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Major determinants of death in patients hospitalized with COVID-19 during the first epidemic wave in Madrid, Spain

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Abstract

Spain is one of the European countries most largely affected by COVID-19, being Madrid the epicenter. A good knowledge of the main features of hospitalized patients during the complete lockdown should improve the management of new COVID-19 surges.

All patients hospitalized at one large tertiary hospital in Madrid for suspected COVID-19 pneumonia from March 1 to May 31 were retrospectively identified.

A total of 1752 patients were admitted with suspected pneumonia due to SARS-CoV-2 infection during the 3-month study period. The peak of daily admissions (n = 84) was reached on March 24, whereas the maximal cumulative number of hospitalized patients (n = 626) occurred on March 30. Overall, 85.3% had a positive PCR test for SARS-CoV-2 at least once during admission. Their median age was 65 (54–77) and 59.9% were male. The median length of hospitalization was of 7 (4–13) days. Roughly 6.5% were admitted at the intensive care unit.

Death occurred in 242 (13.8%). Overall, 75% of deaths occurred in patients older than 75 years-old. It was 38.2% in patients hospitalized older than 80 years-old versus 2.2% in patients younger than 60 years-old ($p < 0.001$). Up to 94 (38.8%) of deceased patients had been transferred from nursing homes. The median Charlson co-morbidity score was 6 in deceased patients.

The in-hospital mortality rate during the first wave of COVID-19 in Madrid was 14%. It was largely driven by older age, the presence of underlying chronic conditions (≥2) and living at nursing homes.

Abbreviations: CCI = Charlson co-morbidity Index, ICU = intensive care unit, IQR = interquartile range.

Keywords: coronavirus, COVID-19, mortality, pneumonia, SARS-CoV-2, Spain

1. Introduction

A novel human coronavirus, SARS-CoV-2, that causes pneumonia and other complications named as COVID-19 was first reported in Wuhan, China, at the end of 2019.[1] During the first trimester of 2020, worldwide spreading occurred and in March the WHO considered COVID-19 as pandemic. To date, more than 14 million confirmed cases have been reported globally, with nearly 600,000 deaths.[2]

Spain has been one of the European countries most largely affected by COVID-19.[3] The first death caused by COVID-19 was reported in Valencia on February 13. Rapid increases in local and community transmissions were soon recognized in large cities, such as Madrid and Barcelona. Complete nationwide lockdown measures were implemented on March 14th in order to reduce viral transmission and avoid the collapse of the health care system. The confinement was extended during 15 days and dragged on during Eastern until April 13th. The plan for easing lockdown restrictions begun on May 8th. By then, a nationwide epidemiological survey reported an overall 5% seroprevalence rate, although it was above 11% in Madrid.[4,5]

The region of Madrid has a population of 6.6 million and was particularly hit by COVID-19, with an official count of 79,884 cases reported up to June 30th with 9,193 deaths.[6] During the peak of the pandemic wave, hospital admissions due to COVID-19 collapsed most hospitals in the city,[3] very much resembling

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what occurred in Milan and New York city.[7,8] Information and knowledge derived from those days, in particular at reference hospitals, might help to preparedness for confronting new surges of SARS-CoV-2 infection. Herein, we analyze COVID-19 hospital admissions and deaths at one large tertiary hospital located in northern Madrid during the complete lockdown and the total period of the stay-home policy.

2. Patients and methods

This retrospective study included all patients initially attended at the emergency unit with suspected COVID-19 pneumonia that subsequently were admitted at the Puerta de Hierro-Majadahonda University Hospital from March 1 to May 31, 2020. This is a large tertiary university hospital located in Northwestern Madrid. Its catchment population approaches 375,000 persons, of whom 69% are aged 14 to 64 years-old. Overall, 13% are above 65 years-old. The health district includes 69 nursing homes that offer a total of 6,755 places. The hospital has 613 beds in individual rooms, including 22 intensive care unit (ICU) beds, and all medical and surgical specialties.

Our study was approved by the hospital review board (PI134–20) and consent was requested for all patients to include their clinical information within a database for epidemiological and clinical studies.

