

ANALYSIS OF RISK FACTORS FOR HOSPITALIZATION AND DEATH RELATED TO COVID-19 DURING THE FIRST TWO EPIDEMIC PEAKS IN CHILDREN AND ADULTS

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Abstract

Introduction: Clinical manifestations of Covid-19 vary widely from asymptomatic to severe forms requiring intensive care unit admission. Predictive factors of severity associated with risks of hospitalization and death warrant investigation. Objective of our study: Identify epidemiological and clinical risk factors for poor prognosis and Identify risk factors for death among hospitalized patients **Materials and Methods :** This is a descriptive longitudinal study with an analytical aim based on active surveillance of notified cases of Covid-19 with follow-up of the cohort of hospitalized patients in our University Hospital over a period of one year from March 11, 2020, to March 11, 2021. Data collection was done in real-time on a predefined data collection form. Data entry and analysis were performed using Epi Info 6 and Epi Data Analysis software. **Results:** A total of 9788 patients were notified by the epidemiology and preventive medicine service, with 6253 (63.8%) confirmed cases, of which 49% (3064/6253) were hospitalized and 51% (3192/6253) were isolated at home. We recorded 646 deaths, resulting in a hospital lethality rate of 21.08%. Nearly one-third of deaths occurred in October and December. Our study found an increased risk of severe forms and/or death among older patients and those with comorbidities, as well as among male patients with COVID-19. Mortality was significantly higher in diabetic patients (RR=1.25 [1.09 – 1.44], $p<0.001$), those with kidney disease (RR=1.45 [1.13 – 1.85], $p<0.001$), hypertension (RR=1.74 [1.51 – 2.0] $p<0.001$), respiratory diseases (RR=1.40 [1.11 – 1.77], $p<0.01$), immunosuppression (RR=1.58 [1.05 – 2.27], $p<0.01$), and cardiovascular disease (RR=1.27 [1.07 – 1.51], $p<0.001$). For pediatric cases, we observed a significantly higher risk of intensive care unit hospitalization among children with diabetes, hypertension, cardiovascular diseases, and those suffering from cancer. Clinical signs of poor prognosis with death occurrence include fever (RR=1.36 [1.16-1.60], $p<0.001$), cough (RR=1.16, 95% CI [1.01-1.34], $p<0.04$), resting dyspnea (RR=3.69, 95% CI [3.14- 4.33], $p<0.001$) in adults, and confusion in children (RR=23.8, 95% CI [8.35-67.8], $p<0.01$). **Conclusion:** Early medical management should be provided to patients with the disease, including for mild forms, especially when patients have comorbidities, to reduce hospital mortality. Rigorous follow-up is necessary for patients isolated at home to detect any deterioration in their health status early on. It would be interesting to adjust risk factors, particularly age in relation to comorbidities, and even the time to initiation of treatment.

Index Terms: Risk Factors, Deaths, Hospitalized Patients, COVID-19, Adults, Children, Poor Prognostic Signs.

I. INTRODUCTION

Like many other countries, Algeria has faced an unprecedented epidemiological situation. The first confirmed case of Covid-19 was reported on February 25, 2020 (an Italian national). On March 11, we recorded the first death on a national scale at our University Hospital Center (UHC), which also marked the declaration of the pandemic by the WHO¹.

COVID-19, an emerging disease, clinically manifests with a wide inter-individual variability ranging from asymptomatic to severe forms requiring intensive care admission². Although many patients fully recover, several factors contribute to an unfavorable prognosis. Various studies have attempted to identify predictive factors of mortality and progression to severe forms of Covid-19 among diagnosed patients^{3,4}.

Some of these factors can be taken into account in decisions regarding the management of virus-infected patients. A meta-analysis⁵, covering 207 studies, identified prognosis-related factors in patients infected with COVID-19. They were classified into several categories, including sociodemographic characteristics, personal medical history, clinical manifestations and symptoms, biological parameters, and results of radiological examinations.

The ability to predict the severity of the disease and/or its unfavorable progression can help identify patients at risk of complications, optimizing the management of available resources and capacities, especially in critical care. This approach also identifies both modifiable and non-modifiable factors influencing the prognosis of infection for each patient.

