RESEARCH ARTICLE

Characteristic and outcome changes in inpatients with COVID-19 during the four pre - Omicron waves

Martinot M[1], Eyriey M[2], Gravier S[1], Ion C[1], Mohseni-Zadeh M[1], Rougier E[1], Ongagna J-C[2], Henric A[2], Schieber A[2], Kempf C[2]

[1]Infectious Diseases Department
[2]Clinical Research Department
Hôpitaux Civils de Colmar, Colmar, France

Abstract

Background: Four waves of Coronavirus disease 2019 (COVID-19) occurred in France between March 2020 and September 2021. COVID-19 inpatient characteristics change because of the influence of numerous parameters, especially immunization and circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.

Methods: This retrospective single-center study analyzed patients with laboratory-proven COVID-19 admitted from 1/3/2020 to 30/6/2020 (wave one), 1/7/2020 to 31/12/2020 (wave two), 1/1/2021 to 30/6/2021 (wave three), and 1/7/2021 to 30/11/2021 (wave four). We compared the outcomes and baseline characteristics between these waves.

Results: In our center, 1,762 patients were hospitalized for COVID-19: 666 (37.8 %), 425 (24.1 %), 482 (27.3 %), and 189 (10.7 %) during waves 1, 2, 3, and 4, respectively. Patients during the first wave were hospitalized later after the onset of COVID-19 symptoms, had more severe disease conditions at baseline, and suffered higher intensive care unit (ICU) hospitalization rates. Most patients from waves 1-3 were >70 years old, with 88-93 % having ≥1 comorbidity, whereas those from wave four were younger (68.0 years) with less comorbidities. The first two waves showed higher mortality rates (16.8 % and 20.0 %) than the latter (16.6 % and 9.5 %).

Conclusion: Patients during the first wave had more severe disease conditions at baseline and higher mortality and ICU hospitalization rates. Despite the more virulent circulating Delta variant during wave four, the death and hospitalization rates were markedly decreased during wave four. HIPPOKRATIA 2023, 27 (1):1-6.

Keywords: Coronavirus disease 2019, COVID-19, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, waves, mortality, pre-Omicron

Corresponding author: Martinot Martin, MD, Infectious Diseases Department, Hôpitaux civils de Colmar, 39 Avenue de la Liberté, 68024 Colmar, France, tel : +33389124904, fax: +33389124691, e-mail: martin.martinot@ch-colmar.fr

Introduction

Coronavirus disease 2019 (COVID-19), a polymorphic disease that affects predominantly the respiratory tract[1], is associated with numerous extrapulmonary complications[2], which lead to hospitalization and death in the most severe cases. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China in December 2019, and in January 2020, France reported its first case of COVID-19[3]. Different waves, defined by a rise in new cases followed by a peak and then a decline[4], succeeded after that. The first wave began in the spring of 2020 with a major COVID-19 outbreak in Northeastern France. The Hôpitaux Civils de Colmar (HCC) was, during the first wave, one of the most affected French hospitals, with many COVID-19 hospitalizations in March 2020[5]. After that, three successive waves occurred[4]. Implementing a nationwide lockdown from 17/3/2020 to 10/5/2020 decreased the transmission rate until the end of July. Mask-wearing became mandatory in public spaces in the summer of 2020. However, a new steady rise of COVID-19 cases was observed in autumn, followed by a rapid increase, especially in Northeastern France, and this second wave prompted another nationwide lockdown from 30/10/2020 to 15/12/2020[6].

Consequently, a lighter lockdown was implemented from 3/4/2021 to 3/5/2021. Through the implementation of a curfew and sanitary pass in 2021, no further lockdown was enforced in Alsace. The virus had evolved, marked by the emergence of different variants, especially the Alpha variant (onset by the end of 2020, mainly in March 2021) and the Delta variant (onset in May, mainly in July 2021) in France, showing higher diffusion and higher pathogenesis[7]. During these waves, numerous therapeutic changes occurred: i) the extensive use of anti-inflammatory drugs, especially corticosteroids[8] and, in a lesser extent, tocilizumab[9]; ii) the emergency use of remdesivir,