We reviewed electronic medical records and laboratory results for all hospital admitted patients with COVID-19. The main demographics (gender and age), admission to ICU, and diagnosis discharge (including death if so) were recorded for each subject. Deceased patients were subject to particular examination. The case definition for COVID-19 was made following the ECDC criteria.[9] In more detail, clinical criteria included at least one of the following symptoms: cough, fever, shortness of breath, sudden onset of anosmia, and ageusia or dysgeusia. Diagnostic imaging criteria included radiological evidence showing pulmonary infiltrates consistent with COVID-19. Lastly, laboratory criteria included the detection of SARS-CoV-2 nucleic acids in clinical specimens, generally nasopharyngeal and/or oropharyngeal swabs, following WHO protocol. All individuals with clinical symptoms of COVID-19 and compatible imaging criteria were considered as COVID-19 cases despite negative PCR.

For all deceased COVID-19 patients, the presence of co-morbidities was recorded, including arterial hypertension, dyslipidemia, diabetes, chronic kidney disease, cancer, neurocognitive impairment (Alzheimer, other dementias and other mental disorders), heart disease, and chronic obstructive pulmonary disease. The baseline Charlson co-morbidity Index (CCI) was used to estimate the risk of mortality, taking into consideration that the overall 10-year survival rate is 98.3% in patients with a CCI = 0, goes to 77.48% in those with a CCI of 3, and drops to 21.36% in those with a CCI of 5 or more.[10]

2.1. Statistical analysis

Continuous variables were expressed as mean and standard deviations (SD), and medians with interquartile ranges (IQR). Categorical variables were summarized as counts and percentages. Patients were grouped by range age and by median age. Age groups were stratified into 4 groups, as follows: 0 through 59 years; 60 through 69 years; 70 through 79 years; and ≥80 years. Time-to-events were measured in days from the date of hospital admission to the date of hospital discharge or in-hospital death.

The Student *t* test was used for the comparison of continuous variables and the Wilcoxon-Mann-Whitney tests was used for non-parametric variables. Categorical variables were compared using the chi-square test. All analyses were performed using the SPSS version 20.0 software statistical package (SPSS Inc., IBM, Armonk, NY).

3. Results

Between March 1 and May 31, 2020, a total of 1752 patients were hospitalized with suspected COVID-19 pneumonia. Overall, 85.3% of COVID-19 cases had a positive SARS-CoV-2 PCR at least once during admission.

The peak of daily admissions was reached on March 24, with 84 patients. The highest cumulative number of hospitalizations with COVID-19 was reached on March 30, with 626 patients (Fig. 1). It should be noted that hospital beds were doubled (two per room) once it became apparent that the emergency unit was overwhelmed by the continuous arrival of COVID-19 patients.

One month after lockdown begun, the number of hospitalizations fell to figures similar to those recorded at the time the confinement started. Hospital admissions due to COVID-19 reached the lowest levels at the end of April, and since then only sporadic admissions occurred until the end of May.

Overall, 59.9% of admitted patients were male. The median age (IQR) was 65 (54–77). There were no statistical significance differences between positive and negative SARS-CoV-2 PCR individuals for any of the demographics, clinical, radiological and laboratory parameters analyzed. Patients were hospitalized during a median (IQR) length of 7 days (4–13). A total of 116 (6.6%) required admission at the ICU. In this group of patients, the median (IQR) length of hospitalization extended to 36 (22–51) days.

Overall 648 (37%) of COVID-19 hospitalized patients were younger than 60 years-old. The median length of hospitalization was significantly shorter in this group compared to older patients (Table 1). Furthermore, only 6.6% of the younger COVID-19 patient group required admission at ICU, whereas it rose to 10% in the rest ($P < .001$).

Death occurred in 242 (13.8%) of COVID-19 hospitalized patients. The main predictor of in-hospital mortality was older age. The death rate in the younger group was only 2.2%, whereas it rose up to 38.2% in those older than 80 years-old ($P < .001$). Overall 75% of deaths occurred in patients older than 75 years-old.

The median age of deceased patients was 82 (73–87), being 58.7% male. Overall, 10.3% of deaths (25 patients) occurred in patients that had been admitted at the ICU. The median length of hospitalization before death was 6 (3–14) days, being significantly shorter in older than younger patients (Table 2). Overall 38.8% of deaths occurred in patients that were living at nursing homes before hospitalization. It should be noted that 28.6% of COVID-19 deaths in the younger group corresponded to institutionalized individuals, many of them suffering from serious conditions, mostly neurocognitive impairment, cancer and/or lung disease.

