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Research note

Not all COVID-19 pandemic waves are alike

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ABSTRACT

Objective: We aimed to assess differences in patients' profiles in the first two surges of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in Barcelona, Spain.
Methods: We prospectively collected data from all adult patients with SARS-CoV-2 infection diagnosed at the Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. All the patients were diagnosed through nasopharyngeal swab PCR. The first surge spanned from 1st March to 13th August 2020, while surge two spanned from 14th August to 8th December 2020.
Results: There were 2479 and 852 patients with microbiologically proven SARS-CoV-2 infection in surges one and two, respectively. Patients from surge two were significantly younger (median age 52 (IQR 35) versus 59 (40) years, respectively, $p < 0.001$), had fewer comorbidities (379/852, 44.5% versus 1237/2479, 49.9%, p 0.007), and there was a shorter interval between onset of symptoms and diagnosis (median 3 (5) versus 4 (5) days, $p < 0.001$). All-cause in-hospital mortality significantly decreased for both the whole population (24/852, 2.8% versus 218/2479, 8.8%, $p < 0.001$) and hospitalized patients (20/302, 6.6% versus 206/1570, 13.1%, p 0.012). At adjusted logistic regression analysis, predictors of in-hospital mortality were older age (per year, adjusted odds ratio (aOR) 1.079, 95%CI 1.063–1.094), male sex (aOR 1.476, 95%CI 1.079–2.018), having comorbidities (aOR 1.414, 95%CI 0.934–2.141), ICU admission (aOR 3.812, 95%CI 1.875–7.751), mechanical ventilation (aOR 2.076, 95%CI 0.968–4.454), and coronavirus disease 2019 (COVID-19) during surge one (with respect to surge two) (aOR 2.176, 95%CI 1.286–3.680).
Conclusions: First-wave SARS-CoV-2-infected patients had a more than two-fold higher in-hospital mortality than second-wave patients. The causes are likely multifactorial. **Pere Domingo, Clin Microbiol Infect 2021;27:1040.e7–1040.e10**

Introduction

The first wave of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic hit Spain strongly, almost collapsing the public health system [1]. After lockdown measures, the number of patients steadily decreased [1,2]. However, scattered patients continued to be diagnosed during the summer, despite restrictions on population movement. By the end of August 2020, the number of SARS-CoV-2-infected patients began to rise again. By mid-October 2020, the pandemic figures were high enough to force a new, although partial, lockdown together with an extended curfew throughout the country [1]. Although the number of patients admitted to the hospitals was not threatening the ability of institutions to receive new ones, attending physicians soon realized that patient characteristics from the two pandemic waves were somewhat different.

Methods

Study design and sample

We prospectively collected data from all consecutive laboratory-confirmed SARS-CoV-2-infected patients diagnosed at the Hospital de la Santa Creu I Sant Pau, Barcelona, Spain, a tertiary university

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urban hospital covering a metropolitan area of 500 000 inhabitants. We analysed characteristics of all diagnosed SARS-CoV-2 patients and those admitted at our Hospital between 1st March and 8th December 2020. We categorized patients into surge one if they were diagnosed and admitted between 1st March and 13th August 2020, and into surge two if they were diagnosed and admitted between 14th August and 8th December 2020. These dates were the lowest incidence rates during the two surges in our area. The study was approved by the Ethics Committee of the Hospital de la Santa Creu i Sant Pau (Ref. Nr. HSCSP-20/117).

Laboratory methods

Nasopharyngeal swabs were obtained according to a standardized hospital protocol. Detection of SARS-CoV-2 was done through RT-PCR (Xpert® Xpress SARS-CoV-2, Cepheid Iberia, Barcelona, Spain).

Statistical methods

We summarized continuous variables as means (and standard deviations) or medians (and interquartile ranges) depending on their distribution, and categorical variables as percentages of the total sample for that variable. We used the Student t (or Wilcoxon rank-sum) and χ^2 tests (or Fisher's exact tests when appropriate) to evaluate group differences (patients from surges 1 and 2) for continuous and categorical variables, respectively. A multivariable logistic regression model was used to identify factors independently associated with a higher risk of mortality. Any variable tested in univariate analysis with $p < 0.25$ and all known clinical significance variables were selected as the first multivariate model candidates. We then followed the purposeful selection of covariates method described by Hosmer et al. [3]. Final parameter estimates are shown as odds ratios (ORs) with their corresponding 95% confidence intervals (CIs); $p < 0.05$ was considered significant for all statistical tests. Data were analysed using IBM® SPSS®, statistics, version 26.0 (Armonk, NY, USA).