a ribonucleic acid (RNA) polymerase inhibitor antiviral, for COVID-19 on 1/5/2020; iii) cessation of utilizing hydroxychloroquine and lopinavir in the treatment[10]; iv) the use of convalescent plasma, especially in B-cell–depleted patients[11], and monoclonal antibodies directed against SARS-CoV-2 for mild and moderate COVID-19, and then severe COVID-19[12,13]; and v) enhanced oxygen therapy mostly via a high-flow nasal cannula (HFNC)[14]. By the end of December 2020 and mainly in January 2021, vaccination started to be implemented among older people in long-term care facilities and healthcare workers; by the end of October 2021, 73 % and 68.3 % of the overall population received one and two doses, respectively[4]. However, the emergence of different variants initiated the third wave. The Alpha variant emerged by the end of 2020 (predominant variant in March 2021) in conjunction with the Beta and Gamma variants (first semester of 2021) to a lesser extent, followed by the Delta variant, which initiated the fourth wave (first circulation in May 2021, accounting for 99 % of all variants in September 2021); in November 2021, the new variant Omicron emerged and surged drastically because of viral antibody evasion and patients waning immunity[15]. During the four waves, more than 7 million people were diagnosed with COVID-19 in France, with 460,000 hospitalizations, 94,000 intensive care unit (ICU) hospitalizations, and 116,000 deaths[4]. However, the characteristics of inpatients diagnosed with COVID-19 in each wave remain unclear. Hence, this retrospective study aimed to analyze the data of all inpatients with COVID-19 during the first four pre-Omicron waves in a tertiary-level institution with a 1,000-bed capacity in France. We assessed the differences in baseline characteristics, mortality, ICU hospitalization rates, and extrapulmonary complications to determine the changes in inpatient characteristics.

Methods

We analyzed retrospective data regarding all consecutive patients hospitalized for >24 hours in the HCC with COVID-19 (emergency, medical, or surgical departments) from 1/3/2020 to 30/11/2021. A positive nucleic acid amplification for SARS-CoV-2 confirmed COVID-19. We defined nosocomial COVID-19 based on a negative polymerase chain reaction (PCR) upon admission and subsequent positive PCR 48 hours after admission, except for the first wave where PCR was not yet performed on admission and where a positive PCR more than 48 hours after admission was retained. According to the national/regional dataset[4], COVID-19 presented four waves: wave one from 1/3/2020 to 30/6/2020, wave two from 1/7/2020 to 31/12/2020, wave three from 1/1/2021 to 30/6/2021, and wave four from 1/7/2021 to 30/11/2021. We performed all methods according to the relevant French guidelines and regulations. The Ethics Committee of Medicine, Odontology, and Pharmacy Faculties and Hospitals (University Hospital of Strasbourg, decision No CE-2020-32, date 30/3/2020) approved the study and waived the need for informed consent.

Data collection and endpoints

The HHC computer-based patient records (Crystal Link®,Hôpitaux Civils de Lyon, Lyon, France) were used to collect the following data: gender, age, body mass index (BMI), symptoms at admission, medical history, and routine blood examinations [complete blood cell count, lactate dehydrogenase (LDH), and C-reactive protein (CRP)]. The type of hospitalization (ICU or non-ICU) and patient's status at the end of the available follow-up (death or discharge status) were documented with relevant dates.

Statistical analysis

The baseline characteristics are classified and presented according to the COVID-19 wave when hospitalization occurred. We summarize continuous variables by the median and first and third quartiles (Q1, Q3) and compare them using the Kruskal-Wallis test. We present categorical data by the number of missing values and absolute and relative counts and compare them using the Chi-square and Fisher's exact tests, as appropriate. The nonparametric Kaplan-Meier method determined mortality rate curves with 95 % confidence intervals. We also used the odds ratios for mortality and ICU hospitalization rates. Statistical data were analyzed using the SAS 9.4 software (SAS Institute Cary, NC, USA).

Results

Baseline characteristics

The patients' main clinical characteristics and laboratory results at baseline are summarized in Table 1. A total of 1,762 patients were hospitalized with COVID-19 during the study period, with 666 (37.8 %), 425 (24.1 %), 482 (27.3 %), and 189 (10.7 %) during waves 1, 2, 3, and 4, respectively. We identified 274 cases (15.6 %) of nosocomial COVID-19 from March 2020 to November 2021, and most of them (74 %) were recorded during waves 2 and 3.