The objective of our work is to identify epidemiological and clinical risk factors for poor prognosis and risk factors for death among hospitalized children and adults. Types of Study

II. MATERIAL AND METHODS

This is a descriptive longitudinal study with an analytical purpose based on active case surveillance and follow-up of patients hospitalized for Covid-19 in our University Hospital Center (UHC).

Study Population

The study population includes patients presenting for suspicion of Covid-19 during the first two epidemic peaks of 2020, whether confined at home or hospitalized in services dedicated to managing this pathology: Gastroenterology, Allergology Pneumology, Pulmonophysiology, Respiratory Functional Exploration, Internal Medicine, Medical-Surgical Emergency, Obstetric Gynecology, Cardiology, Endocrinology, Pediatrics Services A and B, Nephrology, Medical Intensive Care Unit, Hematology. Patients who died upon arrival at the hospital and were captured at the forensic medicine department are also part of this study.

Data collection was done in real-time on the given day by epidemiologists from our department, manually and using a pre-established data collection form.

For diagnostic criteria, we relied on the detection of viral genetic material (SARS-CoV-2 RNA) using the Reverse Transcription Polymerase Chain Reaction (RT-PCR) technique, rapid antigen tests (RATs) which detect the presence of SARS-CoV-2 virus proteins, and we also considered serological tests that detect specific antibodies to SARS-CoV-2.

All biological assessments (CBC, CRP, AST/ALT, LDH, D-dimers, Ferritin, blood glucose, and blood ionograms) were performed at the central laboratory, and for serological tests, they were conducted at the immunology laboratory.

For medical imaging, we considered chest radiography and non-contrast chest computed tomography, which emerged as the first-line examination for suspected cases with respiratory symptoms while waiting for RT-PCR test results or when RT-PCR test results are negative or unavailable.

Statistical analysis

After data validation, their entry and analysis were conducted using Epi Info 6 and Epidata Analysis software. Appropriate statistical tests according to sample sizes and the nature of variables were calculated. An analysis plan was established using Pearson's chi-square test, Yates' corrected chi-square test with a significance threshold set at 5%.

For comparing two means, an ANOVA test was utilized for normally distributed data with homogeneous variances at a 95% confidence level. When variances significantly differed (Bartlett's test of homogeneity of variances), a non-parametric test rather than ANOVA was employed (Mann-Whitney test or Wilcoxon test).

To estimate the strength of association between the risk factor and disease frequency, a crude relative risk (RR) was calculated for qualitative variables with two classes (dichotomous) along with their 95% confidence interval.

III.RESULT

A total of 9,788 patients were captured by the epidemiology and preventive medicine service regarding the epidemiological context and/or clinical aspects. Among them, 570 (5.8%) were children aged between 0 and 16 years old. 6,253 were confirmed cases, accounting for 63.8%, of which 49% (3,064/6,253) were hospitalized and 51% (3,192/6,253) were home-confined. The mean age of the consultants was 47.09 ± 20.61 years (min 1 - max 99). The sex ratio was 0.98 (49.4% were male (4,769/9,788) and 50.6% were female (5,022/9,788)). 52.7% of the recorded consultants had no medical history, 19.9% were over 65 years old, 25.6% (2,610/9,788) had hypertension, 18.7% (1,830/9,788) had diabetes, 8.5% had cardiovascular diseases (832/9,788), and 5.6% had respiratory pathologies (548/9,788).

Among the 3,064 hospitalized patients, 146 (4.76%) were children. 42.10% (1,290/3,064) underwent PCR testing, which returned positive in 53.64% (692/1,290) of cases. 81.46%

(2,496) underwent a TDM examination with findings in favor, and 18.4% (628/3,456) underwent serological testing, which returned positive in 67.7% (407/601) of cases.

