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Comorbidities and their effects on 753 COVID-19 patients in eastern Algeria

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It has been reported that the coexistence of comorbidities with COVID-19 is a risk factor for the severity of COVID-19 and a worse prognosis. The objective of the current study was to examine and highlight risk factors for severe disease as well as the influence of comorbidities on mortality risk in COVID-19 patients in the eastern region of Algeria. A cross-sectional study was conducted on a cohort of 753 COVID-19 patients who were admitted to four hospitals in eastern Algeria in 2020 and 2021. In the population that was enumerated, the average age of patients was 63.56±15.49 years, with a range of 1.29 for the male to female gender ratio. The PCR was positive in 88.1% of patients, the oxygen desaturation was 81.27±12.35%, and the pulmonary affliction was extended or critical in 50.7% and 14.8%, respectively. The most prevalent comorbidities were diabetes (40.4%) and hypertension (26.7%). This group of patients had a wide variety of biological abnormalities. 58.5% of patients had at least a single comorbidity, while 23.6% patients had two or more comorbidities. The average SpO_2 value decreased significantly in proportion to the rise of COVID-19 related comorbidities. A frequency of 24.0% of the patients with a SpO_2<90, had two or more comorbidities. The mortality rate was 28%. It was 9.2% for patients with a single comorbidity and 8% for those with multiple comorbidities. Our research suggested that patients with comorbidities had more severe COVID-19 than those without. Moreover, a higher number of comorbidities was associated with a greater COVID-19 severity and higher biological parameter abnormalities. Due to the high number of infections, biological changes, and deaths among patients with comorbidities infected with COVID19, it is necessary to consider good care of these patients in order to reduce morbidity and mortality rates.

Keywords: COVID-19, Comorbidity, Severity, Mortality, Prognostic factor

Since the start of 2020, the novel severe acute respiratory syndrome coronavirus 2 has been the cause of the coronavirus disease 2019 (COVID-19) pandemic, which has lasted for three years. As of April 2023, statistics from the World Health Organization (WHO) indicate that there were approximately 0.7 billion cases and 7 million fatalities associated with COVID-19[1]. The virus causing Coronavirus 2019 (COVID-19), known as SARS-CoV-2, was initially identified in Wuhan, China, in December 2019 and moved worldwide[2]. The WHO officially designated this respiratory illness as COVID-19 in February 2020. A month later, the WHO declared the SARS-COV-2 epidemic a pandemic because of the rapidly worsening health situation[3]. Over 1.7 million people have died because of the virus as of December 27, which has infected at least 79 million people globally[4].

Algeria is the second African country impacted by the pandemic, with its first case reported on February 25, 2020[5]. As of April 4th this year, 265 691 cases had been reported there, making it one of the countries most affected with a death toll (6874) ranking sixth in this context[6].

This illness is linked to an inflammatory state, multi-visceral insufficiency, suffocating respiratory distress syndrome (SDRA), and, in extreme situations, shock[7]. In spite of this, 81% of COVID-19 cases are moderate, 5% are critical, and 14% are severe. The fatality rate in severe cases is approximately 50%[8]. Numerous risk factors for severe COVID-19 have been identified in China. Older age, male gender, the presence of comorbidities, poor oxygen saturation, and aberrant lab results (high lactate dehydrogenase [LDH], high procalcitonin, low CD4 cell count, low albumin level) have all been shown to be risk factors for severe COVID-19[9,10]. However, research has indicated that a number of concomitant conditions, including diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and other illnesses, may increase the severity of COVID-

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19 and its fatality[11]. However, regional variations exist in aspects connected to patients and diseases, and these variations might have an effect on the clinical severity of COVID-19[12]. In Algeria, particularly in the east, hardly much is known about this topic despite the vast amount of worldwide data. In this sense, the objective of the current study was to examine and highlight risk factors for severe disease and the influence of comorbidities on mortality risk in COVID-19 patients in the eastern region of Algeria.

Materials and Methods

We performed a cross-sectional study using data from four hospital institutions in the eastern region of Algeria: the Internal Medicine Service of the Abdelhamid Ben Badis Hospital-University Center Constantine; the Internal Medicine Service of EL BIR Hospital Constantine; the Houari Boumediene Hospital of Chelghoum Laïd Mila and the Infectiology Service of Ali Boushaba Public Hospital of Khenchela. Data from 753 Covid-19 patients who were hospitalised in these hospitals in 2020 and 2021 are included in this study. The study was conducted in accordance with the Declaration of Helsinki of 1975 and the research investigation was approved by the hospital ethical committee. A full confidentiality of patients' data was maintained.

The inclusion criteria listed below were applied to achieve the investigation's aims. Adult COVID-19 hospitalised patients, both male and female. Positive PCR, positive thoracoscopic symptoms, and/or positive serological test results were the basis for the COVID-19 pneumonia diagnostic criteria. The exclusion criteria were the patients who tested negative for COVID-19, those who had the virus but had insufficient medical records, those who were younger than 18 years old and pregnant women.

