreement with a meta-analysis which found that the main complications associated with SARS-CoV-2 infection and death are acute respiratory distress syndrome (ARDS), disseminate intravascular coagulation and sepsis but in disagreement with intensive care unit-based study in which COVID-19-related multiple organ dysfunction syndrome (MODS) and sepsis were the leading cause of death [23-25].

Factors Associated with the Worsening of COVID-19

Preliminary reports have shown that older people were at a higher risk of COVID-19 complications with higher rates of hospitalization and death [18,26-28]. This result was also well established by our study. Several hypotheses have been proposed as to why more older people may well be more vulnerable to serious COVID-19 infection, including a weaker immune response, age-related decline in respiratory function and frailty [26,29,30]. Nevertheless some studies revealed that COVID-19 does not spare young people [5]. In addition male gender was an independent predictor factor of hospitalization and death. Our result is in concordance with many other studies showing that male sex is a strong predictor for higher risk of hospitalization and death [28,31,32]. This difference is possibly mediated by several factors including sex hormones and high expression of coronavirus receptors (ACE 2) in men [32]. However, the fatality cases are higher in women than men in few countries like India and Slovenia [6]. We found that bed rest during the COVID-19 infection was independently associated with hospitalization and death. In fact, prolonged immobility on COVID-19 patients has several consequences on the neuromuscular system, on cognition and also on the cardiovascular system [33]. We found also that the practice of regular physical activities was a protective factor of COVID-19 hospitalization and death. This result was in concordance with another study which found that patients with COVID-19 who were consistently inactive had a greater risk of hospitalization and death than patients who were consistently meeting physical activity or who were doing some physical activity [34]. Obesity was not independently associated with hospitalization and death. Our finding was in contrast with a metanalysis which found that patients with obesity are at high risk of mortality from COVID-19 infection [35]. However, similar to our results, a previous study reported that obesity was not associated with an increased risk of mortality among patients presenting with mild disease [36]. Moreover, according to another metanalysis, obesity in COVID-19 patients was associated with poor outcomes which comprised severe COVID-19, intensive care unit and invasive mechanical ventilation use but not the risk of mortality [37]. Moreover, cardiovascular diseases were not independently associated with hospitalization and death which was in line with another study among patients presenting with mild disease which found that comorbidities were not independently associated with COVID-19 severity [36]. CT scan COVID 19 signs was a predictor factor of hospitalization. This result was in agreement with another study suggesting that chest CT scan features may serve as potential risk factors helping clinicians to identify patients with poor prognosis [38]. Despite being a respiratory illness, COVID-19 is proved to be associated with a high risk of venous and arterial thromboembolic events. According to the literature, the anticoagulation drug therapy reduces the probability of severe forms which was in

contrast with our study [39]. Plausibly, it could be explained by the fact that interviewed patients did not distinguish whether they took this treatment for preventive or curative purposes. Finally, the findings of univariate analysis indicated that smoking was significantly associated with COVID-19 hospitalization and death. Nevertheless, in the multivariate logistic regression, smoking was not an independent predictor factor of COVID-19 hospitalization and death. In the literature, evidence on the role of smoking in COVID-19 has been inconsistent [40,41].

Limits

To the best of our knowledge, this original study is the first survey in our city illustrating the evolution of COVID-19- outpatient. Starting from an exhaustive sample, this study gave an insight into the predisposing factors of COVID-19 hospitalisation and death that have been reported in many published studies. However, it had some limitations: First, we failed to call some patients and we probably underestimated the proportion of COVID 19 hospitalisation and death. Besides, data collection by three different clinical investigators through a telephone interview may cause information bias and to avoid this we used a standardized questionnaire, and the three clinical investigators were well trained. Finally, the predictive factors of death had adjusted odds ratio with wide confidence intervals. In fact, the number of deceased patients was low because we chose initially non-serious forms.

Conclusion

Our data indicates that older people, men, and bedridden patients are the most vulnerable to the worsening of COVID-19. Medical follow-up and appropriate management at the onset early symptoms would prevent late hospitalization and death. Our study was conducted before the start of vaccination in Tunisia. Further studies are recommended to assess the impact of vaccination on COVID-19 outbreaks in Tunisia.

Authors' contribution

Hanen Maamri, Jihen Jdidi, Nouha Ketata , Mouna Baklouti and Hamami Rania: Substantial contribution to conception and design of the study, to data acquisition, or to data analysis and interpretation.

Hanen Maamri, Jihen Jdidi and Hamami Rania, wrote the article and/or revised the article for important intellectual content.

Hanen Maamri , Olfa chakroun, Fadhila Isaaoui, Sourour Yaich, Mejdoub Yosra and Hammami Rania read and approved the final version of the submitted manuscript.

All Authors revised the manuscript and gave their contribution to improve the paper.

All authors read and approved the final manuscript

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