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Original Article

Impact of Comorbidities on the Risk of Death and Intensive Care Admission in COVID-19 Patients Hospitalized in a North-African Center

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Background: The Coronavirus Disease 2019 (COVID-19) pandemic has posed significant challenges to global health, with variations in outcomes among affected individuals. Comorbidities are known to influence the prognosis of various diseases, but their specific impact on COVID-19 patients in North-African settings remains to be elucidated. To evaluate the risk of death and intensive care unit (ICU) transfer in patients with COVID-19 by stratifying on comorbidity status.

Methods: Data of confirmed hospitalized patients at the university hospital of Kairouan (Tunisia) between September 2020 and August 2021 were collected. Composite endpoints including admission to an ICU or death were analysed. The risk of reaching the composite endpoint was compared according to the presence and number of comorbidities. Kaplan-Meir methods and Cox proportional hazards regression models were used to study the time to composite endpoint and estimate its prognostic factors.

Results: A total of 866 patients were included. The mean age was 65 ± 14 years. Most common comorbidities were arterial hypertension (41.1%) and diabetes mellitus (31.2%). Overall, 316 (36.5%) patients reached the composite endpoint: 263(30.4%) patients died and 53 (6.1%) were admitted to the ICU. Cardiovascular disease and chronic renal failure were associated with higher risk of reaching the composite endpoints.

Conclusion: COVID-19 patients with comorbidities were more likely to experience severe outcomes. Aggressive strategies to control the COVID-19 pandemic should target patients with chronic diseases, especially cardiovascular disease, and chronic renal failure, as a priority.

Keywords: Arterial Hypertension, Comorbidity, Diabetes Mellitus, Hospital Mortality, Intensive Care Units, Kaplan-Meier Estimate, Proportional Hazards Models, SARS-CoV-2, Tunisia

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INTRODUCTION,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, also called coronavirus disease of 2019 (COVID-19), is a novel, emerging, rapidly propagating infectious disease that first appeared in December 2019 in China (1). COVID-19 quickly spread throughout China and then worldwide declared a global pandemic by the World Health Organization (WHO) in March 2020 (2). Statistics revealed a total number of infected cases of around 569 million and more than 6 million deaths worldwide until July 2022 (3). It is overwhelming most of the resources of efficient healthcare systems, and numerous hospitals suffered a lack of intensive care unit (ICU) beds for critically ill COVID-19 patients (4). Tunisia has been severely affected by COVID-19. Until July 2022, Tunisia registered around one million confirmed cases of coronavirus since the beginning of

the pandemic and a total of 28.900 deaths (5). On the African continent, Tunisia ranks among the countries with the highest number of deaths since the beginning of the pandemic (3, 5). The governorate of Kairouan was deeply touched by the pandemic in the third large wave (from May to July 2021), as the highly contagious, most devastating Delta variant of the coronavirus began to spread around the world, leading to a higher risk of hospitalization, ICU admission, and mortality (6). In July 2021, ICU beds were in high demand, and hospitals ran out of oxygen (7). COVID-19 has a variable and vast clinical spectrum, ranging from a simple, pure asymptomatic infection to more severe pneumonia pictures, severe respiratory distress syndrome, cardiovascular and thromboembolic complications, and even death (8).

Identifying risk factors associated with the increased severity of COVID-19 still remains one of the research priorities in countries affected by the pandemic (9-13). Pre-existing medical conditions in COVID-19 cases were identified as a risk factor for complications leading to ICU hospitalization and death. Several studies, which were conducted mainly in Asia, have reported that COVID-19 patients with diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVDs), arterial hypertension, malignancies, and other comorbidities could develop a life-threatening situation (14). However, information on how the combination of these risk factors affects the severity of COVID-19 is rare. The study of comorbidities and the evaluation of their repercussions on the prognosis of the disease, especially the risk of complications and death, will allow physicians to identify subgroups of individuals where the application of preventive measures, including vaccination, would be a priority to limit the burden and complications related to COVID-19. Moreover, detecting risk factors for severity is even more important when the demand for critical care is surging and the resources for healthcare are limited, as in the Tunisian context. We also thought that data on prognosis factors associated with a poorer outcome is needed for this public health emergency and for practical health care resource assignment. To the best of the authors' knowledge, until the end of July 2023, no published study evaluating the impact of pre-existing conditions has been carried out in North-Africa, mainly in Tunisia.

The present study aimed to investigate the impact of comorbidity burden on mortality and ICU transfer in patients with confirmed COVID-19 hospitalized at Ibn Al Jazzar university Hospital in Kairouan (Tunisia) between September 2020 and August 2021.