Statistical analysis

An exploitation file including the following details was used to gather the data: gender, age, comorbidities, oxygen saturation, PCR, TDM, and antecedents, as well as the length of hospitalisation. Continuous variables were expressed with mean and standard deviation (SD), and categorical variables were presented as frequencies and percentages (%). The comparison between different groups was carried out by *chi-square* test for categorical variables and ANOVA test followed by its post-hoc Tukey's test for continuous variables. Multivariable Cox proportional hazard regression models were used to assess the relationship between having comorbidities on admission and COVID-19 in hospital survival time, and to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Comorbidities on admission were modelled as a time-dependent variable. The multivariable Cox regression models were adjusted to baseline covariates selected by the method of backward selection from the following: age, gender, SARS-CoV-PCR, parenchymal involvement, oxygen saturation, leucocytes, lymphocytes, haemoglobin, platelets count, D-dimer, prothrombin time, CRP, ASAT, ALAT, glycemia, plasma creatinine, urea, natremia and kalemia. In hospital Survival time was defined as time from hospital admission to date of death. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM, New York) and $P<0,05$ was considered statistically significant.

Results and Discussion

Of the 753 enrolled patients, 56.4% are male. Consequently, the gender ratio of males to women is 1.29. The recorded average age is 63.56 15.49 years old. With 27.6% of the population, those in the 65 to 74 years age range make up the majority of the population. Patients stay in the hospital for an average of 8.69±7.43 days. The Polymerase Chain Reaction (PCR) test yielded positive findings in 88.1% of the cases (n=326). Combining oxygen saturation with radiological extent of the lesions to determine the distribution of patients based on the severity of COVID-19 at admission revealed that the oxygen saturation rating is 81.27±12.35% on average and 711% of patients had oxygen saturation (SpO_2) less than 90%. According to an analysis of the chest computed tomography (CT) data 312 patients, or 50.7% of the total, had extended parenchymal lesions that ranged from 50% to 75%. Diabetes (40.4%), hypertension (26.7%), cardiovascular diseases (6.2%), respiratory diseases (4.7%) and obesity (4.3%) were the most common comorbidities in all COVID-19 patients. Concerning the laboratory parameters, we noted several disturbances. The most important are leucocytosis, lymphopenia, an increase in the mean values of D-dimers, CRP and glycemia was noted (Table 1).

Relationship of demographic and clinical characteristics with COVID-19's severity

Relationship of demographic and clinical characteristics with oxygen saturation

With the decrease in oxygen saturation, we observed a statistically significant rise in the average

Table 1 — Baseline demographic and clinical characteristics of patients.

Variable	Available data		% or $\bar{x} \pm SD$
Age (years)	753		63.56 ± 15.49
Gender	753	Male	56.4%
		Female	43.6%
Duration of hospital stay (days)	545		8.69 ± 7.43
SARS-CoV-2 PCR	370	Positive	88.1%
		Negative	11.9%
Parenchymal involvement	615	< 25 Minimum	12.7%
		[25-50[Moderate	21.8%
		[50-75[Extended	50.7%
		> 75 Critical	14.8%
SpO_2 (%)	575		81.27 ± 12.35
		<90	71,1%
		[90-94[	22,4%
		≥94	6,4%
Comorbidity on admission	75	Diabetes	40.4%
		Hypertension	26.7%
		Cardiovascular diseases	6.2%
		Respiratory diseases	4.7%
		Obesity	4.3%
		Euthyroid goiter	2.8%
		Hypothyroidism	2.1%
		Asthma	1.2%
		Kidney failure	1.1
		Sinusitis	0.9%
		Hyperthyroidism	0.8%
		Prostate diseases	0.8%
		Bronchitis	0.5%
		Liver diseases	0.5%
		Cancers	0.4%
		Splenectomy	0.4%
		Pulmonary emphysema	0.3%
		Transplantation	0.3%
		Respiratory allergies	0.1%
		Stroke	0.1%
		Adrenal insufficiency	0.1%
		Tuberculosis	0.1%
Biological characteristics	Leucocytes ($\times 10^9$/L)	Leucopenia	5,7%
	Lymphocytes ($\times 10^9$/L)	Leucocytosis	32,9%
	Haemoglobin (g/dL)	Lymphopenia	45,6%
	Platelets count ($\times 10^9$/L)	Lymphocytosis	29,7%
	D-dimer (ng/L)	Weak	41,4%
	Prothrombin Time (%)	High	2,7%
	CRP (mg/L)	Thrombocytopenia	19,8%
	ASAT (U/L)	Thrombocytosis	4,1%
	ALAT (U/L)	Positive	45,6%
	Glycemia (g/L)	Hypoprothrombinemia	22,3%
	Plasma creatinine (mg/L)	Positive	93,9%
	Urea (g/L)	Positive	33,7%
	Natremia (mEq/L)	Positive	28,1%
	Kalemia (mEq/L)	Hypoglycemia	1,9%
		Hyperglycemia	57,3%
		Positive	21,9%
		Positive	37,6%
		Hyponatremia	34.7%
		Hypernatremia	4.0%
		Hypokalemia	15.6%
		Hyperkalemia	20.8%

Table 2 — Demographic and clinical characteristics of COVID-19 patients according the COVID-19 severity

According the SpO_2

Variable	SpO_2 (%)	Total	<90	[90-94[	≥94	*P*-value
		% or $\bar{x}$ ± SD				
Age (years)		63.84±18.06	65.02±14.29	62.41±17.68	56.77±18.06	0.000
Gender	Male	57.4%	40.2%	13.9%	3.3%	0.403
	Female	42.6%	31.0%	8.5%	3.1%	
hospital stay (week)	1 week	57.9%	37.6%	17.1%	3.1%	0.010
	2 weeks	26.7%	15.8%	7.6%	3.3%	
	3 weeks	8.2%	6.0%	1.8%	0.4%	
	4 weeks	3.6%	2.9%	0.4%	0.2%	
	More than 4 weeks	3.6%	2.7%	0.0%	0.9%	
Positive SARS-CoV-2 PCR	Total	100%	68.6%	28.6%	2.9%	0.002
	Positive	87.4%	62.9%	22.3%	2.3%	
	Negative	12.6%	5.7%	6.3%	0.6%	
Parenchymal involvement	Total	100%	72.2%	22.9%	4.9%	0.000
	Minimum	11.6%	10.4%	0.8%	0.4%	
	Moderate	19.7%	10.6%	6.4%	2.7%	
	Extended	52.3%	37.1%	13.6%	1.5%	
	Critical	16.5%	14.0%	2.1%	0.4%	