Among COVID-19 deceased individuals, a median of 2 (1–3) comorbidities were present before hospitalization, being the most prevalent: hypertension (62.2%), dyslipidemia (38.8%), heart disease (37.6%), diabetes (28.1%), cancer (20.2%), neurocognitive impairment (16.9%), lung disease (12.4%) and chronic kidney insufficiency (11.2%). As expected, hypertension,

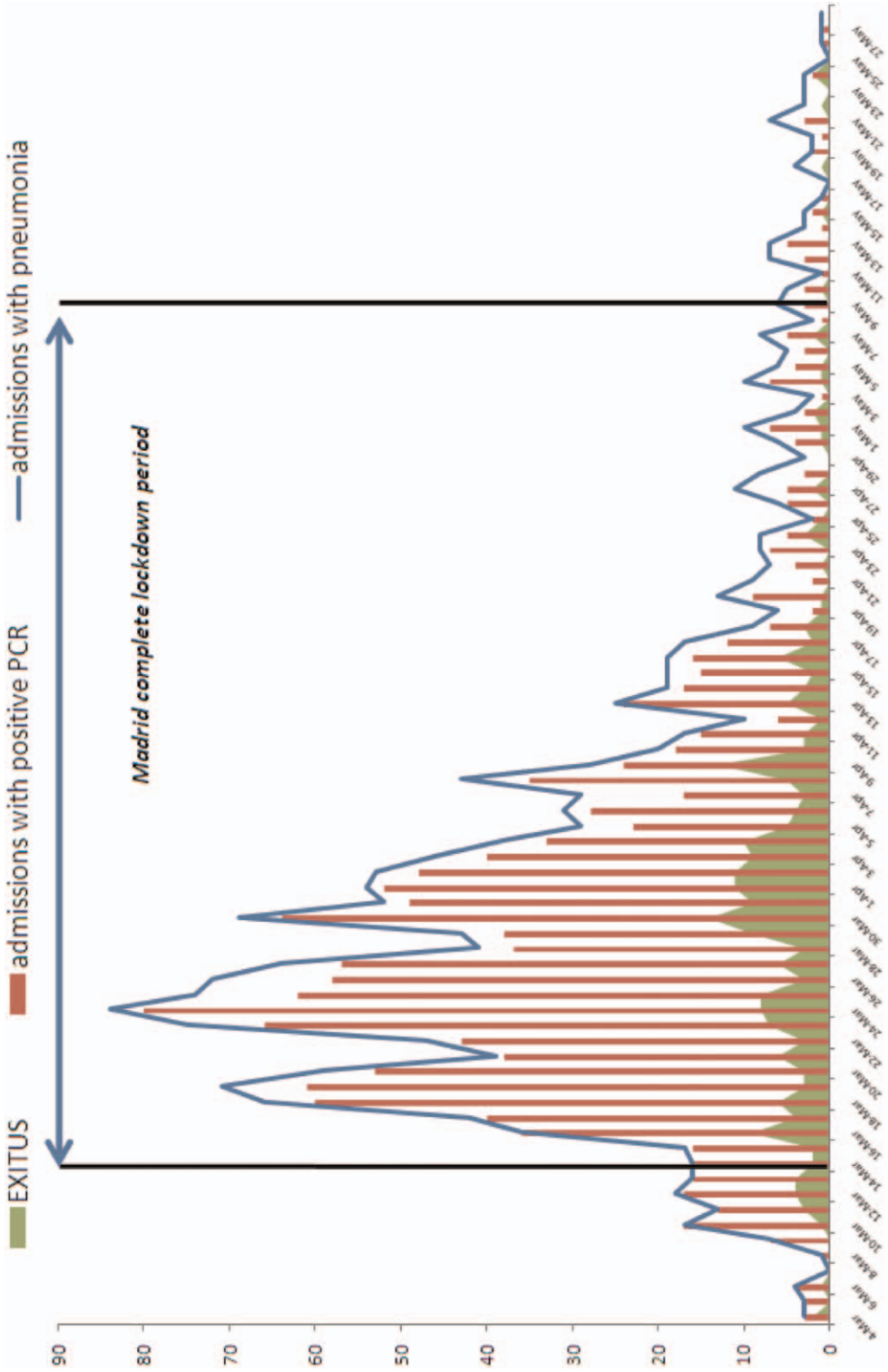

Figure 1. Daily hospital admissions with suspected COVID-19 from March 1st to May 31st at a tertiary Hospital (Madrid, Spain).

Table 1

Main characteristics of patients hospitalized with COVID-19 according to age.