Table 1: Distribution of comorbidities among patients affected by Covid-19

	Adults (N=5904)			Children (N=349)		
	Hospitalized 2918	Confined 2986	p-value	Hospitalized 146	Confined 203	p-value
Gender: Male	49.2%	47.9%	NSD	46.6%	43%	NSD
Female	51.06%	52.1%		53.4%	57%	
Sex-ratio	1.29	0.9	-	0.87	1.03	-
Average Age	58.68+/- 22.09	47.50+/- 21.26	<0.01	7.57+/- 4.14	8.48+/- 4.49	NSD
Age > 65 years	46%	9.27%	<0.01	-	-	-
Arterial hypertension	44.65%	25.1%	<0.001	16.4%	5.8%	<0.01
Diabetes	35.9%	17.6%	<0.001	16.4%	5.2%	<0.01
Cardiovascular diseases	15.4%	9%	<0.001	6.2%	2.3%	<0.01
Respiratory diseases	6.4%	5.9%	NSD	5.5%	4.7%	NSD
Kidney diseases	5.3%	2.8%	NSD	4.1%	1.2%	NSD
Obesity	2.7%	3.4	NSD	4.1%	4.7%	NSD
Cancer	3.5%	3.01%	NSD	18.5%	2.46%	<0.001

Non-Significant Difference: NSD

Table 2: Clinical Signs of Patients Hospitalized for Covid-19

	Hospitalized Adults N=(2918)	Children Hospitalized (N=146)	p-value
Fever	65.3%	74%	<0.03
Cough	54.2%	52.7%	NSD
Fatigue	66.6%	61.7%	NSD
Headache	16.9%	22.6%	NSD
Resting dyspnea	45.44% (1326)	21.23% 31	<0.01
Muscle pain	11.7%	19.2%	<0.01
Anosmia (loss of smell)	7.3%	8.2%	NSD
Ageusia (loss of taste)	6.7%	3.4%	NSD
Nausea	5.6%	9.6%	<0.05
Headache	13%	18.5%	NSD
Resting dyspnea	1.6%	6.8%	<0.001

Children exhibited certain symptoms, such as fever (74% versus 65.3% in adults, $p < 0.03$), muscle pain (19.2% versus 11.7%, $p < 0.01$), nausea (9.6% versus 5.6%, $p < 0.05$), and confusion (6.8% versus 1.6%, $p < 0.001$), which are significantly less common in adults, with a significant difference. However, dyspnea was significantly more pronounced

in adults, while cough, fatigue, and ageusia were slightly more marked in adults but without significant difference.

Table 3: Risk factors for death among hospitalized adults and children with COVID-19

	N=(2918)				(N=146)			
	Recovered Discharged (2283)	Deceased (635)	P value	Relative Risk and 95% Confidence Interval	Recovered Discharged (135)	Deceased (11)	P value	Relative Risk and 95% Confidence Interval
Gender: Male	59.2%	65.1%		1.22	48.1 %	27.3%	NSD	
Female	40.7%	34.8%	< 0.01	[1.06-1.41]	51.9%	72.7%		
Sex-ratio	1.45	1.87		-	0.9	0.3		-
Average Age	57.6± 20.2	67.41± 17.36	< 0.01		7.44±4.43	9.09±3.88		
Age > 65 years	37.7%	66.3%	< 0.01	2.52 [2.17-2.92]	-	-		-
Age ≥ 10 years	-	-		-	85,7%	14,3%	<0.01	4.29 [1.2-15.4]
< 10 years	-	-		-	96,67%	3,33%		
Arterial hypertension	40.08 %	58.4%	< 0.01	1.74 [1.51- 2]	16.29% 22	18.18%	NSD	-
Diabetes	34.42%	41.2%	< 0.01	1.25 [1.09-1.44]	5.9% 8	9%	NSD	-
Cardiovascular diseases	14.45%	18.7%	< 0.01	1.27 [1.07-1.51]	5.18% 7	9%	NSD	-
Respiratory pathologies	5.8%	8.8%	< 0.01	1.4 [1.11- 1.77]	5.18% 7	9%	NSD	-
Renal pathology	4.73%	7.55%	< 0.01	1.45 [1.13-1.85]	2.9 % 5	18.18	NSD	-
Immunosuppression	1.57%	2.83%	< 0.01	1.55 [1.05-2.27]	5.9 %	18,8 %	NSD	-
Obesity	2.58%	3.3%	DNS	-	3.7% 5	9%	NSD	-
Cancer	2.6%	1.4%	DNS	-	14.1 % 19	81,81%	< 0.01	18.96 [18.9-82.9]
Smoking	2.2%	1.57%	DNS	-	-	-		

