Clinical features and outcomes of hospitalized COVID-19 patients in a low burden region.

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Abstract

Data on the clinical features and outcomes of COVID-19 patients from countries with low disease burden are rare. Greece, however, presented a low burden of COVID-19 disease during the first pandemic outbreak. This is a retrospective study of COVID-19 hospitalized patients in Greece. Clinical data were extracted from medical records using univariable and multivariable logistic regression analysis to assess the factors associated with ICU admission and in-hospital death. Eighty five patients were included in this study, 49 (57.7%) male with median (25^{th}-75^{th}) age 60 (49-72) years old. Sixty-one (72%) of them had at least one comorbidity with hypertension being the most common (45,6%). More than half (56%) had severe or critical disease, 20% required ICU care (14% received invasive ventilation) and 10.7% died. Solid tumor (p=0.021) and NEWS score (p=0.048), thrombocytopenia (p=0.036) or involvement of all lung fields in chest x-ray (p=0.002) on admission were independent risk factors of ICU admission. Immunosuppression (p=0.032) and thrombocytopenia (p=0.049) were independent predictors of death. Hospitalized COVID-19 patients in a European country with a low burden of the disease, in which hospital capacities had not been overwhelmed, had lower mortality rate compared to those reported patients hospitalized in regions with a high burden of the disease.

Introduction

In December 2019, an outbreak of pneumonia, of an unknown cause, occurred in Wuhan (Hubei, China) [1]. A novel coronavirus was isolated from lower respiratory tract specimens and identified as the causative agent of the later designated Coronaviruses Disease 2019 (COVID-19) spread rapidly worldwide, and ultimately, characterized as a pandemic by WHO in early March [2, 3]. The clinical spectrum of COVID-19 is wide, ranging from little or no symptoms, to severe or critical illness that in 6-26% of the hospitalized patients require Intensive Care Unit (ICU) admission [4] and results in death [4-5]. Interestingly, hospital mortality varies considerably between different countries ranging from 4% to 20% and may be up to 40% among patients requiring ICU admission. [5]. This variability is not clearly explained and may reflect variations of disease severity between different cohorts or different availability of treatment resource in different institutions and different periods. Most of the available information comes from areas with a high pandemic burden and very little is known about patients from a low incidence region [6].

Greece is one of the countries with a low burden of COVID-19 disease during the first pandemic outbreak. The first COVID-19 case was reported in February 2nd and a generalized lockdown was applied in March 3d when the community spread of the infection was still low. This held back the epidemic protecting the National Health Care System from excessive demand. Here, we describe the clinical characteristics, the

clinical course, the risk factors, and the outcomes of patients with COVID-19 treated at a major Greek hospital during the spring pandemic outbreak.

Methods

Study design

This retrospective, observational study, was performed at Evaggelismos Hospital (Athens, Greece), specifically, a referral center for patients with SARS-CoV2 infection. We analyzed patients who were admitted between March 11 and May 18, 2020. We included patients: with laboratory (real-time reverse-transcriptase polymerase-chain reaction assay on nasopharyngeal swab specimens) confirmed SARS-Cov-2 infection who were then immediately admitted in the COVID-19 ward. Patients admitted to the ICU were afterwards transferred to the COVID-19 ward. The final date of follow up was July 22. The Ethics Committee of Evaggelismos Hospital approved this study.

Clinical Data

The medical records of the patients were reviewed to obtain data on age, sex, as well as exposure history, presenting symptoms, vital signs and laboratory values on admission, and treatment. Radiologic assessment included chest radiography for all patients on admission also computed tomography (CT), to some of them, when required. Chest x-rays were scored with grades 0-4 according to how many of the four lung fields appeared abnormal, by two experienced pulmonologists, generating a Lung Field Score (LFS). We defined the clinical severity at the time of admission using the National Early Warning Score (NEWS) 2 [7]. The overall disease severity i.e. the most severe state during the disease was defined according to the Chinese management guideline for COVID-19 (version 7) [8]. Specifically, the outcomes under consideration were ICU admission and death.

