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Short communication

Evolution of baseline characteristics and severe outcomes in COVID-19 inpatients during the first and second waves in Northeastern France



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ABSTRACT

Objectives: Two COVID-19 epidemic waves occurred in France in 2020. This single-center retrospective study compared patients' characteristics and outcomes.

Patients and methods: We included all patients with confirmed COVID-19 admitted to Colmar Hospital in March ($n = 600$) and October/November ($n = 205$) 2020.

Results: Median ages, sex ratio, body mass index, and number of comorbidities were similar in wave 1 and 2 patients. Significant differences were found for temperature (38°C vs. 37.2), need for oxygen (38.6% vs. 26.8%), high-flow cannula (0% vs. 8.3%), and steroid use (6.3% vs. 54.1%). Intensive care unit (ICU) hospitalizations (25.5% vs. 15.1% , OR: 0.44 , 95% CI [0.28 ; 0.68], $P = 0.002$) and deaths (19.2% vs. 12.7% , OR: 0.61 , 95% CI [0.37 ; 0.98], $P = 0.04$) decreased during the second wave. Except for cardiovascular events (5.5% vs. 10.2%), no change was observed in extrapulmonary events.

Conclusions: Deaths and ICU hospitalizations were significantly reduced during the second epidemic wave.

1. Introduction

COVID-19 is a polymorphic disease that mainly affects the respiratory tract [1]. However, extrapulmonary complications are frequently reported [2,3]. A major COVID-19 outbreak occurred in the spring of 2020 beginning in Northeastern France. The Hôpitaux Civils de Colmar (HCC) was one of the most affected hospitals during the first wave, with a large number of hospitalizations for COVID-19 in March 2020 [3]. The implementation of a national lockdown from March 17 to May 10 resulted in a lower trans-

mission rate until the end of July. However, in autumn, a new steady rise was observed, followed by a rapid increase in the spread of SARS-CoV-2, including in Northeastern France. This new wave prompted another countrywide lockdown on October 30 [4]. In-between these two epidemic waves, therapy for COVID-19 evolved with the extensive use of remdesivir, corticosteroids [5], cessation of hydroxychloroquine and lopinavir treatment [6], use of convalescent plasma [7], and enhanced high-flow nasal oxygen therapy [8]. We present the results of a single-center retrospective analysis of all patients hospitalized in the HCC with laboratory-confirmed COVID-19 at the beginning of each epidemic wave, in March (wave 1) and October/November (wave 2) 2020. Differences in baseline characteristics, deaths, ICU hospitalizations, and extrapulmonary complications were assessed.

2. Study design

We retrospectively analyzed the data of all consecutive patients with COVID-19 hospitalized in the HCC from March 1 to March 31, 2020 and from October 1 to November 31, 2020. COVID-19 was confirmed by a positive nucleic acid amplification for SARS-CoV-2. Patients with healthcare-associated COVID-19, which was defined by a negative PCR test upon admission and a positive PCR test 48 hours after admission, were excluded.

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2.1. Data collection and endpoints

We retrospectively collected all data from the computer-based patient records (Crystal Link®) as previously described [3].

2.2. Statistical analysis

Continuous variables were compared using the Wilcoxon rank sum test and categorical data were compared using Fisher's exact test. Death rate curves with 95% confidence intervals (CI) were determined using the nonparametric Kaplan–Meier method. Odds ratio (OR) were determined for deaths and ICU hospitalization (SAS 9.4 software).

3. Results

3.1. Baseline characteristics

A total of 600 patients were hospitalized at the HCC for COVID-19 during wave 1. During wave 2, 247 inpatients were diagnosed with COVID-19. We identified 42 cases (17%) of healthcare-associated COVID-19 in wave 2 patients. These patients were excluded from the analyses. Thus, 205 patients were included in the analysis for wave 2. Table 1 summarizes the patients' main clinical characteristics at baseline (wave 1 vs. wave 2) and treatments during hospitalization.

Several baseline biological results at admission were significantly different, including lymphocyte counts (0.75 vs. 0.83 G/L, $P=0.04$), ASAT (42 vs. 33 IU/L, $P<0.001$), LDH (326 vs. 259 IU/L, $P<0.001$), CRP (75.0 vs. 49.5 mg/L, $P<0.001$), and calcium (2.10 vs. 2.20 mmol/L, $P<0.001$).