According the parenchymal involvement

Parenchymal involvement		Total	<25	[25-50[	[50-75[	≥ 75	*P*-value
			%				
Gender	Male	54.1	6.5	11.4	28.6	7.6	0.723
	Female	45.9	6.2	10.4	22.1	7.2	
Duration of hospital stay (day)	1 week	60	2.7	12.4	35.2	9.7	0.153
	2 weeks	27.4	1.5	6.9	14.9	4	
	3 weeks	6.9	0	1.1	4.2	1.7	
	4 weeks	2.9%	0	0.2	1.9	0.8	
	More than 4 weeks	2.7	0.4	0.4	0.8	1.1	
Positive SARS-CoV-2 PCR	Positive	88.4	5.3	11.4	55.4	16.3	0.000

age. The patients in the group whose oxygen saturation level is less than 90% had the greatest average age, 65.02±14.29 years old. 40.2% of the patients in this group were male, and 62.9% of them had positive SARS-CoV-2 PCR results. Table 2 shows that 51.1% of patients had extended or critical parenchymal involvement together with an oxygen saturation below 90%. A saturation level of oxygen below 90% in this patient group is associated with comorbidities (Table 3). Patients with arterial hypertension and diabetes, accounting for 21.9% and 32.3% of cases, respectively, also had less than 90 % oxygen saturation. Patients whose oxygen saturation is less than 90% exhibit the highest rates of biological parameter disturbances, including essentially elevated CRP (63.2%), hyperglycemia (52.1%), hyperproteinemia (36.7%), Increase of D-dimer (32.5%), Increase of urea (30.3%), lymphopenia (29.6%) and leukocytosis (26.3%).

Relationship of demographic and clinical characteristics with the parenchymal involvement

We noted a significant increase in the average value of the age of patients proportionally with the increase in the percentage of parenchymal involvement. Patients with more than 75% lesions had the greatest average age, around 69.37±15.56 years. Additionally, those with lesions between 50 and 75 % had the greatest probability of SARS-CoV-2 PCR test positive (55.4%) (Table 2). At admission, we observed that 60.5% of patients had comorbidities related to COVID-19; of these, 28.3% had lung lesions ranging from 50 to 75 %. According to our study, parenchymal involvement ranges from 50 to 75% when arterial hypertension or diabetes is present (Table 3).

Comorbidities and outcomes of COVID-19

We noted that 441 (58.5%) patients had at least a single comorbidity, while 178 (23.6%) patients had two or more comorbidities. We did not find a statistically significant difference in the average age when we analysed the demographic characteristics of COVID-19 patients based on comorbidities at admission. However, individuals with many comorbidities hospitalised for longer periods of time.

Table 3 — Relationship of Comorbidities on admission and severity

			Relationship with SpO2			
Variables (%)	Total		<90	[90-94[	≥94	*P*-value
Arterial hypertension	25.7		21.9	2.3	1.6	0.000
Diabetes	44.2		32.3	9.9	1.9	0.182
Cardiovascular diseases	6.8		6.5	0.3	0	0.003
Obesity	5.7		5.7	0	0	0.009
Kidney failure	1.4		1.4	0	0	0.193
Cancers	0.5		0.5	0	0	0.542
Respiratory diseases	6.1		6.1	0	0	0.001
Bronchitis	0.7		0.5	0.2	0	0.870
	0.2		0.2	0	0	0.816
Pulmonary emphysema						
	0.2		0.2	0	0	0.816
Respiratory allergies						
Asthma	1.0		0.9	0	0.1	0.290
Sinusitis	1.2		1.0	0	0.2	0.289
Transplantation	0.3		0.3	0	0	0.665
Splenectomy	0.5		0.5	0	0	0.542
Hypothyroidism	2.8		2.8	0	0	0.035
Hyperthyroidism	1.0		1.0	0	0	0.292
Euthyroid goiter	3.1		2.4	0.5	0.2	0.813
Prostate diseases	1.0		1.0	0	0	0.292
Liver diseases	0.7		0.7	0	0	0.442
Stroke	0		0	0	0	-
Adrenal insufficiency	0.2		0	0.2	0	0.177
Tuberculosis	0		0	0	0	-
Relationship with parenchymal involvement						
Variables (%)			%			*P*-value
Comorbidity on admission	60.5	10	14.2	28.3	8.1	0.000
Arterial hypertension	24.4	6.8	6.3	8.3	2.9	0.000
Diabetes	44.6	5.4	9.8	23.1	6.3	0.943
Cardiovascular diseases	45	16	13	15	1	0.000
Obesity	4.9	2.5	1.2	1.2	0	0.000
Kidney failure	1.3	0.7	0	0.2	0.5	0.001
Cancers	0.5	0.2	0	0.2	0.2	0.466
Respiratory diseases	5.7	2.4	0.5	2.3	0.5	0.000
Bronchitis	0.3	0	0.2	0	0.2	0.297
Pulmonary emphysema	0.4	0.2	0	0	0.2	0.149
Respiratory allergies	0.2	0	0.2	0	0	0.309
Asthma	1	0	0.5	0.5	0	0.275
Sinusitis	0.7	0	0.5	0	0.2	0.045
Transplantation	0.3	0.3	0	0	0	0.003
Splenectomy	0.5	0.3	0	0.2	0	0.042
Hypothyroidism	2.6	1.3	0.5	0.8	0	0.000
Hyperthyroidism	1	0.3	0	0.5	0.2	0.338
Euthyroid goiter	2.6	0.3	1	0.7	0.7	0.160
Prostate diseases	1	0.3	0.2	0.3	0.2	0.478
Liver diseases	0.7	0.3	0.2	0	0.2	0.080
Stroke	0.2	0	0	0.2	0	0.808
Adrenal insufficiency	0.2	0	0.2	0	0	0.309
Comorbidity on admission	60.5	10	14.2	28.3	8.1	0.000