Statistical analysis

Continuous variables were expressed as medians and in interquartile ranges. Categorical variables were summarized as counts and percentages. Univariable and multivariable logistic regression analysis was used to assess the impact of variables measured on admission on each of the two dichotomous outcomes (admission to ICU, death during hospitalization). Adjusted odds ratios were obtained with the corresponding 95% confidence intervals

Results

Patients' characteristics

Eighty-five patients, 49 (57.7%) male, with median (25^{th}-75^{th}) age 60 (49-72) year-old (y.o,), were included in the study (table1). The age distribution is as follows: 15 (17.7%) patients were 20-39 y.o., 31 (36.5%)

were 40-64 y.o. and 39 (45.9%) were ≥ 65 y.o. Twenty-six patients (30.6%) were smokers or ex-smokers. In 50%, there was no history of contact, yet in 16% there was a contact with a SARS-CoV2 (+) subject, 10% had recently traveled in places with increased community dissemination of the infection and 14.9% of the cases were health-care associated (including nursing homes). The median (25^{th}-75^{th}) duration of the symptoms until admission was 7 (5-10) days. The majority (72%) of the patients had comorbidities including hypertension (45,6%), diabetes (20%), solid tumors (17.7%), chronic obstructive pulmonary disease (COPD, 9.4%), coronary artery disease (9.4%), immunosuppression (treatment with corticosteroids or anti-TNFα agents or active hematologic malignancy, 8.5%) and chronic kidney disease (4.7%).

Chest x-ray appeared normal in 20 (23.5%) upon admission. Most of the patients with an abnormal chest x-ray had alveolar opacities, 6 (7%) had reticular and 6 (7%) as well as mixed alveolar-reticular opacities. The median (25^{th}-75^{th}) LFS was 2 (1-3.5). A Chest CT was conducted in 21 patients within 48 hours upon admission (supplementary table 1). All CTs demonstrated bilateral disease. Lower lobe-predominance was observed in 20/21 patients. The lesions were predominately peripheral in most patients. Even though a variety of parenchymal lesions were identified, all patients exhibited ground glass opacities.

Treatment and disease progression

Hydroxychloroquine 400mg/bid for the first day, 200mg/bid for 7 days and azithromycin 500mg/qd for 5-7 days were administered in 76 (90.5%) of the patients according to the national guidelines for the treatment of COVID-19. Remdesivir and Colchicine was given in 3 and 7 patients, respectively, in the setting of clinical trials (13,14). One patient was given convalescent plasma in the setting of a clinical trial. Steroids were administered in 5 patients during ICU stay. Thromboprophylaxis was adopted as standard therapy unless already in full anticoagulant therapy for previously diagnosed diseases.

On admission, 29/85 (34%) had hypoxemic respiratory failure. Within a median (25^{th}-75^{th}) 3 (1-4) days from admission 17 (20%) patients critically deteriorated and were transferred to the ICU, for monitoring and treatment with high-flow nasal oxygen (HFNO, 9 patients) or a non-rebreather mask (8 patients). Twelve of them (14% of the whole cohort) finally received mechanical ventilation. Three of them required renal replacement therapy. The median (25^{th}-75^{th}) duration of ICU stay was 23 (11-99) days. Several clinical and laboratory features at the time of hospital admission, including male gender, immunosuppression, solid tumor and markers of severe respiratory disease and systemic inflammation (table 2), were associated with subsequent ICU admission. Multiple logistic regression analysis revealed that solid tumors, thrombocytopenia, increased NEWS2 score and involvement of all lung fields in chest x-ray present independent risk factors for ICU admission (Table 3).

Based on their entire disease course and according to previously proposed criteria (12), 18 (21%) of the patients turned out to have mild disease, 19 (22%) had moderate disease, 36 (42%) had severe disease and finally 12 (14%) had critical disease. Overall, the median (25^{th}-75^{th}) duration of hospital stay was 11

(6-17) days. Importantly, no dissemination of the virus resulting in infection of patients or members or personnel occurred in the unit.