PATIENTS AND METHODS

Study Design

It was a cross-sectional study to gather information about the possible impact of comorbidities on the course of COVID-19 (***i.e.***, death or ICU admission) among hospitalized adult patients at Ibn El Jazzar University Hospital (Kairouan, Tunisia). The study was performed between September 1^{sts} 2020 and August 31st, 2021, at the COVID-19 unit constituted of the medicine and gastroenterology departments, which are made of 19 and 37 beds, respectively. All patients presenting a hypoxemic pneumonia (whatever the comorbidities) and with suspicion of COVID-19 were hospitalized in medicine department, and the confirmed ones in the gastroenterology department. Then, and with the explosive increase in the admissions flow, all patients were hospitalized within the two departments even without the confirmation of the disease. The ICU was created in October 2020 in response to the eminent need, with a capacity of nine beds.

The information consent has been acquired for all the hospitalized patients. Ethical approval was obtained from the local hospital ethics committee.

Study Setting and Participants

The study covers all confirmed COVID-19 patients until August 31, 2021. Confirmed cases denoted the patients whose real-time reverse transcriptase-polymerase chain reaction (Rt PCR) assay findings for nasal and pharyngeal swab specimens were positive. Patients with a negative PCR test and those admitted to other wards were not included. Patients with missing medical records were excluded (Figure 1).

Data Analysis

Data was collected from the medical records of patients using a standardized data form performed by the preventive medicine department of Ibn Al Jazzar University Hospital. A trained team of family medicine and preventive and community residents accomplished the data collection. The variables comprised sociodemographic details, including age (categorized as < 65 years and ≥ 65 years), sex, profession, and address. We also considered comorbidities such as CVDs, arterial hypertension, dyslipidemia, coronary artery disease, diabetes mellitus, and chronic conditions like respiratory diseases (including COPD and asthma), kidney diseases, and malignancy. Symptoms and signs at admission spanned fever/chills, dry cough, rhinorrhea, dyspnea, acute respiratory distress syndrome (ARDS), digestive symptoms, asthenia, chest pain, anosmia, and ageusia.

We also noted complications such as thromboembolic events, hemorrhagic occurrences, strokes, and decompensated diabetes mellitus. Furthermore, findings from computed tomography (CT) scans and outcomes like death and ICU admission were included. The ARDS has a codified clinical definition, known as the Berlin definition based on these conditions: Acute onset (within seven days of new or worsening respiratory symptoms), bilateral radiographical opacities that are not fully explained by effusion, atelectasis, or masses, arterial hypoxemia, identified risk factor for ARDS (if no clear risk factor, heart failure was excluded as a cause), not exclusively due to cardiac causes (15).

Comorbidities were determined based on the patient's self-report on admission. They were initially treated as a categorical variable (yes vs. no) and then classified based on the number (single vs. multiple). To compare outcomes between the study groups (namely COVID-19 patients with vs. without comorbidities), we analyzed the main composite endpoints, which consisted of admission to an ICU or death. The risk of reaching the composite endpoint was compared according to the presence and number of comorbidities. The secondary endpoints were the need for non-invasive ventilation (NIV), ARDS, decompensated diabetes mellitus, acute renal failure, thromboembolic accident recorded on the medical records, and the overall length of hospital stay.

Statistical Analysis

Baseline demographics and clinical characteristics were expressed as mean ± standard deviation (SD) or the median with interquartile range (IQR) as appropriate for continuous numerical variables and the frequency (percentage) for categorical variables. Between-group comparisons were performed with Student's t-test for numerical variables and a chi-squared test or Fisher's exact test for categorical variables. Kaplan-Meir methods was used to study the time to composite endpoint. Log rang test was used to compare survival distribution between groups. Cox proportional hazards regression models were applied to determine the potential risk factors associated with the composite endpoint, with the hazard ratio (HR) and 95% confidence interval (CI) being reported. Statistical significance was determined at $p<0.05$. The variables with $p < 0.2$ in the univariate analysis were considered in the multivariable model.