Except for the patient's gender and the need for oxygen at admission, all parameters significantly differed between the four waves. Most patients from waves 1-3 were aged over 70 years, with 88-93 % having at least one comorbidity, whereas those from wave four were younger (68.0 years) with fewer comorbidities. The median time lag between the onset of COVID-19 symptoms and hospitalization was longer for the first than for the other waves, except for wave four. During the first wave, body temperatures at admission were higher, and baseline biological results at admission were more severe (e.g., lower lymphocyte count and higher CRP and LDH levels) (Table 1). Dexamethasone use was lower during the first wave, and antibiotic use was lower during the fourth wave. Furthermore, 356 (20.2 %) patients required ICU hospitalization, with the highest rate in wave one (165 patients; 24.8 %), followed by wave four (47; 24.9 %), wave three (86; 17.9 %), and wave two (58; 13.6 %). The overall mortality rate was 16.7 %, with the highest rates (20 %, 16.8 %, 16.6 %) observed during wave two,

Table 1: Patients' main clinical characteristics, symptoms, laboratory results at baseline, and outcomes for the 1,762 patients hospitalized with COVID-19 in the Hôpitaux Civils de Colmar, in France during the study period according to COVID-19 waves.

	Wave 1 (n =666)	Wave 2 (n =425)	Wave 3 (n =482)	Wave 4 (n =189)	All patients (n =1,762)	p-value
Male	376 (56.5 %)	233 (54.8 %)	268 (55.6 %)	108 (57.1 %)	985 (55.9 %)	0.936
Female	290 (43.5 %)	192 (45.2 %)	214 (44.4 %)	81 (42.9 %)	777 (44.1 %)	
Age (years) Median [Q1, Q3]	71.26 [60.9, 80.9]	76.84 [65.3, 85.6]	72.18 [59.3, 83.3]	67.97 [54.7, 80.1]	72.62 [60.9, 83.0]	<0.001
BMI (kg/m²) Median [Q1, Q3]	26.685 [23.46, 30.80]	25.271 [22.22, 29.39]	26.432 [23.38, 31.02]	26.777 [23.51, 30.63]	26.298 [22.99, 30.49]	0.012
Risk factor(s)	586 (88.0 %)	396 (93.2 %)	445 (92.3 %)	161 (85.1 %)	1588 (90.1 %)	0.002
Chronic renal disease	70 (10.5 %)	75 (17.6 %)	79 (16.4 %)	23 (12.2 %)	247 (14.0 %)	0.002
Chronic liver disease	6 (0.9 %)	15 (3.5 %)	12 (2.5 %)	3 (1.6 %)	36 (2.0 %)	0.002
Chronic cardiovascular	459 (68.9 %)	308 (72.5 %)	354 (73.4 %)	117 (61.9 %)	1238 (70.3 %)	0.028
Chronic pulmonary disease	138 (20.7 %)	127 (29.9 %)	154 (32.0 %)	53 (28.0 %)	472 (26.8 %)	<0.001
Diabetes	189 (28.4 %)	131 (30.8 %)	138 (28.6 %)	42 (22.2 %)	500 (28.4 %)	0.0196
Cancer	132 (19.8 %)	132 (31.1 %)	121 (25.1 %)	37 (19.6 %)	422 (24.0 %)	<0.001
Immunosuppression	2 (0.3 %)	6 (1.4 %)	17 (3.5 %)	7 (3.7 %)	32 (1.8 %)	<0.001
HIV	-	2 (0.5 %)	2 (0.4 %)	1 (0.5 %)	5 (0.3 %)	0.187
Pregnancy	1 (0.2 %)	-	3 (0.6 %)	2 (1.1 %)	6 (0.3 %)	0.087
Neurologic disorders	126 (18.9 %)	84 (19.8 %)	99 (20.5 %)	28 (14.8 %)	337 (19.1 %)	0.003
Dementia	124 (18.6 %)	108 (25.4 %)	104 (21.6 %)	33 (17.5 %)	369 (20.9 %)	0.036
Others	67 (10.1 %)	83 (19.5 %)	57 (11.8 %)	15 (7.9 %)	222 (12.5 %)	<0.001
Symptom duration (days) Median [Q1, Q3]	-6.0 [-9, -2]	-3.0 [-7, -1]	-5.0 [-9, -1]	-6.0 [-9, -3]	-5.0 [-9, -2]	<0.001
Body temperature (°C) Median [Q1, Q3]	38.00 [36.9, 38.6]	37.00 [36.5, 38.0]	37.10 [36.5, 38.1]	36.90 [36.3, 38.0]	37.30 [36.6, 38.3]	<0.001
Ventilation - Needing O_2	226 (33.9 %)	133 (31.3 %)	140 (29.0 %)	64 (33.9 %)	563 (32.0 %)	0.311
Lymphocytes (G/L) Median [Q1, Q3]	0.770 [0.54, 1.11]	0.840 [0.55, 1.22]	0.850 [0.59, 1.26]	0.890 [0.58, 1.36]	0.820 [0.55, 1.19]	0.003
CRP (mg/L) Median [Q1, Q3]	73.0 [35, 127]	48.0 [17, 91]	53.0 [16, 111]	52.5 [18, 109]	60.0 [22, 112]	<0.001
LDH (IU/L) Median [Q1, Q3]	324.0 [241, 431]	261.0 [210, 316]	268.0 [212, 360]	302.5 [201, 392]	282.0 [218, 379]	<0.001
Corticosteroids	74 (11.1 %)	217 (51.1 %)	298 (61.8 %)	130 (68.8 %)	719 (40.8 %)	<0.001
Antibiotics	448 (67.3 %)	276 (64.9 %)	297 (61.6 %)	99 (52.4 %)	1120 (63.6 %)	0.002
ICU hospitalization (%)	165 (24.8 %)	58 (13.6 %)	86 (17.9 %)	47 (24.9 %)	356 (20.2 %)	<0.001
Deaths (%)	112 (16.8 %)	85 (20.0 %)	80 (16.6 %)	18 (9.5 %)	295 (16.7 %)	0.011
Nosocomial	52 (7.8 %)	141 (33.2 %)	62 (12.9 %)	19 (10.1 %)	274 (15.6 %)	<0.001
Vaccination	-	-	49 (10.2 %)	78 (41.3 %)	127 (7.2 %)	<0.001

