JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES
2021, VOL. 11, NO. 6, 747–752
https://doi.org/10.1080/20009666.2021.1978154

Mortality due to COVID-19 infection: A comparison of first and second waves

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ABSTRACT

Background: The USA suffered an initial wave of COVID-19 cases from March to July in 2020. Cases again surged in August 2020 as business restrictions were lifted. We aimed to describe demographic, treatment, and mortality differences between both waves.

Methods: We identified all hospitalized patients with COVID-19 infection in one US six-hospital health system between 1 March 2020 and 31 January 2021. We compared data obtained on patient demographics, treatment received, and mortality between first and second waves of the pandemic.

Results: A total of 4434 hospitalized COVID patients were identified, including 1313 patients in the first wave and 3121 patients in the second wave. Mortality was significantly higher in the first wave as compared to the second wave (23.2% vs. 12.3%, $p < 0.001$). Age and sex were similar in each wave. In the first wave, there were significantly more Non-Hispanic Black patients (28.8 vs. 18.1%, $p < 0.001$) and Hispanic patients (26.6% vs. 14.9%, $p < 0.001$) as compared to the second wave. There was a higher mortality rate in the first wave as compared to the second, which persisted after multivariable adjustment for sex, age, ethnicity, laboratory results at admission, treatment received, high flow use and mechanical ventilation (OR: 2.66, 95% CI: 1.83–3.87, $p < 0.001$).

Conclusion: Mortality in the second wave was lower than the first wave with significantly higher utilization of steroids, remdesivir and convalescent plasma in second wave.

ARTICLE HISTORY
Received 28 June 2021
Accepted 3 September 2021

KEYWORDS
COVID-19; mortality; hospitalization; pandemic; SARS-CoV-2

1. Introduction

The USA suffered an initial wave of COVID-19 cases from March to July in 2020. As business restrictions were lifted in the summer of 2020, cases again surged in the US and Europe, creating a second wave of infection [1,2]. Early in the pandemic, stark racial differences in both infection rates and mortality were reported in the literature and press, of unclear etiology [3,4]. The first wave of disease seemed to affect older patients, more often male, often with multiple comorbidities [5]. However, how the patient demographics, treatments and outcomes have differed between waves is still currently evolving in the literature. We compared the sociodemographic, clinical parameters and mortality rate of patients hospitalized with COVID-19 infection between the first and second waves of the pandemic in one six-hospital health system in the USA.

2. Methods

This study was a retrospective analysis of all hospitalized patients with a positive COVID-19 polymerase chain reaction (PCR) test in an US six-hospital health system between 1 March 2020 and 31 January 2021. The hospital system employed four different testing platforms during the study time period for viral detection (Cepheid 4 Plex SARS-CoV-2 test, Cepheid Inc., Sunnyvale, CA USA; Panther Hologic SARS-CoV-2 test, Marlborough, Ma USA; Abbott ID NOW SARS-CoV-2 test, Abbott Park, IL, USA; BioFIre Respiratory Panel SARS-CoV-2 test, Salt Lake City, UT, USA). We collected data on sociodemographic factors including age at admission, patient-reported sex, race, and ethnicity as collected retrospectively from our electronic health record. We also extracted data on medication administered, use of oxygen including methods of delivery of oxygen, mechanical ventilation, and in-hospital mortality. The presence or absence of any one intervention was collected dichotomously ('yes/no'), and the majority had more than one medication or oxygen delivery method in their hospital stay. The primary endpoint was mortality, which we described as in-hospital death or mortality within 30 days of discharge from index hospitalization. The unit of analysis was the individual patient, and each patient was

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counted once, even if they had multiple hospital admissions.

Patients were included if they were 18 years and older and if they were hospitalized between March 2020 and January 2021 and had the positive polymerase chain reaction (PCR) COVID-19 test.

Patients admitted between March and 31 July 2020 were analyzed in the first wave, while those admitted between August 2020 and 31 January 2021 were analyzed in the second wave.

We investigated the differences in the patient demographics, laboratory findings at admission, medications received, and mortality between waves of the pandemic. Categorical variables were reported as numbers and percentages, while continuous variables were reported as mean with standard deviation or median with interquartile range for skewed data. We compared demographic and clinical characteristics between the first and second waves of the pandemic using univariate analysis (Chi-square or Fischer's exact testing, where appropriate). Age at admission, sex, ethno-racial group, laboratory results at admission (used as a surrogate for disease severity), COVID-19 treatment received, use of high flow oxygen and mechanical ventilation were included in our model. A probability of less than 0.05 was accepted as statistically significant in the final multivariable analysis. Individual variables were removed from the equation in backwards elimination using the Wald statistic. Results reported included the variables remaining in the model, Odds ratio along with the 95% confidence interval of the Odds ratio. Statistical analysis was performed using STATA version 15.0 (STATACorp, LLC, College Station, TX), as well as SPSS v25.0 (IBM, Chicago IL). This project was approved by the Hospital institutional review board (IRB 069–20).