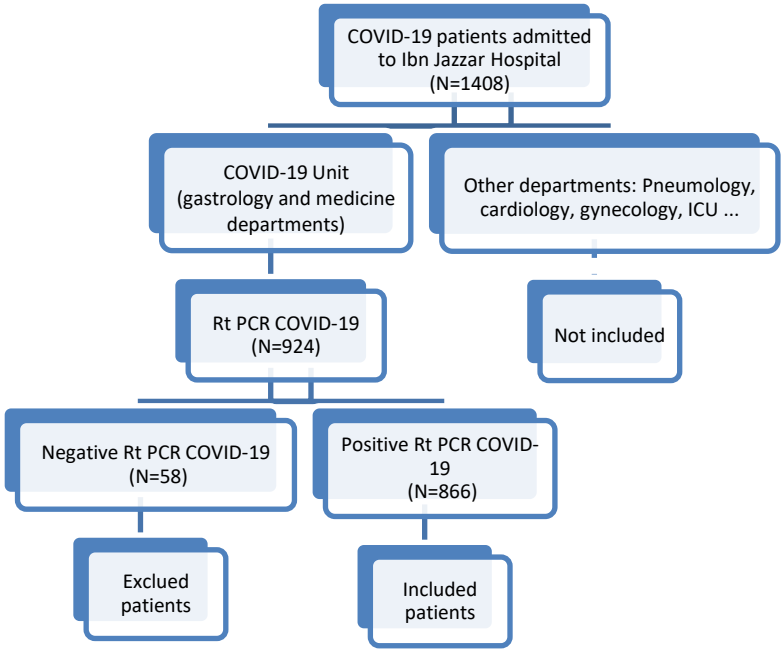
A Cox regression model was considered more appropriate than a logistic regression model because it considered the potential impact of the various durations of follow-up from individual patients (16). Statistical analysis was performed using the SPSS statistical package (version 20.0, SPSS Inc, Chicago, IL, USA). Excel was used to generate figures, and forest plots from the Cox model.

RESULTS

Demographic and clinical characteristics

The study population included 866 patients with COVID-19 who fulfilled the specified inclusion criteria (Figure 1).

Figure 1. The study's flow chart



COVID-19: Coronavirus disease 19, Rt-PCR: Reverse Transcriptase Polymerase Chain Reaction, ICU: Intensive care unit

Sociodemographic profile showed that 484/866 (55.9%) were men. The overall mean age was 65 ±14 years. There was no significant difference in the mean age between men and women (p=0.21). In fact, the mean ± SD of ages were 65±15.7 years for women, and 66 ±13.1 years for men.

The most common symptom was dyspnea (83%), followed by fever (64%), dry cough (48.6%), and asthenia (46.3%). Anosmia (3.5%), abdominal pain (3.4%) and ageusia (2.9%) signs were less common. The CT scan results revealed pathologic chest CT imaging in 84% (n=734) of patients.

Baseline Comorbidities

Regarding the presence of chronic conditions, 269/866 (31.2%) of patients had no comorbidities, while 255/866 (29.4%) presented one chronic condition, 342/866 (39.5%) had two comorbidities or more (Table 1). The most prevalent comorbidities were arterial hypertension (41.1%) and diabetes mellitus (31.2%), followed by dyslipidemia (10.5%) and chronic lung diseases (9.8%). The percentages of patients with chronic renal disease and malignancy were 5% and 2.1%, respectively.

Outcomes

A total of 263/866 (30.4%) had died, 53/866 (6.1%) had required ICU admission, and 210/866 (24.3%) received NIV (Table 2). The death rate was higher among older patients with COVID-19 hospitalized. During the study period, 316/866 (30.4%) patients reached the composite endpoint. The rate of reaching the composite endpoint was significantly different between the comorbidity and non-comorbidity groups (39.7% vs. 29.4%, p = 0.003) (Table 2). Patients with comorbidities (mean age: 67±13 years) were significantly older than patients without any comorbidities (mean age: 62 ± 15 years), were more likely to have severe cases and tended to reach the composite endpoints (39.7% vs. 29.4%), to need NIV (27.6% vs. 17.1%), and to die (34.3% vs. 21.6%). The death rate was significantly higher in cases with comorbidities (34.3% vs. 21%) (p < 0.001). In addition, patients with comorbidities needed NIV more than those without comorbidities (27.6% vs. 17.1%, p = 0.001). Secondary outcomes were most seen among patients with pre-existing comorbidities: ARDS (27.9% vs. 20.1%; p = 0.015), decompensated diabetes mellitus (13.9% vs. 2.6%; p < 0.001), acute renal failure (3.5% vs. 0.4%, p = 0.009).

Table 1. Comorbidities distribution based on age of confirmed COVID-19 patients (n=866)