Mortality

At the time of data analysis, 84/85 patients had definite outcomes: 9/84 (10.7%) patients died. Specifically, 5 in the ICU, 2 at our COVID-19 unit during the acute phase of the disease, and 2, having survived the acute phase, were transferred to a second hospital due to their prolonged recovery from COVID-19. One patient was recovering in the wards after a long stay in the ICU and yet the rest were discharged. The four patients who died in the wards were elderly (81-91 y.o.) with multiple co-morbidities and bacterial infections. Four out of the five patients who died at the ICU were immunocompromised because of active hematological malignancies and relevant therapies. The fifth patient had tetraplegia due to a neck trauma. A case of acute myocardial infraction treated with primary percutaneous coronary intervention was the only clinically evident thrombotic event. Age, solid tumors, immunosuppression and several clinical (increased NEWS score and respiratory rate, respiratory failure, dyspnea) and laboratory (increased serum CRP, troponin and d-dimer levels and decreased lymphocyte and platelet counts) features on admission, were linked with a fatal outcome (table 2). However, multiple logistic regression analysis revealed that only immunosuppression and thrombocytopenia were independent risk factors for death (table 3).

Discussion

This is to report on the clinical/laboratory features, the clinical course, and the outcomes of 85 patients with COVID-19, admitted in a COVID-19 designated department in a low burden European region. Our main findings are: 1) more than half (56%) of the patients had severe/critical disease, 20% required ICU care (14% received mechanical ventilation) and 10.7% died; 2) NEW2 score, solid tumors, thrombocytopenia and involvement of all lung fields in chest x-ray were independent risk factors of ICU admission; 3) Immunosuppression and thrombocytopenia were independent predictors of death.

This is the first report of Greek COVID-19 patients treated at the designed hospital wards. Greece experienced a relatively low community spread of SARS-CoV2 resulting in a moderate burden imposed on its health-care system. Until the 22th of July (date of the last follow-up assessment of our patients) only 137 patients were admitted at the ICUs and 200 died (mortality 1.865/100,000) throughout the country (data obtained by the national COVID-19 registry- https://eody.gov.gr/epidimiologika-statistika-dedomena/ektheseis-covid-19). The clinical findings of our patients on presentation are similar to those reported elsewhere [5]. Significantly, most of them had severe/critical disease and 20% required ICU support. The hospital mortality was 10.7%, mainly restricted to patients with hematological malignancy and elderly patients with several comorbidities and bacterial infections. In general, COVID-19 hospital

mortality is thought to be 15-20% [5]. As expected, most data, come from severely hit countries. Liang et al. Compared to the outcomes of patients hospitalized in, or outside, Hubei (the pandemic epicenter) [6] Hubei hospitals had higher mortality, which most likely should be attributed in the substantially higher rate of comorbidities and severe disease compared to those from other regions in China. Therefore, to compare the outcomes observed in our patients with those reported elsewhere, the severity of the disease and the underlying health problems of patients should be considered. In China, Guan et al, have reported probably the lowest percentages of ICU admission (5%) and death (1.4%) in the literature [9]. However, only 15,7% of the patients had severe/critical disease and 23.7% com-morbidities – in our cohort these percentages were 56% and 72%, respectively. In contrast, Zhou et al, in patients with disease severity similar to ours but with lower prevalence of comorbidities (48%), reported 26% ICU admission and high (28.3%) mortality [10]. New York City was another region with high incidence of COVID-19 and heterogeneity in reported outcomes. Richardson et al, report 14% ICU care and 21% mortality among hospitalized patients, with median age 63 (ours 60) y.o. and 94% of them having at least one comorbidity. On admission, 20% of the patients had respiratory failure – 34% in our cohort [11]. In other words, these patients, despite being less severely ill and less often admitted in ICU, experienced double mortality compared to our patients. The higher prevalence of comorbidities may have contributed to that discrepancy. In the UK, among 20,133 patients, 17% required ICU care and 26% died [12]. The comparison of the UK cohort with ours is difficult due to the fact that the authors do not report the disease severity while, at the time of their observations' release, 1/3 of the patients were still hospitalized. Nevertheless, mortality was significantly higher than ours, despite the similar percentage of comorbidities (76%).