3. Results

A total of 4434 hospitalized patients with the positive COVID-19 test were identified between March 2020 through January 2021 across 6 health care facilities in our system. There were 1313 (29.6%) and 3121 (70.4%) patients in the first and second waves, respectively. The first wave had its highest hospitalization rates in April, while the second wave peaked in December 2020, as shown in Figure 1. The demographic and clinical characteristics of the patients are shown in Table 1. The average age of patients was lower in wave 1 as compared to wave 2 (66.7 ± 17.1 years vs. 68.0 ± 16.9 years, $p = 0.021$). However, there was no significant difference in age category at admission and sex between the first and second waves. The proportion of Hispanic patients and non-Hispanic black patients among hospitalized COVID-19 patients was higher in the first wave than in the second (26.6 vs. 14.9%, $p < 0.001$ and 28.8% vs. 18.1%, $p < 0.001$). Non-Hispanic whites were a significantly smaller percentage of the patients in the first wave as compared to the second (44.6% vs. 67.0% respectively, $p < 0.001$) (Table 1). Median ferritin, c-reactive protein, lactate dehydrogenase, and D-dimer were higher in the first wave when compared with the second wave ($p < 0.05$) (Table 2). A lower proportion of patients received remdesivir, convalescent plasma and steroids in the first wave, while more received hydroxychloroquine in the first wave in comparison to the second wave ($p < 0.001$). A higher proportion of patients required invasive mechanical ventilation in the first wave compared to the second wave (11.8% vs. 7.4%, $p < 0.001$). There was no significant difference in the use of high-flow oxygen between the two waves.

A total of 690 deaths were recorded over the study period representing 15.6% of all hospitalized COVID patients. Of the 690 deaths, there were 305 patients (23.2% of admissions) and 385 (12.3% of admissions) in the first and second waves, respectively ($p < 0.001$). The odds of dying were higher in the first wave when compared to the second wave, which persisted after multivariable adjustment for age, sex, ethnicity, laboratory results at admission, medications administered, and mechanical ventilation (OR 2.66, 95% CI 1.83–3.87, $p < 0.001$) (Table 3). Age greater than 65 (OR 22.36, 95% CI 5.83–85.82), high-flow oxygen (OR 3.80, 95% CI 2.60–5.55), and mechanical ventilation (OR 14.24, 95% CI 8.65–23.47) were independently associated with mortality.

4. Discussion

We described the sociodemographic, clinical parameters, and mortality of patients hospitalized with COVID-19 infection and compared the mortality between the first and second waves of the pandemic in this study. Our study showed the odds of dying was higher in the first wave of the COVID pandemic after adjusting for age, sex, ethnicity, and medical and oxygen treatments. Steroid use, high flow oxygen, and mechanical ventilation were also independently associated with mortality.

A decline of COVID cases occurred after strict lockdowns was implemented in the US, similar to what we saw in June and July of 2020. However, we suspect that upsurge in the number of cases from August 2020 may have occurred when business restrictions were lifted as also seen in other European countries [1,2]. Our second wave onset occurred later than others reported in the literature. Japan noted a steep rise in cases in June 2020, while Malta reported a second wave rising in July 2020 [2,6]. Our study showed that first wave peaked in April, while the second wave peaked in December 2020, as shown in Figure 1.