	Total, N = 866	Age < 65 years, N = 353	Age ≥ 65 years, N = 513	p-value
Cumulative comorbidities, No. (%)				
No	269 (31.1)	139 (39.4)	130 (25.3)	< 0.001
Yes	597 (68.9)	214 (60.6)	383 (74.7)	< 0.001
1	255 (29.4)	105 (29.7)	150 (29.2)	< 0.001
≥ 2	342 (39.5)	109 (30.9)	233 (45.4)	< 0.001
Type of comorbidities, No. (%)				
Diabetes mellitus (yes)	270 (31.2)	100 (28.3)	170 (33.1)	0.133
Type 1	47 (17.4)	19 (19)	28 (16.5)	0.597
Type 2	223 (82.6)	81 (81)	142 (83.5)	0.597
Arterial hypertension	356 (41.1)	96 (27.2)	260 (50.7)	< 0.001
Cardio-vascular diseases	112 (12.9)	24 (6.8)	88 (17.2)	< 0.001
Coronary artery disease	79 (9.1)	18 (5.1)	61 (11.9)	0.001
Chronic lung diseases	85 (9.8)	34 (9.6)	51 (9.9)	0.880
COPD	36 (4.2)	6 (1.7)	30 (5.8)	0.003
Asthma	32 (3.7)	20 (5.7)	12 (2.3)	0.011
Bronchiectasis	6 (0.7)	4 (1.1)	2 (0,4)	0.195
Renal diseases	43 (5.0)	25 (7.1)	18 (3.5)	0.017
Chronic renal failure	38 (4.4)	24 (6.8)	14 (2.7)	0.004
Hemodialysis	27 (3.1)	20 (5.7)	7 (1.4)	< 0.001
Cerebrovascular disease	21 (2.4)	5 (1.4)	16 (3.1)	0.109
Thromboembolic diseases	66 (7.6)	18 (5.1)	48 (9.4)	0.020
Dyslipidemia	91 (10.5)	31 (8.8)	60 (11.7)	0.169
Malignancy	18 (2.1)	8 (2.3)	10 (1.9)	0.748
Others*	48 (5.5)	19 (5.4)	29 (5.7)	0.864

COPD: Chronic obstructive pulmonary disease. **COVID-19**: coronavirus disease of 2019.

*Others: Rheumatic diseases; trisomy 21; thyroid disorders; chronic anemia; Parkinson disease; Alzheimer's disease; systemic diseases.

p-value: chi-squared test or Fisher's exact test as appropriate

Table 2. Characteristics of Patients with or without any Comorbidities (n = 866)

	Comorbidities		
	No, n =269	**Yes, n =597**	**p-value**
Age, years	62±15	67±13	< 0.001
Age ≥ 65 years old	130 (48.3)	383 (64.2)	< 0.001
Sex			0.061
Male	163 (60.6)	321 (53.8)	
Female	106 (39.4)	276 (46.2)	
Symptoms			
Dyspnea	220 (82.1)	500 (83.8)	0.545
Fever	186 (69)	375(62)	0.071
Dry cough	132 (49)	284(48)	0.687
Asthenia	123 (45.9)	275(46.5)	0.863
Headache	55 (20.7)	89(15.2)	0.046
Chills	33 (12.4)	60(10.2)	0.343
Vomiting	21 (7.9)	39(6.6)	0.504
Diarrhea	14 (5.3)	21(3.6)	0.25
Thoracic pain	13 (4.9)	21(3.6)	0.362
Anosmia	13 (4.9)	17(2.9)	0.144
Abdominal pain	8 (3)	21(3.6)	0.67
Ageusia	7 (2.6)	18(3.1)	0.727
Chest computed tomography			
Abnormal chest image	230(85.5)	504(84.4)	0.682
% of lung lesion			
< 50%	135(50.2)	288(48.2)	0.596
≥ 50%	134(49.8)	309(51.8)	
Length of stay, day			
All patient	7±8	8±7	0.073
Discharged patient	7±8	8±7	0.176
Main outcomes			
Death	58(21.6)	205(34.3)	<0.001
Admission to ICU	21(7.8)	32(5.4)	0.165
Composite endpoint	79(29.4)	237(39.7)	0.003
Secondary outcomes			
Non-invasive ventilation	46(17.1)	164(27.6)	0.001
ARDS	54(20.1)	164(27.9)	0.015
Decompensated diabetes mellitus	7(2.6)	81(13.9)	<0.001
Acute renal injury	1(0.4)	20(3.5)	0.009
Thromboembolic accident	10(4)	22(3.9)	<0.001

Data in table are presented as Mean ± SD or No. (%)

ARDS: Acute respiratory distress syndrome. ICU: Intensive care unit. SD: Standard deviation.

p-value: Student's t-test for numerical features (age mean and length of stay) and a chi-squared test or Fisher's exact test for categorical features.