3.2. ICU hospitalization

A total of 153 (25.5%) patients required ICU hospitalization in wave 1 vs. 31 (15.1%) patients in wave 2 (OR [wave 2 vs. wave 1] 0.44, 95% CI [0.28; 0.68], $P=0.002$). Sixteen (10.5%) ICU patients were hospitalized directly or from the emergency department during wave 1 and 14 (43.7%) during wave 2, the remaining patients being transferred from medical departments. The median ages of ICU patients were 68.7 vs. 66.6 years (NS), 71.2% vs. 58.1% (NS) were males, median body mass indexes (BMIs) were 28.0 vs. 29.4 kg/m² (NS), and 81.7% vs. 87.1% (NS) had at least one high-risk condition in waves 1 and 2, respectively. When comparing ICU patients in wave 1 vs. wave 2, the only statistical difference between the two groups was symptom duration at admission (7 days vs. 5 days, $P=0.02$). High-flow nasal cannulas were used exclusively during the second wave in 17 out of the 31 ICU patients (54.8%).

3.3. Deaths

During wave 1, a total of 115 patients (19.1%) died, of whom 44 (38.3%) were hospitalized in the ICU. During wave 2, 26 (12.7%) patients died (OR [wave 2 vs. wave 1] 0.61, 95% CI [0.37; 0.98], $P=0.018$) of whom 10 (32.2%) were hospitalized in the ICU (Fig. 1). Among the patients who died (wave 1 vs. wave 2), the median age was 79.9 vs. 80.1 years (NS), 64.3% were males vs. 61.5% (NS), median BMI was 27.5 vs. 24.2 kg/m² (NS), and 94.8% vs. 100% (NS) had at least one high-risk condition. The differences between deceased patients (wave 1 vs. wave 2) were preexisting chronic renal diseases (17.4% vs. 38.5%, $P=0.03$), cancer (27.8% vs. 53.8%, $P=0.02$), and body temperature at baseline (38 vs. 37.25, $P=0.04$).

3.4. Extrapulmonary complications

Table 2 shows the extrapulmonary events that occurred during wave 1 vs. wave 2.

4. Discussion

In this large single-center retrospective cohort study of patients hospitalized with laboratory-confirmed COVID-19 in France, we described the differences between patients hospitalized during wave 1 (March) and wave 2 (October/November). Baseline characteristics of hospitalized patients during the two waves did not differ in terms of age, sex ratio, BMI, and total comorbidities known to be high-risk conditions for severe COVID-19 [9], although patients of the second wave more frequently had chronic renal diseases, liver diseases, and cancer at baseline. These discrepancies may be related to our hospital being nearly exclusively dedicated to COVID-19 activities during wave 1 in opposition to wave 2, which was less overwhelming and when normal activities were carried out in parallel to the COVID-19 activities. With better access for non-COVID-19 patients, better knowledge of the risk factors for poor outcome, and a known effective treatment (corticosteroids), we may therefore hypothesize that patients with the highest risk factors were more prompt to consult and be hospitalized either directly or via their family physicians in the COVID-19 departments. This may also partly explain why patients during the second wave were hospitalized earlier after COVID-19 symptom onset though the result was not statistically significant. These earlier hospitalizations were not associated with healthcare-associated COVID-19, which is usually diagnosed sooner, as we chose to exclude healthcare-associated COVID-19 cases defined by a negative PCR test upon admission and a positive PCR test 48 hours after admission. We could not precisely define healthcare-associated COVID-19 with this definition in March 2020 as PCR tests upon admission were not performed at that time. However, with a definition based on a positive PCR test after 72 hours without symptoms evocative of COVID-19 at baseline, we only found 19 (3.2%) possible cases of healthcare-associated COVID-19 in March.

Wave 2 patients appeared to have less serious symptoms, as highlighted by lower body temperature, lower oxygen requirements, lower CRP and LDH levels, and higher lymphocyte counts at baseline [10–14]. One of the main results of our analysis is the reduction in both ICU stays and death rate during wave 2 vs. wave 1. Various factors may have contributed to this reduction in COVID-19 mortality. Hospitalization of patients at an early stage and thus, in a less serious condition allowed for a prompt and adaptive treatment. Among these treatments, corticosteroids are known to reduce mortality [5] and were used more widely during the second wave. During the first wave, corticosteroids were mostly used in late March and with more stringent criteria for more serious patients [15]. Remdesivir was also used more frequently in our department during the second wave, especially in case of early diagnosis, corresponding to the virological phase. Use at this time was not limited to clinical trials after the WHO Solidarity trial results [6]. As per the French guidelines, lopinavir and hydroxychloroquine were deemed non-effective and potentially toxic treatments; their use was stopped during the summer. In this study, we did not evaluate thromboprophylaxis as these therapeutics were already widely used during both waves. Non-invasive oxygen therapy with high-flow nasal cannulas was much more frequently used in the ICU during the second wave (54% of ICU patients), avoiding the use of frequently unnecessary invasive mechanical respiratory assistance and longer stays in the ICU, as highlighted by previous studies [8]. Another key element that contributed to improve survival was the differences in intensities between the two waves. During the

Table 1
Patient baseline characteristics and treatments during wave 1 and 2.