P-values are calculated using ANOVA test.

In terms of gender, both male and female patients had the same percentage of patients presenting with multiple COVID-19-related illnesses. The number of COVID-19-related comorbidities increased, there was a correspondingly large drop in the average oxygen saturation value. Two or more comorbidities were present in 24.0% of the individuals with a $SpO_2<90$. However, neither the number nor the existence of

Table 4 — Effects of comorbidities at admission on :

			Demographic characteristics of COVID-19 patients			
Variable	Available data	% or $\bar{x}$ ± SD				
				Comorbidity		
		Total	No	Single comorbidity	More than one	*P*-value
			41.4	34.9	23.6	
Age (years)	753	63.56 ± 15.49	63.56 ± 15.49	63.56 ± 15.49	63.56 ± 15.49	0.058
Gender Male	753	56.4	125.8	18.9	11.8	0.020
Female		43.6	15.7	116.1	11.8	
Duration of hospital stay (day)	545	8.69 ± 7.43	46.2	39.8	13.9	0.095
			8.43 ± 7.06	8.53 ± 7.00	10.00 ± 9.50	
Positive SARS-CoV-2 PCR		100	46.8	43	10.3	0.383
			COVID-19's severity			
Variable	Available data			% or $\bar{x}$ ± SD		
				Any comorbidity		
		Total	No	Single	More than one	*P*-value
SpO_2 (%)	575	81.27 ± 12.35	82.76 ± 11.36	81.50 ± 13.72	78.72 ± 11.47	0.007
< 90		71.1	25.6	21.6	24	0.000
[90-94[		22.4	10.3	11	1.2	
≥ 94		6.4	3.3	2.3	0.9	
Parenchymal involvement	528	42.35 ± 21.61	43.89 ± 21.14	42.25 ± 20.92	39.97 ± 23.29	0.222
<25 Minimal		12.7	2.8	2.8	7.2	0.000
[25-50[Moderate		21.8	7.6	7.8	6.3	
[50-75[Important		50.7	22.4	20.8	7.5	
≥ 75 Critical		14.8	6.7	5.2	2.9	
			Clinical outcome			
Evolution				% or $\bar{x}$ ± SD comorbidity		
	Total = 753	No	Single comorbidity	More than one	Total = 753	*P*-value
Death	28	10.9	9.2	8	28	0.154

comorbidities seem to be associated with the extent of parenchymal involvement. In terms of the clinical result, there was a 28% (211) death rate. In patients with a single comorbidity, it was 9.2%, however for individuals that had multiple comorbidities, it was 8%, but this difference is not statistically significant (Table 4). Data regarding gender, age, SARS-CoV-PCR, parenchymal involvement and oxygen saturation were considered potential prognostic factors affecting COVID-19 in hospital survival. The Omnibus tests of model coefficients showed that the new model (with explanatory variables) is significantly better fit [$\chi^2(7) = 31.666$, $P<0.000$] than the null model. The multivariable Cox proportional hazard regression's findings revealed that a very significant overall impact was noted with the covariates single comorbidity (RC:-1.849, HR: 0.157, 95% CI: 0.081-0.308 and $P<0.000$), more than one comorbidity (RC: -1.621, HR: 0.198, 95% CI: 0.107-0.365 and $P<0.000$) and Parenchymal involvement (RC: 0.367, HR: 1.444, 95% CI: 1.012-2.060 and $P<0.043$). Non-significant effects were revealed with the covariates gender, age, SARS-CoV-PCR and oxygen saturation (Table 5). A positive regression coefficient means that there is a positive relationship between the covariate and the COVID-19 in hospital survival time. However, negative regression coefficient means that there is negative relationship between the studied covariate and the COVID-19 in hospital survival time.