Results

There were 2479 and 852 patients with microbiologically proved SARS-CoV-2 infection in surges one and two respectively. Patient demographics and clinical characteristics are summarized in Table 1. Patients from the second pandemic wave were significantly younger (median age: 59.0 (35) versus 51.5 (40) years, $p < 0.001$), while gender distribution was not different between the two waves. Patients with comorbidities were overrepresented during surge one (Table 1). However, this ratio was reversed when patients admitted to the hospital were considered (Table 2). In surge two, a microbiological diagnosis was obtained fewer days after the onset of symptoms, and infiltrates in chest x-ray were less common (Table 1). Significantly more patients from the first wave were admitted to the hospital, although the length of hospital stay was not significantly different (Tables 1 and 2).

Regarding all SARS-CoV-2-diagnosed patients, those admitted to the hospital were older, although patients hospitalized in surge two were still younger than those hospitalized in surge one (Table 2). We found that inpatients in surge two had more comorbidities and more often required intensive care unit (ICU) admission and mechanical ventilation; despite this, the all-cause mortality was substantially lower, particularly in patients older than 65 years. After adjusting for relevant clinical variables (Table 3), first-wave patients had a more than two-fold higher all-cause in-hospital mortality than second-wave patients.

Discussion

We found striking differences between patients with SARS-CoV-2 infection presenting during the first two waves of the pandemic

Table 1
Sociodemographic, comorbidity, clinical and outcome characteristics in patients diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surge 1 and surge 2

	Surge 1 ($n = 2479$)	Surge 2 ($n = 852$)	p
Age, years—median (IQR)	59.0 (35.0)	51.5 (40.0)	<0.001
<18 years, *n* (%)	24 (0.9)	46 (5.4)	<0.001
18–64 years, *n* (%)	1433 (57.8)	531 (62.3)	0.0230
≥65 years, *n* (%)	1022 (41.2)	275 (32.3)	<0.001
Gender			
Male, *n* (%)	1136 (45.8)	417 (48.9)	0.1249
Female, *n* (%)	1343 (54.2)	435 (51.1)	
Onset symptoms (PCR), days—median (IQR)	4.0 (5.0)	3.0 (5.0)	<0.001
Comorbidities[a], *n* (%)	1237 (49.9)	379 (44.5)	0.0071
Arterial hypertension, *n* (%)	862 (34.8)	241 (28.3)	0.0006
Diabetes mellitus, *n* (%)	327 (13.2)	93 (10.9)	0.0957
CKD, *n* (%)	169 (6.8)	74 (8.7)	0.0831
Dementia, *n* (%)	155 (6.3)	25 (2.9)	<0.001
COPD, *n* (%)	136 (5.5)	38 (4.5)	0.2838
Heart disease, *n* (%)	133 (5.4)	52 (6.1)	0.4684
Cancer, *n* (%)	116 (4.7)	53 (6.2)	0.0933
Obesity, *n* (%)	115 (4.6)	33 (3.9)	0.4012
Pregnancy, *n* (%)	33 (2.4)	26 (6.0)	<0.001
Hospital admission, *n* (%)	1534 (61.9)	302 (35.4)	<0.001
Chest x-ray infiltrates, *n* (%)	1332 (53.7)	147/647 (22.7)	<0.001
All-cause mortality, *n* (%)	218 (8.8)	24 (2.8)	<0.001
<18 y, *n* (%)	0 (0)	1 (0.2)	—
18–64, *n* (%)	32 (2.2)	5 (0.9)	0.0924
>65 y	186 (18.2)	18 (6.5)	<0.001
Male, *n* (%)	120 (4.8)	13 (1.5)	<0.001
Female, *n* (%)	98 (3.9)	11 (1.3)	<0.001

Values are expressed as numbers and percentage or as median and interquartile ranges (IQR) unless otherwise specified. IQR, interquartile range; PCR, polymerase chain reaction; CKD, chronic kidney disease; COPD, chronic pulmonary obstructive disease.
[a] A patient can have more than one comorbidity or therapeutic intervention.