		Age range (yr-old)				
	Total	**<60**	**60-69**	**70-79**	**≥80**	***P***
N (%)	1752	648 (37)	388 (22.1)	355 (20.3)	361 (20.6)	–
Male, N (%)	1050 (59.9)	397 (61.3)	252 (64.9)	222 (62.5)	179 (49.6)	<.01
SARS-CoV-2 PCR positive, N (%)	1495 (85.3)	554 (85.5)	347 (89.4)	307 (86.5)	287 (79.5)	ns
Median length of hospital admission (d) (IQR)	7 (4–13)	6 (3.75–10)	9 (5–15)	10 (6–16)	7 (4–13)	<.01
Intensive Care Unit, N (%)	116 (6.6)	43 (6.6)	35 (9.0)	38 (10.7)	–	<.001
Death, N (%)	242 (13.8)	14 (2.2)	26 (6.7)	64 (18)	138 (38.2)	<.001

IQR = interquartile range; ns = no significant.

dyslipidemia and heart disease were significantly more frequent in older than younger COVID-19 deceased patients (Table 2). Overall, the median Charlson co-morbidity index was 6, being 3 in the younger group and 7 in the older group. Unfortunately, body mass index was not recorded regularly in all hospitalized patients during the first months of COVID-19 pandemic. For this reason, it was not possible to evaluate this factor, which has been associated with higher mortality in previous studies.[11]

4. Discussion

The arrival of the first COVID-19 wave in Spain was very abrupt, with rapid surges in large cities such as Madrid. During the week that followed the nationwide lockdown on March 14th, the health system became stressed and overwhelmed as never before.[3] High pressure with more than 30 new daily hospitalizations was sustained for one month, with a peak of more than 80 admissions per day. The number of deaths due to COVID-19 rose with peaks of more than 10 per day, with an average of two weeks of delay after hospital admission. This unprecedented scenario was accompanied by a complete switch of allocation resources, doubling the number of beds per room and expanding and converting spaces as ICU and intermediate care units. Almost all available physicians and nurses were assigned to care for COVID-19 patients. Schedules were forced and protective equipment was often scarce. The hit was tremendous and encouraged us to assess what could we learn from this unique experience. In this study we aimed to identify the most relevant information that could be used for an adequate preparedness in case of new COVID-19 surges.

During the whole 3-month study period, a total of 1752 COVID-19 patients were admitted at our hospital. Infection with SARS-CoV-2 was confirmed using PCR in more than 85%. Clinical parameters as well as outcomes did not differ for the remaining 15% of suspected COVID-19 pneumonia cases. False negative PCR results have been reported occasionally, mainly as result of poor sampling or too long symptom deferral.[12,13] During the first days of the pandemic, we excluded influenza, syncytial respiratory virus and other potential etiological respiratory agents in the subset of non-confirmed but suspected COVID-19 cases.

The median age of patients hospitalized with COVID-19 was 65 years-old and 58% were male. Only 38% had less than 60 years of age. In the younger group of patients, most admissions were short with a median of 6 days, and only 6.5% required transfer to the ICU. Thus, critically ill COVID-19 patients younger than 60 years-old are rare. Indeed, the overall fatality rate in this group was low (2.2%) and mainly occurred in patients with serious pre-existing conditions and co-morbidities. Similar findings have been highlighted by others.[14–17] Therefore, gaps in knowledge about the coronavirus infection early on during the first days of the pandemic could have led to avoidable hospital admissions that would have benefited from adequate home care. In the future, a distinct consideration for younger patients with COVID-19 could relieve emergency units and hospital wards.

Table 2

Main characteristics of deceased patients with COVID-19 according to age.

		Age range (years-old)		
	Total	**≤ 65**	**> 65**	***P***
N	242	21	219	–
Male, N (%)	141 (58.3)	13 (61.9)	88 (40.2)	.06
Admission length (d) (median, IQR)	6 (3–14)	15 (6–38)	6 (3–11)	.002
Prior living at nursing homes (%)	94 (38.8)	6 (28.6)	88 (40.2)	ns
Charlson Co-morbidity Score (median, IQR)	6 (5–8)	3 (2.5–5.5)	7 (5–8)	<.001
o-morbidities (median, IQR)	2 (1–3)	1 (0–2)	2 (1–3)	<.001
Hypertension, N (%)	150 (62)	3 (14.3)	147 (67.1)	<.001
Dyslipidemia, N (%)	94 (38.8)	3 (14.3)	91 (41.5)	.018
Diabetes, N (%)	68 (28.1)	5 (23.8)	63 (28.8)	ns
Heart disease, N (%)	91 (37.6)	2 (9.5)	94 (42.9)	.004
Chronic kidney disease, N (%)	27 (11.2)	1 (4.8)	26 (11.9)	ns
Cancer, N (%)	49 (20.2)	3 (14.3)	46 (21)	ns
Lung disease, N (%)	30 (12.4)	5 (23.6)	25 (11.4)	.15
Neurocognitive impairment, N (%)	41 (16.9)	4 (19)	37 (16.7)	ns

IQR = interquartile range; ns = no significant.