Table 4: Clinical Signs of Poor Prognosis in Adults and Children

	Hospitalized Adults N=(2918)				Children Hospitalized (N=146)			
	Recovered Discharged (2283)	Deceased (635)	p Value	Relative Risk and 95% Confidence Interval	Recovered Discharged 135	Deceased 11	p Value	Relative Risk and 95% Confidence Interval
Resting dyspnea	37.14 (848)	75.27 (478)	<0.001	3.66 [3.10-4.31]	14.07 (19)	18.18 (2)	NSD	1.40 [0.33-6.01]
Fever	65.48 (1495)	73.7 (468)	<0.01	1.36 [1.16-1.60]	72.6 (98)	90.9 (10)	NSD	3.52 [0.47-6.58]
Cough	53.96 (1232)	58.26 (370)	<0.01	1.15 [1.15-1.32]	51.11 (69)	72.72 (8)	NSD	2.39 [0.66-865]
Confusion	1.92 (40)	0.47 (7)	NSD	0.68 [0.34-1.35]	0.74 (3)	81.81 (7)	<0.01	23.8 [8.35-67.8]

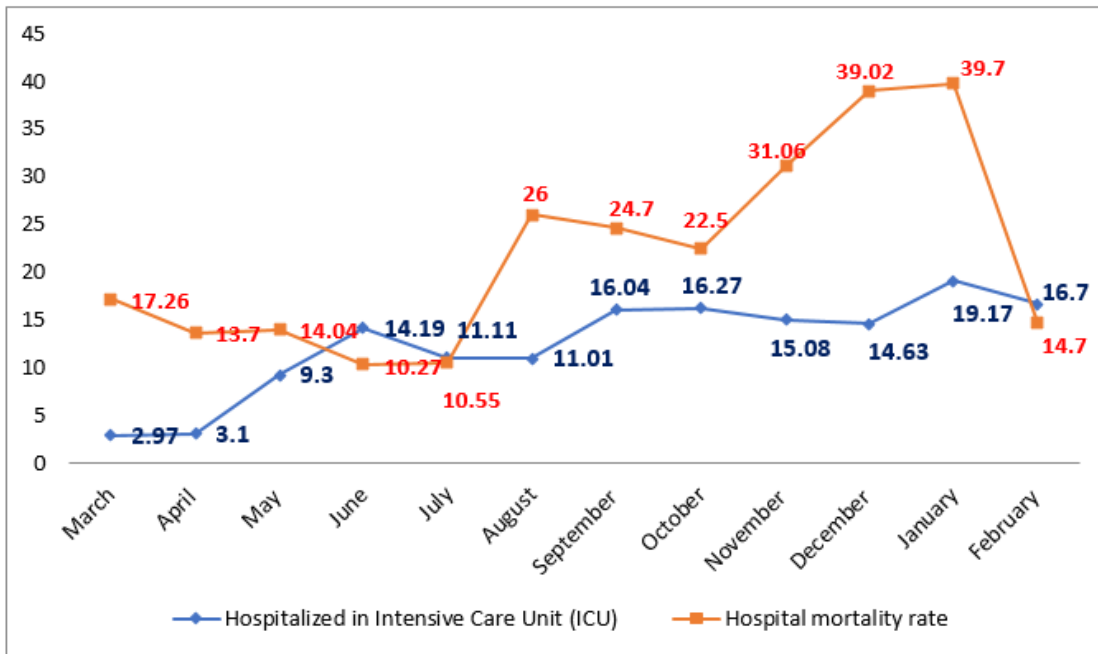


Figure 1: Monthly Evolution of the Intensive Care Unit (ICU) Hospitalization Rate and Hospital Mortality Rate

IV. DISCUSSION

During the first two epidemic peaks of 2020, 9788 individuals consulted for suspected Covid-19 within our University Hospital Center (CHU), of whom 6253 were confirmed cases. The disease presents as a common upper respiratory tract infection, with symptoms including fatigue (65.2%), fever (60.2%), cough (59.6%), headache (27.4%), and muscle pain (19%), making it clinically indistinguishable from other viral infections. In rare cases, the initial presentation may be dominated or limited to digestive symptoms such as diarrhea (17.4%) and nausea (7.4%). Anomalies in taste and smell, ranging from mild disturbances to complete anosmia and/or ageusia, were observed in 15.5% and 11.15% of cases, respectively.