Table 2
Sociodemographic, comorbidity, clinical and outcome characteristics in surge 1 and surge 2 hospitalized patients with coronavirus 2019 disease (COVID-19)

	Surge 1 (n = 1570)	Surge 2 (n = 302)	p
Age, years—median (IQR)	68.0 (27.0)	67.0 (24.0)	0.071
<18 y, *n* (%)	3 (0.2)	2 (0.7)	0.344
18–64 y, *n* (%)	713 (45.4)	138 (45.7)	
≥65 y, *n* (%)	854 (54.4)	162 (53.6)	
Gender male, *n* (%)	824 (52.5)	185 (61.3)	0.005
Onset symptoms PCR, days—median (IQR)	5.0 (5.0)	4.0 (5.0)	0.249
Comorbidities[a], *n* (%)	998 (63.6)	223 (74.3)	<0.001
Arterial hypertension, *n* (%)	719 (45.8)	149 (49.3)	0.258
Diabetes mellitus, *n* (%)	291 (18.5)	56 (18.5)	0.997
CKD, *n* (%)	146 (9.3)	25 (8.3)	0.573
COPD, *n* (%)	115 (7.3)	28 (9.3)	0.243
Heart disease, *n* (%)	114 (7.3)	34 (11.3)	0.018
Cancer, *n* (%)	88 (5.6)	26 (8.6)	0.046
Obesity, *n* (%)	101 (6.4)	28 (9.3)	0.075
Dementia, *n* (%)	113 (7.2)	5 (1.7)	<0.001
Pregnancy, *n* (%)	10 (0.6)	6 (2.0)	0.032
Therapeutic interventions			
HCQ + AZR, *n* (%)	1122 (71.5)	0 (0)	—
Antibiotics, *n* (%)	620 (39.5)	129 (42.7)	0.4973
DRV/c/TAF/FTC, *n* (%)	47 (2.9)	0 (0)	—
Corticosteroids, *n* (%)	0 (0)	44 (5.2)	—
Tocilizumab, *n* (%)	58 (3.7)	28 (9.3)	<0.001
IFN, *n* (%)	2 (0.1)	0 (0)	—
LPV/r, *n* (%)	1 (0.06)	0 (0)	—
Remdesivir, *n* (%)	0 (0)	1 (0.3)	—
ICU admission, *n* (%)	172 (10.9)	53 (17.5)	<0.001
Mechanical ventilation, *n* (%)	124 (7.9)	35 (11.6)	0.018
Hospital stay, days—median (IQR)	5.0 (6.0)	5.0 (8.0)	0.751
All-cause in-hospital mortality, *n* (%)	206 (13.1)	20 (6.6)	0.012
<18 years, *n* (%)	0 (0)	0 (0)	—
18–64 years, *n* (%)	31 (4.4)	4 (3.2)	0.749
>65 years, *n* (%)	175 (20.5)	16 (9.9)	0.012
Male, *n* (%)	114 (13.8)	13 (8.2)	0.069
Female, *n* (%)	92 (12.3)	7 (6.8)	0.139

Values are expressed as numbers and percentages or as medians and interquartile ranges (IQRs) unless otherwise specified. PCR, polymerase chain reaction; CKD, chronic kidney disease; COPD, chronic pulmonary obstructive disease; HCQ, hydroxychloroquine; AZR, azithromycin; DRV/c/TAF/FTC, darunavir/cobicistat/tenofovir/alafenamide/emtricitabine; IFN, interferon; LPV/r, lopinavir/ritonavir; ICU, intensive care unit.
[a] A patient can have more than one comorbidity or therapeutic intervention.