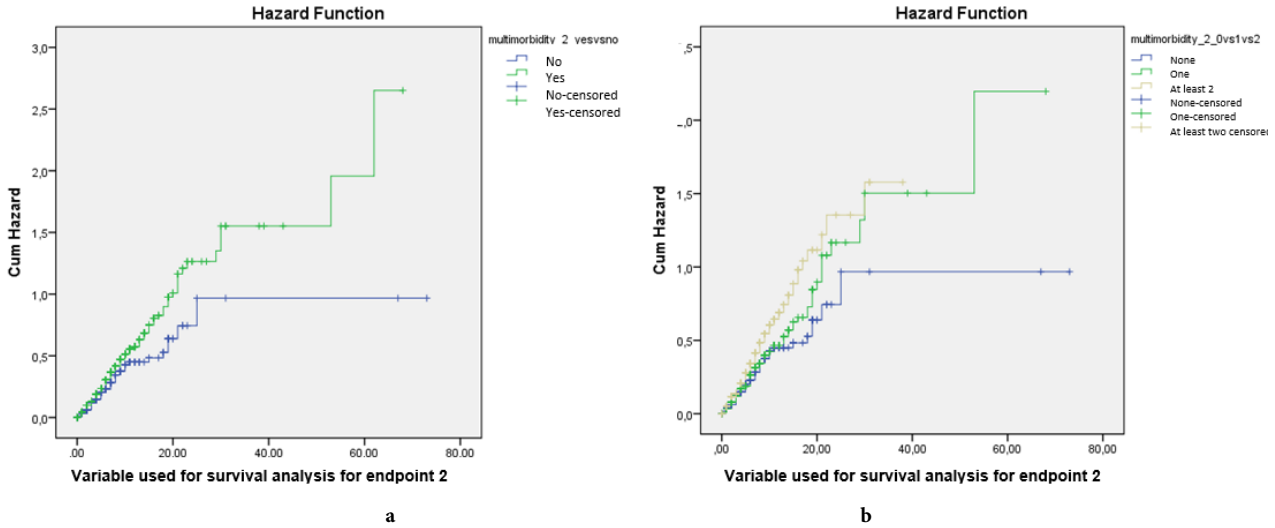
Table 3. Characteristics of patients with 1 or ≥ 2 comorbidities (n = 866)

	Comorbidity		p-value
	1 (n = 255)	**≥ 2 (n = 342)**	
Age, year	63 ± 13	66 ± 12	0.029
Age ≥ 65 years	150(58.8)	233(68.1)	< 0.001
Length of stay, days			
All patient	9±8	8±6	0.029
Discharged patient	9±8	8±6	0.162
Main outcomes			
Death	84(32.9)	121(35.4)	0.001
Admission to ICU	15(5.9)	17(5)	0.342
Composite endpoint	99(38.8)	138(40.4)	0.013
Secondary outcomes			
Non-invasive ventilation	70(27.6)	94(27.6)	0.004
ARDS	67(26.4)	97(29.1)	0.040
Acute renal injury	6(2.4)	14(4.4)	0.011
Thromboembolic accident	9(3.6)	13(4.1)	0.957

Data in table are presented as Mean ± SD or No. (%)

ARDS: Acute respiratory distress syndrome. ICU: Intensive care unit. SD: Standard deviation.

p-value: (Student's t-test for numerical features (age mean and length of stay) and a chi-squared test or Fisher's exact test for categorical features)



a b

Figure 2. a) The time-dependent risk of reaching the composite endpoints between patients with or without any comorbidity. **b)** The time-dependent risk of reaching the composite endpoints between patients without any comorbidity, patients with a single comorbidity and patients with two or more comorbidities.

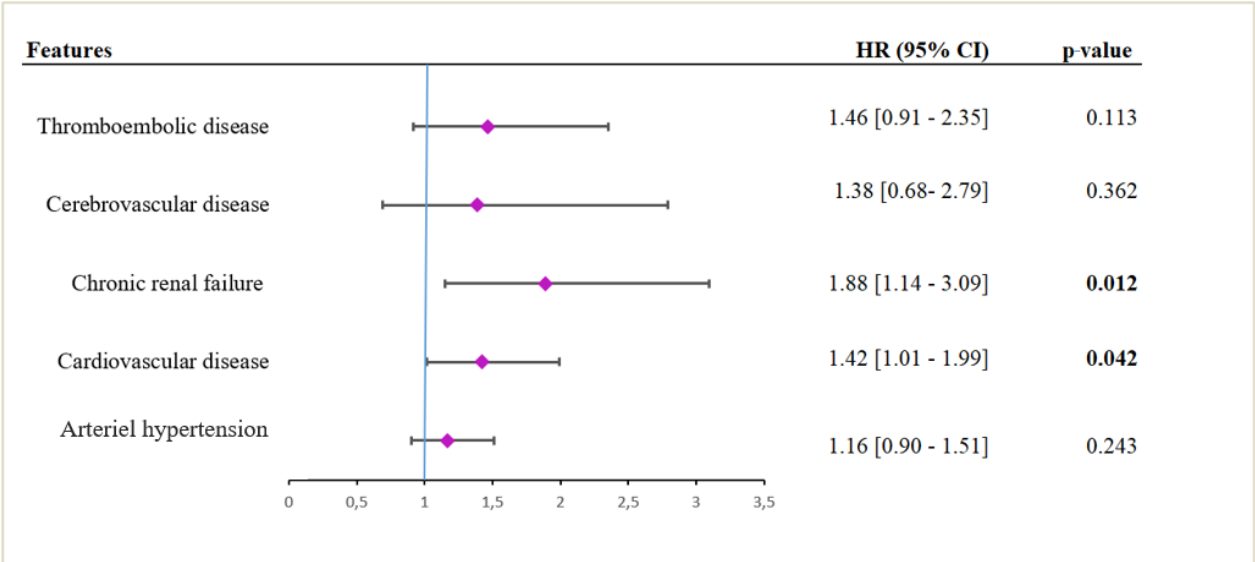


Figure 3: Predictors of the composite endpoints in the proportional hazards model. Hazard ratio (HR) (95% confidence interval (CI)) are shown for the comorbidities analyzed with the composite endpoints (admission to intensive care unit, or death).