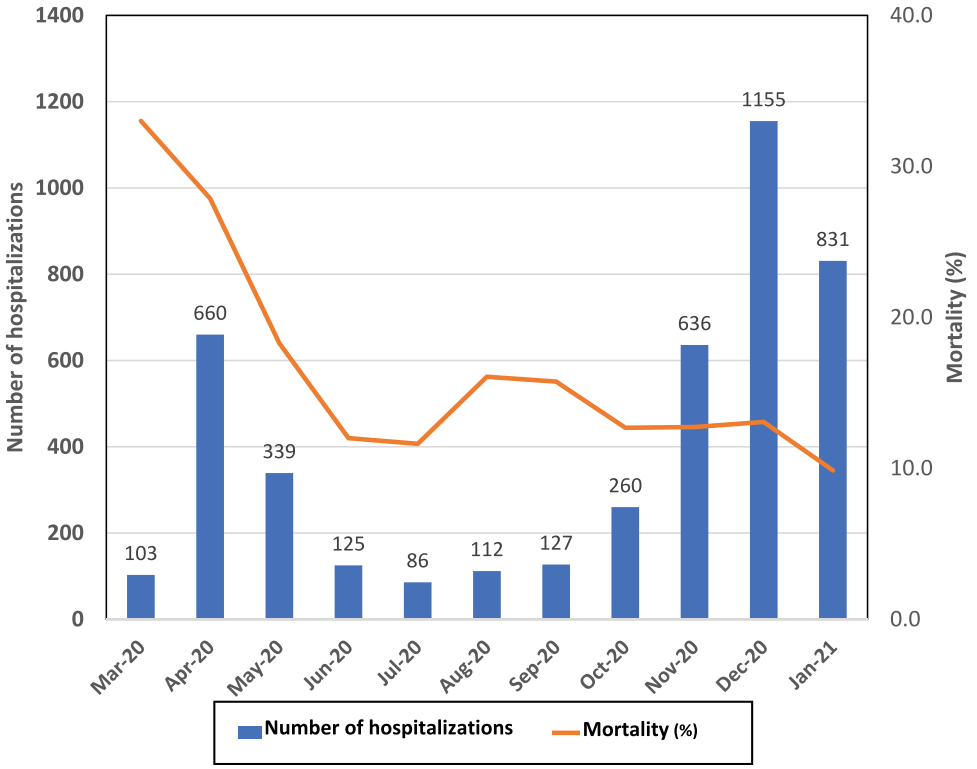

Figure 1. Graph showing number of hospitalization and mortality rate.

Our study showed that there was no age and gender differences between the first and second waves of the pandemic similar to findings reported by Contou et al. in critically ill patients [7]. Iftimie et al. also reported no gender difference between waves but similarly noted that the mean age in the second wave was younger than in the first wave [8].

A total of 690 deaths were recorded over the study period representing 15.6% of hospitalized patients with COVID-19. Although more patients with COVID-19 were hospitalized in the second wave, a lower mortality rate was observed in the second wave compared with the first (23.2% vs. 12.3%, $p < 0.001$). Logistic regression also showed increased odds of mortality in the first wave as compared to the second wave, which persisted after multivariable adjustment for age, gender, ethnicity, laboratory results at admission, treatment received, and mechanical ventilation (OR 2.66, 95% CI 1.83–3.87, $p < 0.001$).

This finding of lower mortality in the second wave of the pandemic was also reported in other studies [6,8,9]. Numerous factors could have contributed to the difference in mortality in waves. Early in COVID management, corticosteroids were thought to be harmful based on prior experience with the H1N1 pandemic. Not until the release of the British dexamethasone RECOVERY trial [10] did we fully understand the benefits of corticosteroids and regularly use them in patients with COVID. That may explain the differences by wave in corticosteroid use in our health system (31.8% vs. 80.8%) and may have contributed to the improvement in mortality. Hydroxychloroquine was initially believed to be of some benefit [11,12] and only later determined to be ineffective in improving clinical outcomes [13,14], as reflected in our system's declining use of this drug in the second wave. Remdesivir was not only in short supply in the first wave but was best used early in disease course. Unfortunately, testing turnaround times were so long in the first wave [15,16] that patients often did not receive a formal diagnosis in time to get a benefit from early remdesivir. Guidelines also recommended early mechanical ventilation for patients in respiratory failure [17,18], but later experience and the literature favored trials of non-invasive ventilation, which may have both reduced intubation and potentially reduced morbidity and mortality from complications of ventilation [19,20]. Finally, it is possible the fact that the sickest population of patients with the most comorbidities died with the first wave, where nursing homes had early outbreaks, which may have affected mortality rates of the second wave.

Our study showed that there were significantly higher proportion of non-Hispanic black patients (28.8 vs. 18.1%, $p < 0.001$) and Hispanic patients (26.6% vs. 14.9%, $p < 0.001$) in the first wave versus the second wave. This suggests that these patient populations were over-represented among hospitalized patients as compared to the catchment area of the health system's main hospital, where the ethnic makeup is 8.7% Black and 18.7% Hispanic [21].

Table 1. Demographics, laboratory results, treatments, and outcome by Wave of pandemic.