The multivariate cox survival and hazard plots calculated from the mean of covariates indicates that more the COVID-19 in hospital stay is important more the proportional survival time is weak, and the proportional hazard ratio is strong. Cox survival and hazard plots of subgroup analysis by stratifying patients according to comorbidities on admission points that patients with more than one comorbidity reveal significantly substantial escalated risks of reaching to the composite endpoint compared with patients who had a single comorbidity ($P< 0.000$) and even more than those with no comorbidities

Table 5 — Multivariate Cox proportional hazards regression model

		RC	HR	95% CI	p value
Risk factors linked to COVID-19					
Age		0.041	1.041	0.921 - 1.177	0.571
Gender		0.134	1.144	0.794 - 1.647	0.471
Positive SARS-CoV-2 PCR		0.078	1.081	0.559 – 2.093	0.817
Parenchymal involvement		0.367	1.444	1.012 - 2.060	0.043
SpO2 (%)		-0.243	0.784	0.511-1.204	0.266
Comorbidities	No comorbidity	Reference	Reference	Reference	Reference
	Single comorbidity	-1.849	0.157	0.081 - 0.308	0.000
	More than one	-1.621	0.198	0.107 - 0.365	0.000
Diabetes, Arterial hypertension and cardiovascular diseases association to COVID-19					
		RC	HR	95% CI	*P*-value
Diabetes		0.420	1.522	1.019 - 2.272	0.040
Arterial hypertension		1.868	6.477	3.641–11.521	0.000
Cardiovascular diseases		-12.813	0.000	0.000-0.000	0.948

*RC: Regression Coefficient, HR : Hazard Ratio, 95% CI : Confidence Interval

($P< 0.000$) (Fig. 1). So, patients with more than one comorbidity tended to have poorer prognosis. For better comprehension of the involvement of Comorbid diseases on COVID-19 in hospital survival, the more three frequent comorbidities were analysed as categorical covariates. The model coefficient omnibus tests showed a significantly better fit [$\chi^2(8) = 42.729$, $P<0.000$] compared to the null model. The multivariable cox proportional hazard regression's results shown a very significant effect with the arterial hypertension (RC: 1.868, HR: 6.477, 95% CI: 3.641-11.521 and $P<0.000$) and diabetes (RC: 0.420, HR: 1.522, 95% CI: 1.019-2.272 and $P<0.040$). Non-significant effects were assigned with the cardiovascular diseases (Table 5).

The multivariate cox survival and hazard plots calculated from the mean of covariates confirmed the precedent finding, more the COVID-19 in hospital stay is important more the proportional survival time is weak, and the proportional hazard ratio is strong. Cox survival and hazard plots of subgroup analysis by stratifying patients according to the present of diabetes or arterial hypertension on admission indicates that patients suffering from diabetes and arterial hypertension have bad prognosis (Fig. 2).

COVID-19 pandemic attributed to the SARS-CoV-2 virus represented a significant challenge to healthcare systems at the worldwide level[13]. Numerous risk factors have been reported for COVID-19; such as gender (more likely males), older age, and pre-existing comorbidities[14]. Our data showed that 56.4% were male with men to women gender ratio of 1.29. Several research surveys highlights the disparities in COVID-19 results according on gender. Using data from China's Infectious Disease Information System through February 11, 2020, researchers examined 44,672 confirmed cases of COVID-19 and found that 51.4% of patients were males[15]. Independent of age, numerous recent investigations have shown that gender, particularly males were more at risk for severity and death after viral infection. Males to females mortality ratio was of 2.4[16]. Six countries (China, France, Germany, Iran, Italy and South Korea) have reported mortality by gender. Hence, the percentage of deaths among confirmed cases among men and women differs by more than 50% in four countries (China, Italy, France, and South Korea). Males over 50 years of age with non-communicable illnesses were at greatest danger of dying due to COVID-19 complications, according to a Wuhan observational research[17]. Furthermore, the incidence of cases was identical for males and females, according to an examination of the 1,320,488 confirmed COVID-19 cases in the United States recorded between January 22, 2020, and May 30, 2020. Of all the cases who were reported, 51.1%. Nonetheless, per 100,000, the cumulative incidence for men and women was 401.1 and 406.0 cases, respectively[18]. It has been hypothesised that men might be more vulnerable than women to contract COVID-19 due to endocrine factors such as hormones that affect inflammatory processes differently, variations in cell receptor levels (ACE2, angiotensin-converting enzyme), molecules (TMPRSS2, transmembrane protease serine 2) involved in SARS-CoV-2 entrance through virus-cell membrane fusion and lifestyle variations such as tobacco smoking[19].