The composite endpoint was documented in 99 (38.8%) patients with at least one comorbidity, and in 138 (40.4%) patients with two or more comorbidities (Table 3). Patients in two or more comorbidities' subgroup were older than those in the non-comorbidity subgroup (≥65 years old: 68.1% vs. 58.8%; p ≤ 0.001). The higher the number of comorbidities, the older the patients were (66±12 vs. 63±13 years for ≥ 2 and 1 comorbidity, respectively; p = 0.029) (Table 3).

Prognosis Analysis

Time to Composite Endpoint: Survival Analysis

Compared with patients without comorbidities, those with comorbidities had a significantly higher risk of reaching the composite endpoint (p = 0.026). As the number of comorbidities increased, the risk of reaching the composite endpoint also increased (p = 0.011) (**Error! Reference source not found.** 2).

Cox Regression Analysis

In the univariate Cox regression model, cases with CVDs, cerebrovascular diseases, and thromboembolic diseases showed a significant higher risk of reaching the endpoints, as HR in CVDs was 1.52 (95%CI [1.13 - 2.03]; p = 0.005), in cerebrovascular diseases was 1.83 (95%CI [1.07- 3.14]; p = 0.026) and in thromboembolic disease was 1.63 (95%CI [1.15 - 2.31]; p = 0.006) (Table 4).

In the multivariate Cox regression, only CVDs (HR [95%CI]: 1.42 [1.01–1.99], p=0.042) and chronic renal failure (HR [95%CI] 1.88 [1.14–3.09], p=0.012), showed higher risk for reaching the composite endpoints (Figure 3).

Table 4. Univariate cox regression analysis of comorbidities associated with risk to reach endpoint (n=866)

	Univariate cox regression			
	Endpoint (N= 316)		HR [95%CI]	p-value
	n	%		
Diabetes mellitus				0.660
No	214	35.9	Ref	
Yes	102	37.8	1.05 [0.83 - 1.33]	
Arterial hypertension				0.139
No	176	34.5	Ref	
Yes	140	39.3	1.18 [0.94 - 1.47]	
Cardiovascular diseases				0.005
No	261	34.6	Ref	
Yes	55	49.1	1.52 [1.13 - 2.03]	
Chronic lung diseases				0.786
No	288	36.9	Ref	
Yes	28	32.9	0.94 [0.64 - 1.39]	
COPD				0.952
No	303	36.5	Ref	
Yes	13	36.1	1.01 [0.58 - 1.77]	
Asthma				0.933
No	306	36.7	Ref	
Yes	10	31.2	1.02 [0.54 - 1.93]	
Cerebrovascular disease				0.026
No	302	35.7	Ref	
Yes	14	66.7	1.83 [1.07- 3.14]	
Chronic renal failure				0.072
No	298	36.0	Ref	
Yes	18	47.4	1.54 [0.96 - 2.49]	
Thrombo-embolic disease				0.006
No	280	35.0	Ref	
Yes	36	54.5	1.63 [1.15 - 2.31]	
Malignancy				0.327
No	307	36.2	Ref	
Yes	9	50.0	1.39 [0.71 - 2.70]	
Dyslipidemia				0.951
No	282	36.4	Ref	
Yes	34	37.4	0.98 [0.69 - 1.41]	

CI: Confidence Interval. COPD: Chronic obstructive pulmonary disease. HR: hazard ratio. Ref: Reference.

DISCUSSION

Identifying COVID-19 patients at higher risk of severe outcomes represent a major challenge for public health, suggesting the need for studying predictors of severity that can guide patient management in hospital. In our study, arterial hypertension and diabetes mellitus were common among patients with COVID-19. Patients with at least one comorbidity, or even more, were associated with a higher risk of poor outcomes. CVDs and chronic renal failure were risk factors of reaching the composite endpoints.

To the best of the authors' knowledge, this study is the first investigation in Tunisia that evaluates the impact of comorbidities on the clinical characteristics and the prognosis in patients with COVID-19. Our investigation is made over a whole year, from September 2020 to August 2021, including a large sample size. The fact that the study was undertaken in only one tertiary hospital is also a strength because the criteria for admission to the hospital in general and to the ICU were relatively homogenous.