	First wave (n = 600)	Second wave (n = 205)	P-value
Gender (male)	346 (57.7%)	118 (57.6%)	1.000 ^c
Age (years)			
Median [Q1, Q3] ^a	71.09 [60.9; 81.3]	71.98 [57.6; 80.6]	0.326 ^b
BMI (kg/m ²)			
Median [Q1, Q3] ^a	26.90 [23.8; 31.0]	26.30 [22.9; 30.1]	0.182 ^b
Risk factor(s)	518 (86.3%)	173 (84.4%)	0.488 ^c
Chronic renal disease	48 (8.0%)	30 (14.6%)	0.009 ^c
Chronic liver disease	6 (1.0%)	8 (3.9%)	0.012 ^c
Chronic cardiovascular disease	399 (66.5%)	124 (60.5%)	0.127 ^c
Chronic pulmonary disease	125 (20.8%)	44 (21.5%)	0.843 ^c
Diabetes	156 (26.0%)	58 (28.3%)	0.523 ^c
Cancer	109 (18.2%)	50 (24.4%)	0.067 ^c
Missing	36	39	1.000 ^c
Progressive	28 (38.4%)	4 (36.4%)	
Remission	45 (61.6%)	7 (63.6%)	
Immunodeficiency	9 (1.5%)	–	0.122 ^c
Pregnancy	2 (0.3%)	–	1.000 ^c
Neurological disorders	96 (16.0%)	48 (23.4%)	0.020 ^c
Symptom duration (days)			
Median [Q1, Q3] ^a	7.0 [3; 9]	5.0 [2; 9]	0.152 ^b
Body temperature (°C)			
Median [Q1, Q3] ^a	38.00 [37.1; 38.6]	37.20 [36.6; 38.0]	<0.001 ^b
Ventilation			
Missing	33	11	0.003 ^c
Spontaneous ambient air	348 (61.4%)	142 (73.2%)	
Spontaneous O ₂	219 (38.6%)	52 (26.8%)	
O ₂ flow (L/min)			
Median [Q1, Q3] ^a	5.0 [3; 9]	4.0 [3; 6]	0.249 ^b
Length of stay (days)			
Missing	6	0	
Median [Q1, Q3] ^a	8 [4; 14]	7 [3; 13]	0.19 ^b
Treatment			
Corticosteroids	38 (6.3%)	111 (54.1%)	<0.001 ^c
Remdesivir	2 (0.3%)	10 (4.8%)	<0.001 ^c
Convalescent plasma	0	2 (0.9%)	0.06 ^c
High-flow cannula oxygen	0	17 (8.3%)	<0.001 ^c
Lopinavir	11 (1.8%)	0	0.08 ^c
Hydroxychloroquine	57 (9.5%)	1 (0.5%)	<0.001 ^c

BMI: body mass index.

^a Results for continuous variables are shown as median, first and third quartiles [Q1, Q3].

^b Wilcoxon rank sum test.

^c Fisher's exact test.