In Germany, invasive ventilation was required in 17% of hospitalized patients and mortality was 22%. Mortality in the non-mechanically-ventilated population was 16% [13]. It is not clear why, although the percentage of the German patients requiring ICU was comparable to ours, significantly however, mortality was double.

How should one explain the favorable outcome observed in this study? Pharmacological treatment most likely, had no, or only a weak effect. Hydroxychloroquine plus azithromycin was given to 90% of the patients, according to the National guidelines at that time were not proved to be beneficial. Furthermore, in randomized trials [14-15]. Remdesivir, colchicine and steroids which may hinder COVID-19 [16-18] had been administered in very few patients. The use of early prophylactic anticoagulation, as standard treatment, might have positively affected survival since thrombosis is an important component of COVID-19 pathogenetic spectrum [19]. Even though clinically evident thrombotic event, except a case of acute myocardial infraction, did not occur** in our cohort, the impact of anticoagulation in COVID-19 outcomes remains highly doubtful. While pharmacotherapy for COVID-19 is still evolving, high quality supportive care remains the cornerstone of COVID-19 treatment. Therefore, the fact, that the COVID-19-designated wards were not overwhelmed and there was no lack of technical and human resources and available ICU space, made it possible for every patient with severe respiratory failure to be timely transferred from an isolated, unsupervised ward room to a proper place for monitored and advanced respiratory support. This,

certainly may have an impact in overall survival. However, the fact that our patients had better outcomes than that of the German cohort, where health recourses, included ICU space and were also adequate yet inexplicable and may trigger further investigation.

In a potentially fatal disease like COVID-19, predictive and/or prognostic factors on admission are important for guiding decision-making. We found that patients with solid tumors, thrombocytopenia, increased NEWS score and involvement of all lung fields in chest X-ray at the time of their hospital admission, were more likely to need ICU care, while thrombocytopenia and immunosuppression suggested increased risk of death. In our cohort, NEWS score, known to predict in-hospital mortality [7], was found to be a predictor of ICU admission but not death. Though adverse outcomes have been linked to patient's features such as age, male gender, and certain com-morbidities [5], findings differ between studies. For instance, in Metropolitan Detroit patients, male sex, excessive obesity and chronic kidney disease (CDK) were risk factors for ICU admission [20]. In agreement with our results, age was not an independent predictor of their patients' ICU care and needs. However, this cohort has some distinctive characteristics: Most of its patients were female (60.3%), African American (73%), with high prevalence of CKD (36.5%) and BMI>33.6. Zhu et al found older age, d-dimers>1 ng/ml and higher SOFA score on admission to be associated with higher odds of hospital death. However, a greater proportion of patients have critical on hospital admission (26%) compared to our series (14%) [10]. Scores generated to predict COVID-19 mortality differ substantially [21-23[. Iaccarino et al, based on Italian population, identified age and Diabetes Mellitus, COPD and CKD as indicators of mortality [21]. Zhao et al did not find age to be amongst the top predictors [22], while Dong et al concluded that only hypertension and not age could predict an in-hospital death [23]. This divergence may suggest that the risk factors for ICU admission or death may critically depend on the characteristics of the population, in which these scores were developed, meaning that local validation of scores developed elsewhere may be required.

Some limitations of the present study deserve a comment. First, due to its retrospective design, data on parameters, such as BMI or ethnicity, were not available for all patients and not investigated as putative predictors of ICU admission or death. Second, the small size of the cohort and the low number of events might result in low statistical power. However, the COVID-19 ward was based in the largest hospital in the country as well as the busiest, especially, during the spring pandemic, which means that our findings probably provide a representative view of hospital COVID-19 care in low burden European regions.