Sociodemographic Characteristics

Our study population was elderly with a mean age of 65±14 years, similar to an Italian study (17) in which the mean age was 63 [56-70] years. In line with previous studies, COVID-19 predominantly affected men. This result confirmed those reported in China at 57.3% (14). A 2020 study (18) explained this sex distribution by the biological differences in the immune systems between men and women, but also lifestyle such as high levels of

smoking and drinking among men compared to women. In addition, women have a more responsible attitude toward the COVID pandemic, than men (18).

Underlying Comorbidities

In our study, 598(69.1%) patients reported having at least one comorbidity, similarly to what was reported by Wang et al. (72.2%) (14) and Grasselli et al. (68%) (17). Two or more comorbidities were reported in 342 (39.5%) patients, which is consistent with what was found in a United States study (19). Similar to other previous reports (14, 17, 20, 21), arterial hypertension was the most common comorbidity (41.1%), followed by diabetes mellitus (31.2%), CVDs (12.9%) and dyslipidemia (10.5%). Concurrently, multiple studies on COVID-19 evaluating whether the history of arterial hypertension is a risk factor for adverse outcomes have yielded conflicting results (22-24). Specifically, Pan et al. (22) reported that arterial hypertension has a HR of 1.80 for in-hospital mortality in 996 patients with COVID-19. In contrast, two other studies that enrolled respectively 416 and 1591 patients, suggested that after the adjustment for confounders, arterial hypertension was no longer an independent risk factor for COVID-19 (23, 24).

Previous studies reported that diabetes mellitus worsens the prognosis for different viruses, including SARS-CoV2 (25, 26). Additionally, it was proved that diabetes mellitus is a significant contributor to mortality from COVID-19 (27). Similarly, reports have shown that diabetes mellitus is an independent contributing factor to the severity of complications experienced by COVID-19 patients (28, 29). This indicates that diabetic patients infected by COVID-19 are pre-disposed to severe complications and mortality. According to Hussain et al. (25), chronic inflammation, increased coagulation activity, immune response impairment, and potential direct pancreatic damage by SARS-CoV-2 might be among the underlying mechanisms of the association between diabetes mellitus and COVID-19. Li et al. (29) identified that the levels of C-reactive protein, serum ferritin, and erythrocyte sedimentation rate (***i.e.***; inflammation indicators) increased in COVID-19 patients and were associated with the greater severity of the disease. These indicators were higher in the patients with CVDs than in those without (29). This result indicates that COVID-19 exerted an additional impact on cases with a history of CVDs (29).

Outcomes for Composite Endpoints

Overall, 316 (36.5%) patients reached the composite endpoints during the study period: 263 (30.4%) patients died, 53(6.1%) were admitted to the ICU, and 210 (24.3%) received NIV. The composite endpoints were documented in 237(39.7%) patients who had at least one comorbidity as opposed to 79 (29.4%) patients without comorbidities (p=0.003). This implies that pre-existing comorbidities were significant predictors for severe outcomes such as CVD (HR = 1.52, 95%CI, 1.13 - 2.03, p=0.005), cerebrovascular disease (HR=1.83, 95%CI, 1.07-3.14, p=0.026). Our results demonstrated that patients with comorbidities recorded significantly higher percentages of complications, such as ARDS (27.9 vs. 20.1%; p=0.015), compensated diabetes mellitus (13.9 vs. 2.6%, p≤0.001), acute renal failure (3.5 vs. 0.4%; p=0.009), and thromboembolic accidents (p≤0.001). This finding was congruent with the results reported by Wang et al. (18), who revealed that patients with arterial hypertension (Odds Ratio (OR): 2.29, 95%CI: 1.69–3.10, p≤0.001), diabetes mellitus (OR: 2.47, 95%CI: 1.67–3.66, p≤0.001), or COPD (OR: 5.97, 95%CI: 2.49–14.29) were at increased risk of exacerbations and complications.

Our analysis did not provide sufficient evidence that there was a correlation between lung diseases, malignancy, and COVID-19 patients' aggravation. The patients who reached the composite endpoints were older and had a more significant number of comorbid conditions than those who did not reach the composite endpoints; those who died had more comorbidities than surviving patients. An increased number of comorbidities correlated positively with disease severity and poor prognosis. This was consistent with previous findings that the number of comorbidities is a risk factor for a worse outcome (14, 30).

Our fatality rate in COVID-19 patients was 30%. A Chinese study on hospitalized patients reported a nearby rate of 28% in 191 patients (31). Another study conducted in Italy reported a fatality rate of 17.5 (32). We reported that the death rate was higher among older patients and having comorbidities: 34.3% vs. 21.6%. In coherence with recent reports (14, 32), non-invasive respiratory support was needed in 24.3% of COVID-19 patients, and the ICU admission rate was 6.1%, compared to the Chinese (14) study of 1590 COVID-19 patients, which reported an ICU admission rate of 6.2% and an invasive ventilation rate of 3.1%; Benelli et al. (32) reported that of the 411 COVID-19 patients, 6.8% required an ICU transfer, and 27% needed invasive ventilation support.