in Barcelona, Spain. Similar changes have been described in different geographical settings [4,5]. Possible explanations are various, including the increased ability to perform an aetiological diagnosis thanks to the availability of diagnostic tests, the lack of which was a severe drawback during the first pandemic wave. This wider availability may have led to the diagnosis of an increased number of asymptomatic patients or patients in earlier phases of the disease when careful surveillance can be performed early and adequate interventions started promptly. The shorter interval between the onset of symptoms and the microbiological diagnosis among patients in the second pandemic wave exemplifies this point (Table 1). During the first pandemic wave, except for supportive care, there were no interventions to modify the pathophysiology of SARS-CoV-2 infection. However, randomized clinical trials have since shown which pharmacological interventions are useless and which have some clinical benefit, such as remdesivir and dexamethasone [6,7]. Nonetheless, remdesivir was not used in our patients, while corticosteroids (mostly dexamethasone) were used only marginally during the study period (Table 2). The preferred immunomodulating agent in our hospital was tocilizumab, and combination therapy was not often used.

We cannot thoroughly exclude viral changes implying shifts in SARS-CoV-2 pathogenicity. However, the evidence of significant viral variation is limited to patients described in Singapore [8] and the amino acid change documented in the viral spike when it reached Europe some months ago, a change which increased its replicative capacity and transmissibility [9]. Recently, a SARS-CoV-2 variant—referred to as SARS-CoV-2 VUI 202012/01 or B.1.1.7, with multiple spike protein mutations—has been detected in the United Kingdom [10]. It is significantly more transmissible than previously reported variants, although it is not clearly associated with more severe disease [10]. Moreover, a new SARS-CoV-2 variant—known as 20H/501Y.V2 or B.1.351, carrying many mutations in the spike protein—is quickly spreading in South Africa, and the P.1 variant, which is predominant in the Amazon region (Brazil), has three mutations in the spike receptor-binding domain thought to affect its transmissibility and antigenic profile [11]. Unfortunately, we do not have viral sequencing available at our hospital to document these possible changes.

Modification of population structure may have played a significant role in pandemic behaviour, explaining the differential patient profile. It could be that the most fragile patients, especially those institutionalized and those living in nursing homes, had already succumbed during the first pandemic wave. Their excess death rate could partially explain the age shift since older adults represented 41.5% and 32.3% of patients in both pandemic waves, respectively (Table 1). Besides, the enormous efforts made to protect this vulnerable population may have impacted its reduced representation during the second wave.

The decreased hospital admission rates and pulmonary infiltrates during the second pandemic wave suggest milder disease (Table 1). Nevertheless, a diagnostic bias cannot be excluded since, in surge one, microbiological tests were reserved for more severe patients (usually those requiring hospitalization) or perhaps for patients with higher survival chances. Measures for controlling the pandemic, such as more cautious social interaction and wearing

Table 3
Multivariable risk factors for death in Covid-19 inpatients

Risk factor	Adjusted odds ratio (95%CI)	p
Surge 1 (versus surge 2)	2.176 (1.286–3.680)	0.004
Age	1.079 (1.063–1.094)	<0.001
Male sex	1.476 (1.079–2.018)	0.015
Comorbidity	1.414 (0.934–2.141)	0.101
ICU admission	3.812 (1.875–7.751)	<0.001
Mechanical ventilation	2.076 (0.968–4.454)	0.061
Intercept	0	<0.001

R^2 of Nagerkelke = 0.244.

masks, could be associated with decreased viral inoculum, and viral load on admission is related to mortality [12,13]. Asch et al. [4] found that the most substantial risk factor for hospital mortality was community prevalence of COVID-19, consistent with such an assumption.

In-hospital all-cause mortality significantly decreased during the second wave, despite the higher percentage of hospitalized people with comorbidities and disease severity markers such as ICU admission and mechanical ventilation (Table 2). The causes of such a decrease are not entirely understood, but they are probably multifactorial, including an earlier diagnosis with less severe lung involvement, and earlier subsequent interventions. The shorter interval between the onset of symptoms and diagnosis suggests that this was an operating mechanism in the pandemic change. However, an essential factor in this prognostic improvement should be the fast-growing learning of most frontline physicians on the operating pathophysiological mechanisms in COVID-19, thereby understanding better COVID-19 management and timing thereof [14]. It is exemplified by pulmonary thrombosis or thromboembolism, which affects a substantial proportion of COVID-19 patients (around 3% of our hospitalized patients) [15]; this may have been overlooked in the first pandemic wave, but it is now routinely sought and adequately prevented or treated [15].