In conclusion, hospitalized COVID-19 patients in a European country with a low burden of the disease, although possessing similar clinical features and disease severity, they have more favorable outcomes compared with patients from regions with a high burden of the disease. These findings might mostly be explained by the fact that the appropriate health resources were available even at the peak period of the pandemic, thus permitting the proper support of patients with severe and critical disease. This in turn

highlights the vital role of prevention of the COVID-19 spread in ensuring favorable outcomes for those with more advanced disease.

Declarations

The authors declare no conflict of interest

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Tables

Table 1. Patients' clinical and laboratory features on admission (N=85 patients admitted between March 11 and May 18, 2020)

Symptoms and Signs		Laboratory findings	
Respiratory rate (/min)	18 (15, 24)	Lymphocytes (/µL)	1045 (705-1370)
Respiratory rate >24/min	38 (44.7%)	Platelets (x10^3/µL)	193 (151-249)
Heart rate (/min)	90 (80, 100)	C-Reactive Protein (mg/dL)	5.6 (2.5-10.6)
Systolic Blood Pressure (mmHg)	120 (110, 125)	ESR (mm)	45 (29-77)
Fever	76 (89.4%)	Ferritin (ng/mL)	248 (126-555)
Temperature (^{o}C)	37.5 (36.8, 38.2)	Fibrinogen (mg/dL)	521 (431-627)
Dyspnoea	41 (48.2%)	d-dimers (µg/mL)	0.35 (0-1.11)
Cough	51 (60.0%)	LDH (IU/L)	322 (237-379)
Chest pain	13 (15.5%)	Glucose (mg/dL)	110 (96-128)
Sore throat/Nasal Congestion	4 (4.8%)	ALT (IU/L)	24 (16-38)
Diarrhoea/Vomiting	20 (23.5%)	AST (IU/L)	29 (24- 40)
Anosmia/Ageusia	8 (9.4%)	ALP (IU/L)	60 (49-66)
Myalgia	10 (11.9%)	GGT (IU/L)	23 (15-51)
Fatigue	20 (23.8%)	Na^+ (mEq/L)	137 (134-140)
Headache	7 (8.2%)	K^+ (mEq/L)	4.2 (4.0-4.5)
NEWs score	3 (2, 6%)	Ca^{++} (mg/dL)	8.9 (8.4-9.1)
NEWs score >5	31 (37.4%)	CPK (µg/L)	85 (63-198)
		Troponin (pg/mL)	7 (3-15.5)
		Creatinine (mg/dL)	0.9 (0.7-1.1)
		PO_2/FiO_2	343 (276-429)

Data are presented as median (25^{th}-75^{th} percentile) or number (%)

Abbreviations: ESR, Erythrocyte Sedimentation Rate; LDH, Lactate Dehydrogenase ; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline phosphatase; GGT, *Gamma-Glutamyl* Transpeptidase.

Table 2. Patients' features on admission that are statistically significantly associated to ICU admission and/or death