Results are presented as number with percentage (%) in brackets or medians with the first (Q1) and third (Q3) quartiles in brackets. Percentages are calculated for non-missing values only. n: number, BMI: body mass index, CRP: C-reactive protein, HIV: human immunodeficiency virus, LDH: lactate dehydrogenase, ICU: intensive care unit.

one, and three, respectively, and the lowest during wave four (9.5 %) (Figure 1).

Discussion

In the current retrospective single-center large cohort study of inpatients with laboratory-confirmed COVID-19 in France, we clarify the differences between patients admitted for COVID-19 in HCC during the first four waves of COVID-19, focusing on the baseline characteristics and severe outcomes, including ICU hospitalization and death. With a median age of 72 years and a higher proportion of males, the current study's population is similar to that described in previously published large cohort studies concentrating on inpatients with COVID-19[16-18]. However, wave four appeared quite different from the three previous waves in terms of intensity (lowest number of inpatients) and inpatient characteristics (lowest age and least in high-risk conditions for severe COVID-19)[19]. Thus, lower peak and age may be a direct consequence of immunization campaign in the general population; ad-

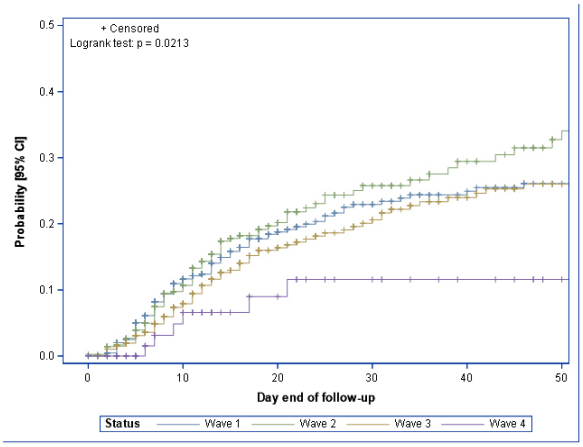

Figure 1: Death rate curve - product limit estimate (Kaplan–Meier) with two-sided confidence interval and number of patients at risk on each of the first four COVID-19 waves. Day 0 is the day of hospitalization. Patients alive at the end of follow-up were censored at the date of last information.
CI: confidence interval

ditionally, older patients who were optimally protected during wave four, owing to an earlier vaccine campaign prioritizing these patients along with the absence of waning immunity and antibody evasion caused by the Omicron variant[4,20].

At baseline, patients in the first wave were hospitalized later after the onset of COVID-19 symptoms than those in the other waves, probably attributed to an overwhelming first wave in Northeastern France, with difficult access to health care institutions and inadequacy in diagnostic tests at that time. For the same reason, wave one patients appeared to have more severe symptoms, such as higher body temperatures, higher CRP and LDH levels, and lower lymphocyte count at baseline[21-25]. Only wave four showed a similar lag; one possible reason is that most of the inpatients were younger, thereby more likely to wait before hospitalization. The first wave was the most significant in terms of inpatients due to its specificity in Northeastern France, which began by a major COVID-19 outbreak in the spring of 2020. During this wave, HCC was one of the most affected French hospitals, with many more hospitalizations than other French hospitals, which led to a relative ICU bed shortage despite the increase in ICU beds and transfer to other healthcare centers.