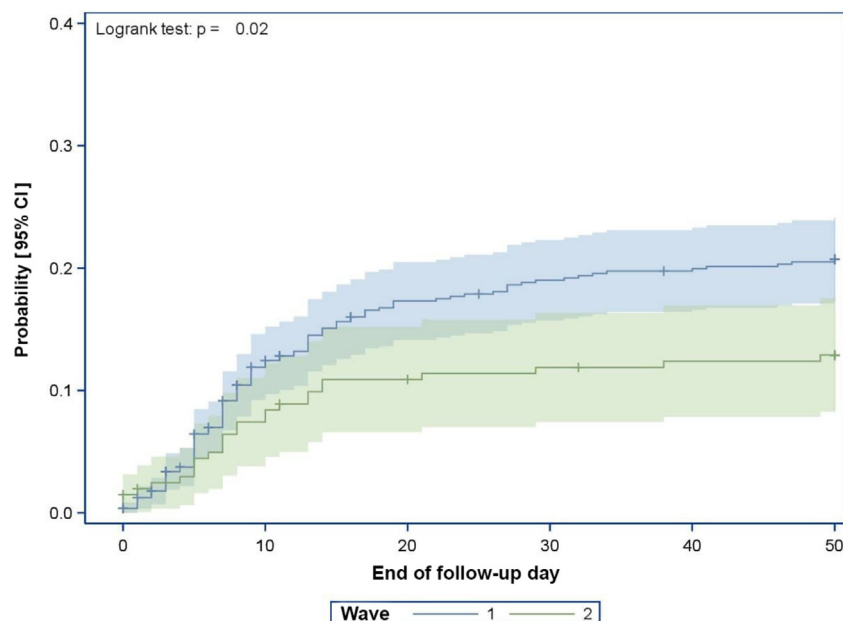


Fig. 1. Death rate curves. Kaplan–Meier product limit estimates with two-sided 95% confidence interval (wave 1 blue, wave 2 green). Day 0 is the day of hospitalization. Patients alive at the date of last available information were censored (+) at that date.

Table 2
Extrapulmonary events during wave 1 and 2.

	Wave 1 (n = 600)	Wave 2 (n = 205)	P-value ^a
At least one (excluding death)	136 (22.7%)	65 (31.7%)	0.011
Thromboembolic event	24 (4.0%)	9 (4.4%)	0.839
Deep vein thrombosis	13 (54.2%)	–	0.005
Pulmonary embolism	16 (66.7%)	9 (100.0%)	0.073
Renal failure	80 (13.3%)	38 (18.5%)	0.086
Rhabdomyolysis	5 (0.8%)	4 (2.0%)	0.243
Hepatic disorder	27 (4.5%)	14 (6.8%)	0.199
Cardiovascular event	33 (5.5%)	21 (10.2%)	0.024
Neurological event	8 (1.3%)	3 (1.5%)	1.000
Pancreatitis	1 (0.2%)	–	1.000
Number of extrapulmonary events			
0	464 (77.3%)	140 (68.3%)	0.055
1	94 (15.7%)	44 (21.5%)	
2	30 (5.0%)	18 (8.8%)	
3	9 (1.5%)	3 (1.5%)	
4	3 (0.5%)	–	
Death	115 (19.2%)	26 (12.7%)	0.043

^a Fisher's exact test.

second wave, hospitalizations were markedly decreased compared to the first wave. The stress put on our medical departments, especially on the ICU, was attenuated during the second wave, with no transfer of patients. In contrast, more than 100 patients had to be sent to other medical facilities in March due to the lack of ICU beds. Hospitals perform better when they are not overwhelmed [16].

SARS-CoV-2 can affect many organs [2]. Occurrence of extrapulmonary events is usually considered to be positively correlated with disease severity, more severe patients being at higher risk of complications. Unexpectedly the lower severity at admission and new therapeutics during wave 2 did not result in decreased extrapulmonary events (22.7% of wave 1 patients and 31.7% of wave 2 patients).

This study had several limitations and potential biases. This was a retrospective study with potentially inhomogeneous data collected at baseline in COVID-19 departments. We arbitrarily chose to study the beginning of both waves, including March and October to November. During the second wave, we chose a two-month period to include enough inpatients. These times encompassed the beginning of each wave and corresponded to the highest number of hospitalizations for COVID-19. However, the lower number of patients during wave 2 also contributed to an improved management as healthcare professionals were less overwhelmed. When comparison of outcomes is performed between the waves, this information should thus be included. Underestimation of some extrapulmonary events, especially in March, is possible because extrapulmonary complications were not as clearly defined during the first wave as they are now. The results should thus be interpreted with caution.

5. Conclusions

This study underscores the main differences in inpatients infected by SARS-CoV-2 during the first and second epidemic waves. A drastic reduction in inpatients was observed during the second wave versus the first wave. Although the sociodemographic characteristics of patients were the same during the two waves, patients of the second wave consulted earlier, had less severe symptoms, and were more frequently treated with steroids. There was a significant reduction in death rate and ICU hospitalizations but not in extrapulmonary events during the second wave.

Contribution of authors

MM conceived and designed the study, analyzed the data and drafted the article. SG, MMZ, DK, CI, ME, APS, JDK and the authors of the Center Alsace COVID-19 Study Group collected and analyzed the data. CK analyzed the data and performed the statistical analysis. All authors read and approved the article.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Disclosure of interest

The authors declare that they have no competing interest.

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