Pediatric cases represented 5.58% (349/6253) compared to 94.41% (5904/6253) for adult cases, a figure similar to that reported in the European region (4%)⁶, but slightly higher than rates documented in China⁷ and Italy⁸, which ranged between 1 and 2%. This low proportion may be due to the lower likelihood of children being tested and the closure of schools (completely during the first epidemic wave and partially during the second wave), but also to a higher proportion of asymptomatic, paucisymptomatic, or atypical clinical presentations^{9,10,11}.

The elderly population has been heavily impacted by the Covid-19 epidemic. According to Izcovich A., et al., the risk of hospitalization or death following infection with this virus increases significantly with age. It has been reported that the risk of hospitalization

doubles in the 60-64 age group, triples in the 70-74 age group, increases sixfold in the 80-84 age group, and increases twelvefold in patients over 90 years old¹². Similar results were reported by D. PAITRAUD¹³, who found a more than two-fold risk of hospitalization in the 60-64 age group (HR 2.29; 95% CI 2.20 - 2.39) and nearly tripled risk in the 70-74 age group (HR 2.99; 95% CI 2.88 - 3.12). In our study, the risk of hospitalization for COVID-19 is nearly twofold in the 60-64 age group (RR= 1.89, CI [1.75 – 2.04], $p < 0.001$), and slightly higher than twofold in those over 65 years old (RR= 2.25; 95% CI [2.15 – 2.36]).

The proportion of pediatric cases hospitalized was 5% (146/3064) compared to the total number of hospitalized cases during the first two waves. A review of the literature has shown that children hospitalized with Covid-19 accounted for between 1.2% and 5% of cases^{14, 15}, which is consistent with our results. The risk of death was significantly higher in older children (>10 years old) with a RR=4.29 (95% CI [1.2-15.4], $p < 0.01$).

Several authors^{16, 17 18, 19, 20} have reported an increased vulnerability of males to Covid-19 compared to females. Regarding the risk of hospitalization, Semenzato *et al.*¹² reported an increased risk of 1.4 times in males, although our study did not identify this risk. However, concerning fatal outcomes, Semenzato¹² reported a 2.1 times higher risk in males, while in our study, the risk of death was slightly higher than one (RR=1.22, 95% CI [1.06 - 1.41], $p < 0.001$).

Comorbidities play a major prognostic role in the risk of developing severe Covid-19 infection, with patients suffering from hypertension, diabetes, or cardiovascular diseases having an increased risk of hospitalization in both adults and children. These findings are in line with the results of the cohort study conducted by D. PAITRAUD¹³, as well as with other similar studies conducted in adults^{21, 22, 23, 24}. Additionally, Sun YK. *et al.*²⁵ also observed a trend towards more frequent hospitalization in children with comorbidities.

The ability to predict disease severity and/or adverse outcomes could help identify patients at risk of complications and fatal outcomes²⁶. Izcovich A⁵ in his meta-analysis identified factors predicting mortality with a high level of evidence, including age, smoking, cerebrovascular diseases, chronic obstructive pulmonary disease (COPD), chronic kidney diseases, cardiac arrhythmias, hypertension, diabetes, and cancer.

In our study, the risk of death was significantly higher for certain comorbidities in adults. These include diabetes with a risk of 1.25 (95% CI [1.09-1.44], $p < 0.001$), cardiovascular diseases (RR=1.27, 95% CI [1.07-1.51], $p < 0.001$), renal pathologies (RR=1.45, 95% CI [1.13-1.85], $p < 0.01$), hypertension (RR=1.74, [1.51- 2], $p < 0.001$), respiratory pathologies (RR=1.4, 95% CI [1.11- 1.77], $p < 0.01$), and immunosuppression with a RR=1.55 (95% CI [1.05-2.27], $p < 0.01$).