	ICU admission		p	Death		p
	No (N=68)	Yes (N=17)		No (N=76)	Yes (N=9)	
Male gender	35 (51.5)	14 (82.4)	0.021	44 (57.9)	5 (55.6)	0.893
Age (year old)	62 (44-73)	60 (53-68)	0.9	60 (47-72)	69 (60-84)	0.041
Solid tumor	8 (11.8)	7 (41.2)	0.004	11 (14.5)	4 (44.4)	0.026
Immunosuppression	4 (6.1)	3 (18.8)	0.103	3 (4.1)	4 (44.4)	<0.001
NEWS score	2 (2, 5)	6 (4, 7)	<0.001	3 (2, 5)	6.5 (4, 8.75)	0.007
NEWS score >5	21 (30.9)	10 (66.7)	0.010	25 (33.3)	6 (75.0)	0.021
Respiratory rate (/min)	18 (15, 22)	25 (20, 30)	<0.001	18 (15, 24)	25 (17, 25)	0.057
Respiratory rate >24/min	23 (33.8)	15 (88.2)	<0.001	31 (40.8)	7 (77.8)	0.035
Respiratory failure	17 (25.0)	12 (70.6)	0.010	22 (28.9)	7 (77.8)	0.003
Temperature (^{o}C)	37.5 (36.8-38.0)	38.4 (37.2-38.9)	0.023	37.5 (36.8-38.2)	37.3 (36.3-39.0)	0.9
PO_2/FiO_2	357 (295-430)	262 (196-371)	0.009	350 (276-430)	276 (127-362)	0.068
Dyspnea	29 (42.7)	12 (70.6)	0.039	32 (42.1)	9 (100.0)	0.001
Chest pain	13 (19.4)	0 (0.0)	0.048	12 (16.0)	1 (11.1)	0.702
C-reactive protein (mg/dL)	4.55 (1.22-9.65)	9.3 (5.5-21.2)	0.002	5.25 (1.5-9.45)	14.9 (7.7-25.8)	0.009
Lymphocytes (/µL)	1115 (722.5-1472.5)	995 (337, 1220)	0.052	1145 (752-1417)	250 (105-510)	<0.001
Platelets (x10^3/µL)	211.5 (162.5-255.75)	130 (102-196)	<0.001	199.5 (159.75-253.25)	105 (77-182)	<0.002
Ferritin(ng/mL)	195 (106-365)	855 (230-2740)	<0.001	230 (119-506)	437 (149-2965)	0.173
LDH (IU/L)	295 (224-370)	355 (325-493)	0.006	315 (226-375)	339 (304-450)	0.191
Glucose (mg/dL)	108 (95-124)	128 (101-214)	0.023	110 (96-129)	106 (96-181)	0.721

ALT (IU/L)	23 (14-31)	34 (20-51)	0.012	23 (15-37)	28 (14-45)	0.602
AST (IU/L)	27 (22-38)	37 (28-74)	0.020	28 (24-39.5)	34 (20-65)	0.475
GGT (IU/L)	22 (15-37)	51 (18-118)	0.010	23 (15-49)	41 (13.5-135)	0.290
Troponin (pg/mL)	7 (3-16)	10 (6.5-13.5)	0.273	7 (3-13)	30 (10-87)	0.002
Fibrinogen (mg/dL)	495 (403-593)	577 (543-778)	0.001	521 (423-631)	548 (469-571)	0.446
d-dimers (µg/mL)	0.365 (0-1.07)	0.195 (0-2.17)	0.706	0.0 (0-1.0)	2.17 (0.5-3.5)	0.005
Lung Field Score						
0	20 (29.9)	0		20 (26.3)	0	
1	9 (13.4)	0		8 (10.5)	1 (12.5)	
2	20 (29.9)	5 (29.4)	<0.001	23 (30.3)	2 (25.0)	0.350
3	8 (11.9)	1 (5.9)		8 (10.5)	1 (12.5)	
4	10 (14.9)	11 (64.7)		17 (22.4)	4 (50.5)	

Data are presented as median (25^{th}-75^{th} percentile) or number (%)

Abbreviations: ESR, Erythrocyte Sedimentation Rate; LDH, Lactate Dehydrogenase ; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline phosphatase; GGT, *Gamma-Glutamyl* Transpeptidase.

Table 3. Risk factors on hospital admission independently associated with increased risk of ICU admission and death (Multiple logistic regression analysis).

ICU admission			
	Adjusted Odds Ratio	*95% CI*	*p-value*
NEWS2 score (per 1 unit)	1.4	1-1.96	0.048
Solid tumor (Yes vs. No)	10.88	1.43-82.85	0.021
Platelets (per 10.000/µL)	0.84	0.71-0.99	0.036
Lung Field Score (4 versus <4)	20.88	3.07-141.1	0.002
Hospital mortality (adjusting for age)			
	Adjusted Odds Ratio	*95% CI*	*p-value*
Immunosuppression	896.8	2.58-311432	0.032
Platelets (per 10.000/µL)	0.69	0.48-1	0.049

CI: Confidence Interval