Our results should be viewed in the light of their inherent limitations. They come from a single hospital experience, and thus they might not be generalizable even for other hospitals in the same geographic area. Unavoidable factors especially prevalent during the first surge, such as the availability of diagnostic tests and therapeutic means, might also have decisively influenced the in-hospital mortality rate. Our analyses are restricted to hospital mortality, and therefore the most vulnerable population such as nursing home permanent residents' fatality rate is averted.

In summary, in a highly dynamic pandemic such as COVID-19, the changes observed between successive waves may reflect population and viral changes and increased medical knowledge and integration of new therapeutic means. The COVID-19 pandemic once more exemplifies the old Heraclitus aphorism that "*There is nothing permanent except change*".

Author contributions

PD devised the concept and developed the idea. VP reviewed raw data, IM performed the bibliographic research, IC and HC reviewed the manuscript draft. NdB performed statistical analyses. All authors coordinated and oversaw the development of the manuscript. All authors participated in data interpretation. The manuscript was drafted by PD. All authors provided input to the report and approved the final version of the manuscript.

Transparency declaration

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References

[1] Red Nacional de Vigilancia Epidemiológica. Situación de COVID-19 en España a 9 de diciembre de 2020. Informe nº 56. Situación de COVID-19 en España. Casos diagnosticados a partir 10 de mayo. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/Informes%20COVID-19/Informe%20COVID-19.%20N%C2%BA%2056_09%20de%20diciembre%20de%202020.pdf.
[2] Sehra ST, Salciccioli JD, Wiebe DJ, Fundin S, Baker JF. Maximum daily temperature, precipitation, ultraviolet light, and rates of transmission of severe acute respiratory syndrome coronavirus 2 in the United States. Clin Infect Dis 2020;71:2482–7.
[3] Hosmer DW, Lemeshow S, Sturdivant R. Model-building strategies methods for logistic regression. In: Hosmer DW, Lemeshow S, Sturdivant R, editors. Applied logistic regression. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2000. p. 89–152.
[4] Asch DA, Shells NE, Islam N, Chen Y, Werner RM, Buresh J, et al. Variation in US mortality rates for patients transmitted with COVID-19 during the first 6 months of the pandemic. JAMA Intern Med 2021;181:471–8.
[5] Fan G, Yang Z, Lin Q, Zhao S, Yang L, He D. Decreased case fatality rate of COVID-19 in the second wave: a study in 53 countries or regions. Transbound Emerg Dis 2020:1–3.
[6] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19—final report. N Engl J Med 2020;383:1813–26.
[7] RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with covid-19. N Engl J Med 2021;384:693–704.
[8] Young BE, Fong SW, Chan YH, Mak TM, Ang LW, Anderson DE, et al. Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study. Lancet 2020;396:603–11.
[9] Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell 2020;182:812–27. e19.
[10] European Centre for Disease Prevention and Control. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations in the United Kingdom—20 December 2020. Stockholm: ECDC; 2020.
[11] CDC. Emerging SARS-CoV-2 variant. Updated Jan 28, 2021, https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html.
[12] Bryan A, Fink SL, Gattuso MA, Pepper G, Chaudhary A, Wener MH, et al. SARS-CoV-2 viral load on admission is associated with 30-Day mortality. Open Forum Infect Dis 2020;7. ofaa535.
[13] Gandhi M, Rutherford GW. Facial masking for Covid-19—potential for "Variolation" as we await a vaccine. N Engl J Med 2020;383:e101.
[14] Domingo P, Mur I, Pomar V, Corominas H, Casademont J, de Benito N. The four horsemen of a viral Apocalypse: the pathogenesis of SARS-CoV-2 infection (COVID-19). EBioMedicine 2020;58:102887.
[15] Benito N, Filella D, Mateo J, Fortuna AM, Gutierrez-Alliende JE, Hernandez N, et al. Pulmonary thrombosis or embolism in a large cohort of hospitalized patients with Covid-19. Front Med (Lausanne) 2020;7:557.