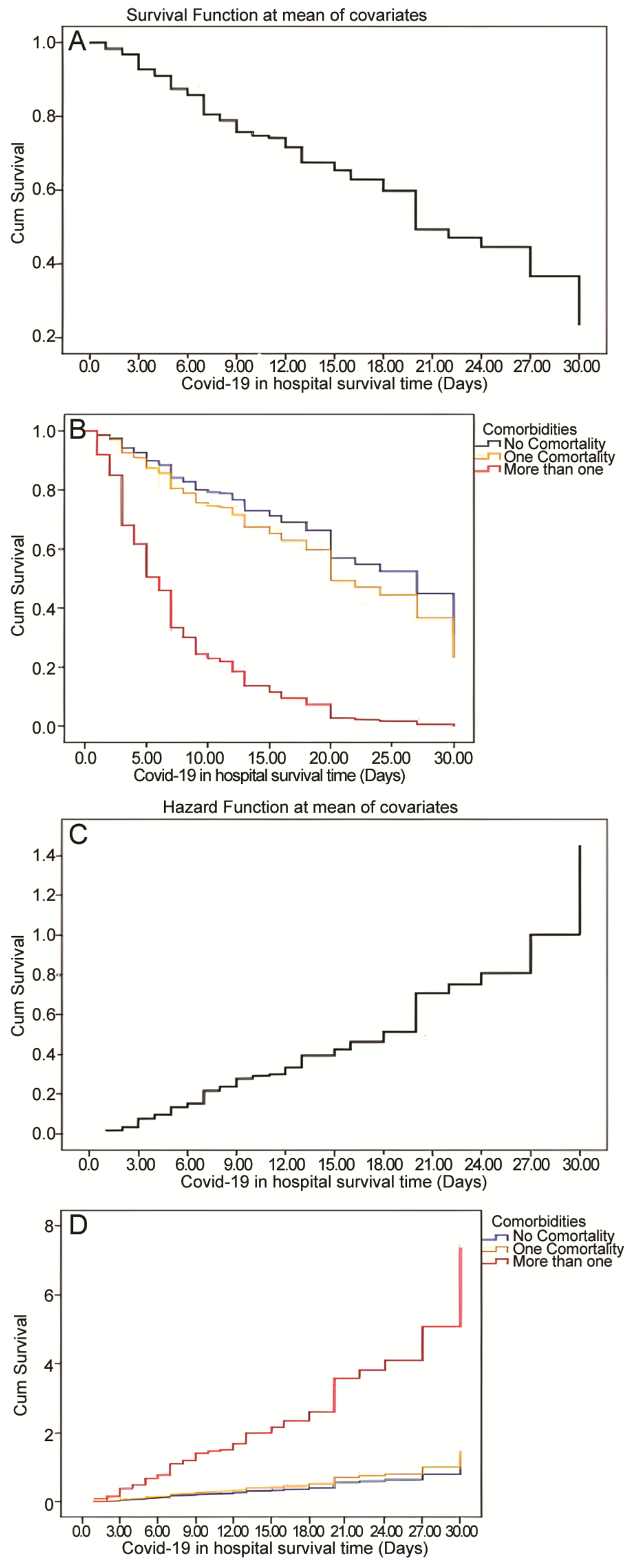

Fig. 1 — Multivariate Cox Survival and Hazard plots. A: Cox survival plot at mean of covariates, B: Cox survival plot according to comorbidities, C: Cox hazard plot at mean of covariates and D: Cox hazard plot according to commorbidities.

In the present investigation, the average age was of is 63.56 ± 15.49 years old. In addition to the high risk of contracting COVID-19, age was incriminated to have an effect on the progression of the infection and increases the mortality of patients. Previous studies found that the rate of infections that result in serious illness or death increases with age, mainly in people over 50[20]. We noted that patients whose oxygen saturation inferior to 90% were older. Furthermore, according to the parenchymal involvement, patients with more than 75% of pulmonary lesions had the highest average age i:e 69.37 ± 15.56 years. Our results concord with those reported in the literature, based on 79,394 Chinese COVID-19 patients study findings[21]. After symptoms manifestation, the fatality percentage for patients over than 59 years was approximately 5.1 times more abundant than for patients in the range of 30 to 59 years old. A higher risk of mortality might result from aging's high frequency of comorbidities and lower reserve capacity of major organs. Furthermore, elderly ought to be more predisposed to a poor prognosis and a death risk from COVID-19 infection because of weak immune system and greater SARS-CoV-2 virus loads[20].

Referring to earlier research, patients with comorbidities are more predisposed to COVID-19 because these heath conditions make them more vulnerable. It was noted that a sizable fraction of COVID-19 patients have other pathologic conditions. Circulatory and endocrine comorbidities were frequent in COVID-19 patients. SARS-CoV-2 is related to a high affinity for ACE-2 receptor, which is present in large rated not only in the lung epithelial cells, but also in the intestine, kidneys, and blood vessels. Thus, several medications used to different illnesses treatment might raise the ACE-2expression, which increase the risk of contracting SARS-CoV-2 and experiencing more serious symptoms as a result[14].

To our knowledge, our study is the first investigation that evaluates the effect of comorbidities on prognosis in COVID-19 patients in Algeria. In our research, 58.5% of patients had at the minimum a single comorbidity, and 23.6% had two at the least. The comorbidities that we observed frequently were diabetes (40.4%), hypertension (26.7%), cardiovascular diseases (6.2%), respiratory diseases (4.7%), and obesity (4.3%). As a matter of fact, our results on the frequency of comorbid illnesses in COVID-19 patients have been consistent with previous studies, but it was shown to be considerably