In a meta-analysis, Mr. Biswas²⁷ found an elevated risk of death for arterial hypertension (RR 1.95: 95% CI 1.58–2.40; $p < 0.001$), diabetes (RR 1.97: 95% CI 1.48–2.64; $p < 0.00001$), respiratory diseases (RR 2.74: 95% CI 2.04–3.67; $p < 0.00001$), cardiovascular diseases (RR 3.05: 95% CI 2.20–4.25; $p < 0.00001$), and renal pathologies

(RR 4.90: 95% CI 3.04–7.88; $p < 0.00001$). Regarding cancer, this factor was found to be significantly associated with fatal outcomes in children. Patients affected had an increased risk of death (RR=18.96, 95% CI [18.96-82.9] < 0.001).

Moreover, we did not find a significant association between smoking and fatal outcomes, nor for obesity, paradoxically contrary to results put forward by several authors^{13, 28}.

Regarding clinical manifestations, they vary according to different databases²⁹, but there are still cases of severe manifestations^{30, 31}. Among the signs associated with poor prognosis, in adults, resting dyspnea (RR=3.66, 95% CI [3.10-4.31], $p < 0.001$), fever (RR=1.36, 95% CI [1.16-1.60], $p < 0.01$), and cough with a risk of 1.16 (95% CI: [1.15-1.32], $p < 0.01$) were observed, while in children, confusion presented a higher risk (RR= 23.8, 95% CI [8.35-67.8], $p < 0.01$). These results are consistent with those of Wynants³ and Izcovich A.⁵, who also found similar conclusions.

Regarding biological manifestations, an increase in CRP was observed with an average maximum value of 148.23 ± 75.16 mg/L. Although results from studies in the literature vary regarding the predictive value of CRP, some studies^{32,33, 34} have found higher levels of CRP in patients who died from Covid-19 compared to those who survived, suggesting that elevated CRP levels could be indicators of Covid-19 mortality. These findings are consistent with the results observed in our cohort of deceased patients, who showed an increase in CRP in 85% of cases. Lymphopenia was also more pronounced in patients who died from Covid-19 than in those who survived, suggesting that the severity of lymphopenia could also be a predictive indicator of Covid-19 mortality. Similar results have been observed by other authors^{32, 34, 35}.

The two most relevant indicators for monitoring the evolution of the epidemic in hospitals are the rate of admission to intensive care units and hospital lethality. Examination of the frequency of patients admitted to intensive care units reveals three peaks, but the first peak observed in June coincides with a period when moderate cases were hospitalized for short durations. The second peak occurs in October, with respective rates of 16.27%, while the third peak is observed in January, with an intensive care unit admission rate of 19.17%.

Regarding deaths from Covid-19, out of 3064 hospitalized cases, two peaks were identified: the first in August, with a rate of 26% (59 deaths out of 225 hospitalized cases), and the second during the December to January period, with respective rates of 39.02% (80/205) and 39.7% (58/146), highlighting the severity of the second wave. The same peaks were also observed in the Wilaya of Oran³⁶.

Indeed, the comparison of the two periods reveals significantly longer delays in seeking care (8.62 days ± 5.27 in December-January versus 6.73 days ± 7.6 in June) due to the biphasic course of the disease, characterized by an initial moderate phase followed by worsening symptoms and the onset of dyspnea towards the end of the first week, when patients with severe forms are hospitalized, often during the cytokine storm.

The lethality rate within our group of children was slightly elevated, standing at 3.1% (11 out of 347), compared to figures available in the literature³⁷. However, it is likely that this rate would have been much lower, as many children with benign illnesses may not have sought medical attention and therefore were not included in this study.

V. CONCLUSION

Early medical management should be provided to patients with the disease, including those with mild forms, especially when patients have comorbidities, in order to reduce hospital lethality. Rigorous follow-up should be ensured for patients confined at home to detect any deterioration in their health status early on. Identifying predictive clinical and epidemiological factors of severity (hospitalization, death) allows for the identification of patients at highest risk of developing complicated forms requiring early medical management to reduce hospital lethality.

However, due to missing data for certain biological parameters and potential biases, we were unable to identify other factors demonstrated at this stage. It would be interesting to adjust risk factors, especially age in relation to comorbidities, and even the time to seek care, and to continue research to identify risk factors for developing severe forms or mortality from Covid-19.

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