		Hospital admission N = 4434		
	N (%)	1st wave n (%)	2nd wave n (%)	p-value
Age (years)				0.053
18–44	488 (11.0)	156 (11.9)	332 (10.6)	
45-64	1217 (27.5)	385 (29.3)	833 (26.7)	
≥65	2728 (61.5)	772 (58.8)	1956 (62.7)	
Sex				0.318
Male	2288 (51.6)	693 (52.8)	1596 (51.1)	
Female	2144 (48.4)	620 (47.2)	1525 (48.9)	
Non-Hispanic White	2519 (60.5)	541 (44.6)	1978 (67.0)	<0.001
Non-Hispanic Black	883 (21.2)	349 (28.8)	534 (18.1)	
Hispanic	764 (18.3)	323 (26.6)	442 (14.9)	
Medications administered	**N (%)**	**N (%)**	**N (%)**	
Remdesivir	1576 (35.6)	76 (5.8)	1500 (48.1)	<0.001
Hydroxychloroquine	411 (9.3)	389 (29.6)	22 (0.7)	<0.001
Tocilizumab	93 (2.1)	93 (7.1)	0(0)	<0.001
Convalescent plasma	1292 (29.2)	91 (6.9)	1201(38.5)	<0.001
Ritonavir-Lopinavir	3 (0.1)	1 (0.1)	2 (0.1)	1.000
Plasmapheresis	5 (0.1)	4 (0.3)	1 (0.03)	0.029
Immunoglobulin	4 (0.1)	1 (0.1)	3 (0.1)	1.000
Steroids	2938 (66.3)	417 (31.8)	2521 (80.8)	<0.001
Treatments	**N (%)**	**N (%)**	**N (%)**	
High flow oxygen	819 (18.5)	245 (18.7)	574 (18.4)	0.834
Mechanical ventilation	386 (8.7)	155 (11.8)	231 (7.4)	<0.001
Mortality	690 (15.6)	305 (23.2)	385 (12.3)	<0.001

Table 2. Group t-test: Laboratory results by wave of the pandemic.

	1st Wave			2nd Wave			
Variable	n	Mean	SD	n	Mean	SD	p-value
CRP (mg/dl)	612	11.7	10.40	1458	9.5	9.84	<0.001
D-dimer (µg/ml)	683	3.1	5.66	1686	2.3	3.7	0.001
LDH (U/L)	705	371.7	198.46	1425	327.0	194.1	<0.001
CK (U/L)	730	365.6	901.94	1660	308.6	874.8	0.146
Ferritin(µg/ml)	683	868.7	1237.74	1376	715.6	1085.7	0.006
N/L ratio	1188	7.99	9.67	2822	7.5	7.87	0.280

CRP = C-reactive protein; LDH = Lactate Dehydrogenase; CK = Creatinine Kinase; N/L = Neutrophil/Lymphocyte

Although the ethno-racial composition differed by wave, there was no mortality difference between the non-Hispanic white and non-Hispanic black in either waves, while Hispanic patients had lower odds of death in both waves. This contrasts with ethno-racial disparities of COVID-19 mortality reported at the national level and in other communities including Denver, Colorado and some other studies. A study done by Millet et al. showed there were more COVID-19 cases in counties with higher proportion of black patients. Between March and October 2020, Hispanic patients had a higher proportion of COVID-19 cases (55%), hospitalizations (62%), and mortality (51%) in Denver, Colorado [22–24].

With regards to treatment, our study showed that proportion of patients who received corticosteroid treatment was higher in the second wave but did not demonstrate a relationship with mortality in multivariable analysis. One important limitation is here is that we did not adjust comorbidities and only laboratory results at admission were used as marker of severity. We also were not able to adjust for the doses of steroids administered or timing of steroid initiation with regards to onset of illness. Some studies have shown higher mortality with corticosteroid use [9], while some others showed reduced mortality with corticosteroid administration, particularly in the critically ill [25].

5. Limitations

These data are from six-hospital health system but may not be generalizable to the entire USA. Co-

Table 3. Logistic regression analysis on mortality.

Variable	Odds Ratio	Lower limit 95% CI	Upper limit 95% CI
Wave 2	Reference	-	-
Wave 1	2.659	1.828	3.865
Age (years)			
18–44	Reference	-	-
45-64	3.331	0.831	13.349
≥65	22.363	5.827	85.821
High Flow Oxygen	3.796	2.597	5.549
Mechanical ventilation	14.244	8.645	23.469
LDH	1.002	1.001	1.003
CRP	1.034	1.015	1.053

CI = confidence interval; CRP = C-reactive protein; LDH = Lactate Dehydrogenase

morbidities that are found to be associated with COVID-19 mortality were not accounted for in this analysis. Important to note is that at the beginning of the pandemic, there were no proven treatments for COVID-19 infection. Treatments were eventually determined later with randomized, controlled studies. However, there were no standardized guidelines for initiating treatment across the six hospitals at the start of the pandemic and for a proportion of the epidemic's first wave. Our demographic analysis was based on racial and ethnic background recorded in our electronic health record but was not independently validated.

6. Conclusion

Mortality in the second wave was lower than the first wave and was associated with significantly higher utilization of steroids, remdesivir, and convalescent plasma in the second wave. Patients were significantly less likely to be intubated in the second wave. Further studies will be needed to understand if these differences can be explained by other factors.

Disclosure of interest

The authors report no conflict of interest

Disclosure statement

No potential conflict of interest was reported by the author(s).

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