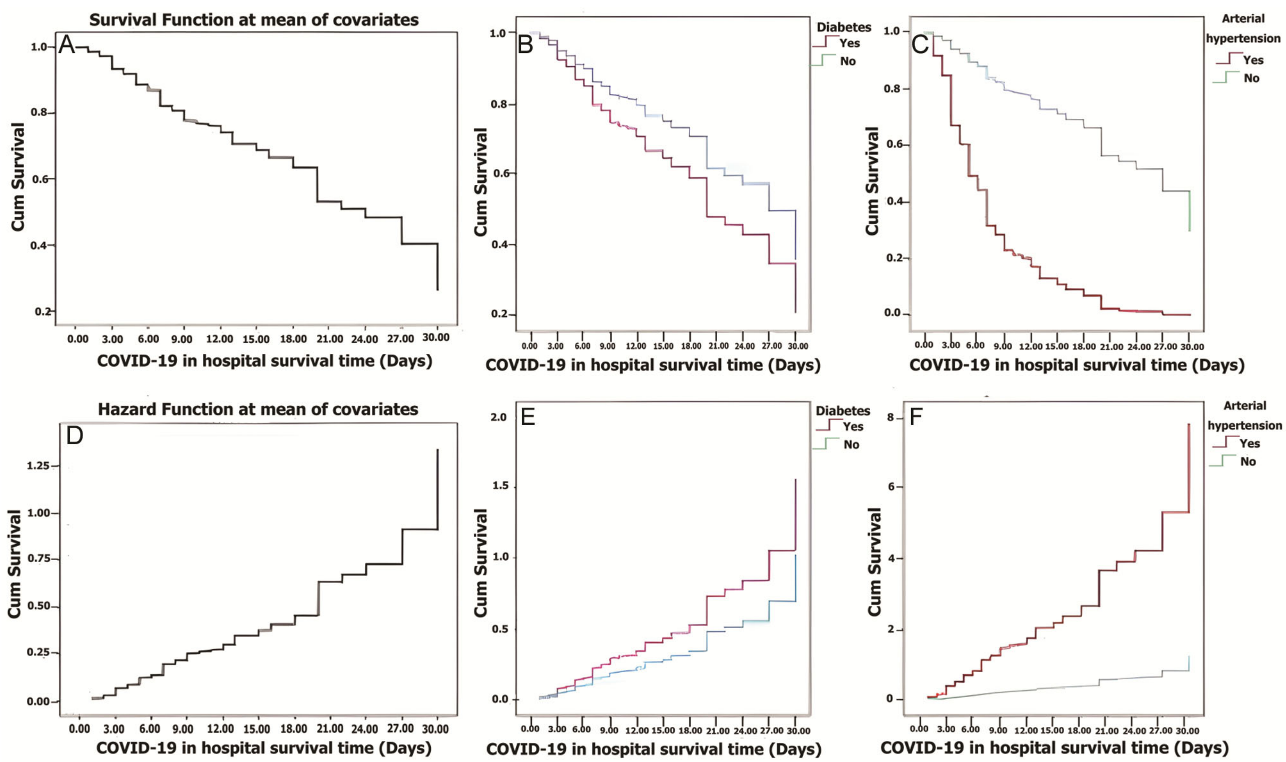

Fig. 2 — Multivariate Cox Survival and Hazard plots from the association of Diabetes and Arterial hypertension and COVID-19 in hospital survival time. A: Cox survival plot at mean of covariates, B: Cox survival plot according to comorbidities, C: Cox hazard plot at mean of covariates and D: Cox hazard plot according to commorbidities.

more prevalent than in the previous studies. Guan *et al.* observed that in the first cohort of 1590 Chinese COVID-19 patients[22], there was at the minimum one comorbidity in 25.1% of patients, and two or more in 8.2% of cases. The most prevalent comorbidities in COVID-19 patients were hypertension (16.9%), diabetes (8.2%), cardiovascular diseases (3.7%), and chronic renal disease (1.3%). However, according to Chen *et al.*[23], 51% of COVID-19 patients reported comorbidities, mainly cardiovascular or cerebrovascular diseases (40.4%), diabetes (12%), digestive system diseases (11%) and malignant tumours (0.01%).

Among our enrolled patients, diabetes was the most prevalent comorbidity. Early studies revealed that endocrine disorders, including diabetes, were common in COVID-19 individuals, despite their occurrence being less frequent than the proportion shown in the current study. Previous investigations shown that among the most frequent comorbidity is diabetes, second only to hypertension[24]. Diabetes patients might be more exposed to COVID-19 due to a set of molecular pathomechanisms. At First, diabetes was related to a reduction in T-cell function, phagocytic activity, neutrophil chemotaxis, and innate and adaptive immunity in general[25].

In addition, diabetic patients were found to have low-level of chronic systemic inflammation that leads to global cellular malfunction, which is the underlying cause of the disease's many symptoms, including a greater danger of respiratory infections. Dysregulated immunological as well as inflammatory responses are related to both of diabetes and COVID-19, while it is unclear why individuals with diabetes have more severe cases of the virus infection. Another important component of COVID-19 is the enzyme ACE2, which is essentiel for the virus's adherence and absorption into cells before replication [26]. Moreover; high glucose levels promotes SARS-CoV-2 multiplication due to the inflammation and immune system dysregulation which might complicate in fatal results. The most abundant immune cell types observed in COVID-19 patients' lungs are monocytes and macrophages, which are thought to play a major role in the pathogenicity of the illness. After infection, these cells modify their metabolism and come to be very glycolytic, which enhance the proliferation of SARS-CoV-2. The infection causes the reactive oxygen species (ROS) generation in the mitochondria, which stabilises hypoxia-inducible factor-1α (HIF-1α) and increases glycolysis. SARS-CoV-2 infection-induced alterations in monocyte metabolism due to HIF-1α directly suppress T cell response and lower epithelial cell survival [27]. lastly, it is clear that the innate immune system, such as natural killer (NK) cells are involved in the pathogenesis of Type 1 diabetes (T1D) [28]. A multivariate results regression analysis shows that NK cell activity is independently risk-dependent for the HbA1c level. NK cell activity is reduced in patients having already Type 2 diabetes (T2DM) and prediabetes in contrast to those without T2DM [29].