The overall mortality rate at our hospital was 13.8%. By far, older age was the major determinant of death, rising up to 38.8% in the subset of patients above 80 years-old. Interestingly, higher mortality rates (28%) have been reported for COVID-19 patients admitted at other hospitals located in the Madrid region as well at other Spanish hospitals during the same period.[18,19] A recent study from 92 US hospitals reported 23% of deaths among 11,210 hospitalized adults with COVID-19.[20] Possible causes of this discrepancy may include the rapid initiation and broader use of corticosteroid therapy at our institution. In a recent report from our hospital,[20] patients received steroid treatment within a median of 10 days after the symptom onset, presumably during the inflammatory surge of the disease. Indeed, the survival of patients with SARS-CoV-2 pneumonia was significantly higher in the group that received corticoids compared to the rest.[21] In addition, a significant number of severely ill COVID-19 patients were treated with tocilizumab (data not shown), a monoclonal interleukin 6 blocker that recently has been shown to reduce mortality up to 45% in the subset of COVID-19 patients under mechanical ventilation.[22] Furthermore, early planning and the possibility for doubling the number of beds per room delayed the early overload of wards and ICUs, contributing to attenuate mortality rates. Finally, the health district covered by our hospital is the wealthiest in Madrid, with a disproportionate representation of patients with high socioeconomic status, hygiene and cleaning, homes with large spaces and garden areas, all of which could have contributed to infections with low inoculums and potentially less severe COVID-19 disease episodes.[23]

It is noteworthy that more than 80% of deaths occurred in individuals with at least one serious underlying illness, such as cancer, heart disease, diabetes and/or other metabolic diseases. In this sense, the median CCI of deceased patients index was 6, with an estimated 10-year survival of 2.25%, reflecting their fragility, comorbidities and low life expectancy. This observation is in agreement with data from China, Italy and the United States, reflecting the linkage between underlying cardiovascular conditions and COVID-19 severity.[24–26]

Finally, and even though there was very important medical and nursery support mobilized from the hospital to the nursing homes that managed the epidemic in these centers, it must be pointed out that 40% of deceased patients with COVID-19 at our hospital had been transferred from there. This was the case not only for the elderly population but also for a significant proportion of younger COVID-19 patients. The rapid spread of the coronavirus among residents within communities has been associated with close contact and prolonged viral exposure.[23,27] Given that the population living in nursing homes is extremely vulnerable due to COVID-19 as result of its dependency, older age and associated co-morbidities, it seems worthy to work providing adequate medicalization and improved protective procedures to reduce harm in these settings to minimize harm facing future COVID-19 surges.

All knowledge drawn from the first COVID-19 wave should encourage to build more efficient measures for reducing harm during a second wave of COVID-19 during fall or anytime. First, hospitals with the capacity to expand the number of beds and staff would be more prepared to contain the stressful flow of patients on need for hospitalization, particularly when the number of daily admissions surpasses 50 per day. Second, most patients under 60 years-old should be assessed carefully and when possible should be managed at home by well-trained primary care physicians and nurses. This decision will alleviate stress and pressure at hospitals. Third, efforts for protecting persons above 80-years-old should be maximized, especially if those living at nursing homes and with co-morbidities. In this regard, periodic SARS-CoV-2 antibody testing in these facilities might help to split out the population still susceptible to infection and focus to protective efforts in this subset of residents.[28]

In summary, the first wave of COVID-19 hit in an unprecedented manner all tertiary hospitals in Madrid. The mortality rate at our institution was 14%, lower than at other clinics in the city, most likely as result of earlier introduction of corticosteroids and tocilizumab in patients with most severe illness. In the absence of a protective vaccine, harm reduction plans confronting new COVID-19 surges should consider expanding home care management for younger patients and improving protective measures for the elderly at nursing homes.

Author contributions

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