One of the main results of the current analysis is the reduction in mortality rates. The overall mortality rate was 16.7 %, with wave four having the lowest rate (9.5 %). Waves two and three had mortality rates quite similar to the first wave, thereby seemingly puzzling in the context of immunization campaigns and extended use of steroids, which had a significant effect on mortality[8]. However, the kinetics of mortality were different between waves, and nosocomial COVID-19, which was most frequent during waves two and three (74 % of nosocomial cases), was most certainly responsible for this death toll. In a previous study investigating the beginning of waves one (March 2020) and two (October and November 2020), where we excluded nosocomial cases, and which were the periods when nosocomial COVID-19 was fewer, occurring after a certain delay, we found that the second wave demonstrated a significantly lower mortality rate (12 %) than the first wave (19 %)[26]. Nosocomial COVID-19 was less notable in the first wave, during which hospital activities were mainly for COVID-19, thereby reducing nosocomial COVID-19 tendency in opposition to the following waves. Nosocomial COVID-19-associated mortality affects older patients with high-risk conditions and is responsible for the significant increase in mortality rate[27,28]; these points may explain the mortality rate in waves two and three. Nosocomial cases affected mainly frail, unvaccinated elderly comorbid patients not eligible for ICU. Conversely, different factors have contributed to the drastic reduction of COVID-19 mortality in wave four, and among these factors included immunization (≥1 dose for 10.2 % of inpatients in wave three and 41.3 % in wave four), which helped patients avoid the most severe forms, and treatments such as corticosteroids, tocilizumab[8], remdesivir, convalescent plasma, antibody prophylaxis, and oxygen therapy using HFNC. There were 21 patients treated with remdesivir, 58 with monoclonal antibodies, and 23 with plasma convalescent therapy during these waves, mainly after the second wave. However, we focused on steroids and antibiotics, which we have been using since March 2020, although we previously published our experience on using HFNC[29,30]. Wave four showed the lowest mortality rate, despite the Delta variant, possibly because of a younger patient age, a less overwhelming wave, therapeutic use, and immunization progres[9]. There was still a high rate of ICU hospitalizations in wave four, but these patients were young and less comorbid; thus, they were more eligible for ICU. Immunization was also key for controlling the intensity of waves and the severity of COVID-19 symptoms.

Lastly, an element that contributed to survival improvement between the first and the other waves was the differences in wave intensities. During the first wave, 600 patients were admitted for COVID-19 in less than one month; this number is beyond all the hospitalization numbers concerning the other waves. In addition, more than 100 patients had to be sent to other medical institutions in March 2020 because of ICU bed insufficiency. Hospitals perform better when not overwhelmed, as demonstrated among American hospitals, where the COVID-19 mortality rate was 9-27 % between January and June of 2020[31].

This study has several limitations and potential biases. For instance, this is a retrospective study conducted in a single center. Wave periods were defined according to national data, not regional data, which are more precise but difficult to collect. Last, our severity analysis utilized the criteria for severity rather than those for ICU hospitalization, such as those explained by the World Health Organization (WHO) working study groups[32]. Notably,

oxygenation using HFNC could be of interest to appreciate patient severity; however, it could not be implemented during the first wave when HFNC was not feasible in HCC due to inadequate available equipment. Nevertheless, this cohort highlights the evolution of inpatients with precise data at admission and may provide insight into their changing characteristics before the surge of the Omicron variant.

In conclusion, this study highlights the main differences in baseline characteristics and severe outcomes among inpatients with COVID-19 stratified by the first four waves before the Omicron variant era. This study also emphasizes the variability of such waves. First, the number of inpatients drastically decreased beginning with the second wave. Second, waves two and three showed a persistently high level of mortality, probably associated with nosocomial COVID-19. Last, despite the virulence of the Delta variant, the fourth wave demonstrated the lowest peak, mortality rate, and ICU hospitalization rate, possibly because of the improvement of therapies, younger age of inpatients, and the extended immunization of the general population without the antibody evasion related to the Omicron variant.

Conflict of interest

Authors declare no conflicts of interest.

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