Disregarding endocrine diseases, we found that hypertension and cardiovascular disorders have the highest frequency, followed by diabetes, aside from endocrine diseases. Nevetheless, in numerous studies, circulatory diseases, were the furthermost common comorbidity category, despite significant changes in the rate caused by the confines of the patient handling area and the tiny sample size [22]. According to some authors, patients with pre-existing cardiovascular conditions are comparatively more vulnerable to the COVID-19 infection [30]. Besides, hypertension may be correlated with a higher risk of contracting SARS-CoV-2 infection, a worse course of COVID-19, and an increase in COVID-19-related mortality [13]. Other studies showed that patients with cardiovascular diseases are more at risk to a severe COVID-19 infection due to their ACE2 receptors overexpression. An increasing amount of data indicates worse outcomes and higher death rates for COVID-19 patients who already have cardiovascular conditions [31]. Because of the virus infection and the host's immunological response, SARS-CoV-2 infection can cause endothelial inflammation in a set of organs [32]. Even though endocrine and circulatory comorbidities were prevalent, COVID-19 patients seldom ever reported having concomitant respiratory illnesses, particularly chronic obstructive pulmonary disease (COPD). Using a meta-analysis of other surveys such as Emami *et al.* who examined the comorbidities of multiple illnesses with COVID-19 and showed that COPD was mentioned in only five studies. When compared to other prior conditions, 0.95% of COVID-19 patients had COPD, which is a very low percentage [33]. However, in our analyses a frequency of 4.7% was noted for respiratory disorders.

There are few explanations for this observation, although they could have resulted from spirometry test in community settings and a lack of information, which together led to an underdiagnosis of respiratory disorders [34]. A change in the inflammatory response, an imbalance in the microbiota, a poor immunity, continuous mucus production, a use of respiratory corticosteroids, and structural damage are all considered to be contributing factors to the beginning of COPD. Infections with MERS (13%) and SARS (1.4%) have also been connected to COPD and other chronic disorders. Even though there may not have been many COVID-19 cases with COPD in earlier research, obviously; the infection has an elevated ACE-2 receptor expression, which may have led to the appearance of severe symptoms in COVID-19 cases, including lung structural damage, weakened immunity, and excessive mucus production [24].

In our series, 4.3% of patients are obese. Nevertheless, several studies reported that, while controlling for other (metabolic) risk factors, a significant association was noted between the Body Mass Index (BMI) and Intensive care unit (ICU) hospitalisation. According to a Dutch study, the disease's severity increased considerably according to the BMI. It was revealed that 90% of SARS-CoV-2 infected patients with respiratory failure had a mean BMI of 30 kg/m2 and a BMI greater than 25 kg/m^2 [35]. Chronic systemic inflammation is tightly associated with metabolic troubles and obesity. Adipose tissue is a source of cytokines that contribute to low-grade inflammation and hypercoagulation. Additionally, obese patients diagnosis and treatment is frequently complicated by respiratory problems and overweight [36].

Consistent with other reports [37] the proportion of individuals who had cancer and renal illness was rather low. According to our study findings, individuals with coexisting diseases had a more severe infection than those without comorbidities. Moreover, a higher total of comorbid conditions was associated to a greater COVID-19 severity and higher biological parameter abnormalities. In our study, poor clinical outcomes have been associated to patients who had one comorbidity or more. Nonetheless, similarly the literature findings, exhibited lower consistency [38]. Thus, our findings showed that the age, the gender, SARS-CoV-PCR, parenchymal involvement and oxygen saturation were considered as potential prognostic factors affecting COVID-19 in-hospital survival. Our findings suggested a tight relationship between concomitant conditions and the outcome. Patients with more than one comorbidity were more likely to have poorer prognosis. Furthermore, patients suffering from diabetes and arterial hypertension have poorer prognosis. Our results suggest that both the number and the type of comorbid conditions should be considered as prognostic variables for COVID-19 patients.

Our results are concord with early research that found that the most significant factors related to a worse prognosis have been identified as male gender, advanced age, and the existence of chronic comorbidities [13]. Numerous investigations have revealed that individuals with severe COVID-19 and with an increased risk of hospitalisation and mortality are more vulnerable to have concomitant conditions, such as hypertension [39], diabetes [40], COPD [41], cardiovascular diseases [42], malignant tumors [43], cerebrovascular illnesses [44] and chronic renal disease [45].

Although methodologically challenging, determining the causal links between COVID-19 comorbidities and consequences is essential from a scientific standpoint. More specifically, a better understanding of the causal connections between clinically significant characteristics and comorbidities and the course of the disease in COVID-19 may identify novel molecular pathways and open up new gateways for the development of novel or repurposed therapeutics. Mendelian randomisation is among the major host genetics strategies that might remove confusion in these kind of interactions. To identify the molecular links between comorbidities in laboratories, host genetics, and epidemiological surveys, further efforts are required. Recognising the differences between COVID-19's three phases might help future investigations determining how comorbidities may affect different molecular pathways. Most of common comorbid diseases have an effect by defective tolerance confluence, defective resistance and decreased functional reserve and frailty's general effects [46].

This study had several limitations, as a matter of fact; the enrolled patients were only those hospitalised, hence, certain important data were missing such smoking history. As such, extrapolating these results to all COVID-19 cases is not possible. Comorbidities self-reported at the time of admission was a significant hindrance. Comorbidities that are not properly reported might have been the outcome of ignorance or a deficiency of diagnostic testing, which might have led to an underestimation of the relationship's real strength with the clinical prognosis. Underreporting comorbidity can also lead over-correlation and a poor outcome. Furthermore, due to the limited follow-up during the the hospital stay the findings were quite brief. Finally, pro-inflammatory cytokines and the early CD8+ T-cell response, which could be correlated to the disease's severity, were not assessed or taken into consideration in our paper.

Conclusion

Our research suggested that COVID-19 patients with concomitant conditions had more severe diseases than those without. Furthermore, a higher number of comorbidities was linked to an increased COVID-19 severity and higher level of aberrant biological parameters. According to our research, poor clinical outcomes have been associated to patients with a single or more comorbidities, essentially patients suffering from diabetes and arterial hypertension.

Conflict of Interest

The authors declare no conflict of interest.

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