Prognosis Analysis

Our analysis identified CVDs, cerebrovascular disease, chronic renal failure, and thromboembolic disease as

significant risk factors for COVID-19 patients. The multivariate analysis indicated that CVDs and chronic renal failure were independent risk factors for poorer prognosis. Alam et al. (33) revealed that patients with any of the existing comorbidities [liver, kidney, heart, lung diseases and diabetes mellitus] where observed to have more risks of COVID-19. Alzoughool et al. (34) reported that cerebrovascular comorbidity increased the risk of disease severity (OR= 4.4; 95%CI: 1.48 to 12.84) and mortality (OR = 7.0; 95%CI: 2.56 to 18.99), and this was consistent with other reports (14, 34, 35). There is evidence that SARS-CoV-2 has neuro-invasive abilities and might spread from the respiratory system to the central nervous system (36). Several studies revealed that patients with chronic renal failure demonstrated a more severe course of COVID-19 and it identified the pre-existing renal disease to be independently associated with higher in-hospital mortality (37, 38). Pranata et al. (35) reported that CVDs were associated with increased poor composite outcome (Risk Ratio (RR)= 2.23 [1.71,2.91], $p<0.001$; $p = 0.004$), mortality (RR=2.25 [1.53,3.29], $p<0.001$) and severe COVID-19 (RR=2.25 [1.51,3.36], $p<0.001$). Recent evidence demonstrates that cardiac damage might be due to a combination of direct damage and indirect damage through cytokine storm (36). A Spanish study (39) identified a deleterious effect of thromboembolic disorders in in-hospital mortality among COVID-19 patients (OR (95%CI) 2.24 (1.17–4.29) p=0.015). Previous reports identified both the relationship of COVID-19 infection and thromboembolic disease (40, 41) and the increased risk of death among patients with thromboembolic disease (42).

Study Limitations

The study had the limitations inherently associated with observational studies. Firstly, causality cannot be inferred from an association between variables, and the absence of a statistically significant association does not rule out clinical relevance (43). Additionally, patients who were transferred to the ICU were not followed up; the outcomes remained unknown. Furthermore, not every patient who required ICU transfer got it because of limited number of intensive care hospital beds. Moreover, there was no post-discharge follow-up to check on the patient's progress. In the other hand, some cases had incomplete documentation, and those were excluded from the final analysis. Finally, we have shown that comorbidities were associated with COVID-19 morbidity; however, it cannot be identified whether comorbidities are acting as an independent factor responsible for this severity and morbidity, or it is just a confounding factor. An essential condition such as elderly age have been reported to be associated with severe COVID-19 and its mortality. In fact, most of the elderly people develop chronic inflammation called "inflammageing"(44), and aging is associated with increased oxidative stress, and decreased endogenous protective mechanisms (45) which makes older people more susceptible to develops "inflammageing", recognized in COVID-19 condition.

CONCLUSION

Our findings suggested that patients with comorbidities had greater disease severity compared with those without. CVDs, cerebrovascular disease, chronic renal failure, and thromboembolic disease were associated with poorer prognosis among COVID-19 patients. This study indicates a worse prognosis in patients with pre-existing comorbidities who have COVID-19 regarding mortality, the occurrence of complications, and the ICU transfer. Furthermore, a more significant number of comorbidities is correlated with a severe disease progression. The existence of more than two comorbidities worsened the survival rate of patients. Our results provide valuable information for the identification of patients at high risk of critical illness and might need early intensive care. Both the category and number of comorbidities should be considered when predicting the prognosis in patients with COVID-19. Given the limitations of this study, further investigations of the relationship between COVID-19 and comorbidities are now warranted, with a focus on the relative risk of death in COVID-19 patients with vs. without comorbidities to prove the association between chronic diseases and poorer outcomes.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ethical approval was obtained from the ethical committee of Ibn Al Jazzar University Hospital, Kairouan, Tunisia.

AVAILABILITY OF DATA AND MATERIALS

Any datasets generated during and/or analyzed during the current study are publicly available, available upon reasonable request, or if data sharing is not applicable to this article.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AUTHORS' CONTRIBUTIONS

D.C and S.R: conception and design. D.C and H.H: analysis and interpretation of the data. S. R, D.C and A.S: drafting of the paper. W.D, H.S, J.A, A.S, B.T, T.B, F.C, C.J: investigation. L.M: revising it critically for intellectual content. All authors gave their final approval to the version that will be published.

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DECLARATION

Not applicable.

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