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ORIGINAL RESEARCH

COVID-19 clinical phenotypes and short-term outcomes: differences between the first and the second wave of pandemic in Italy

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ABSTRACT

Objectives: There are no comparative studies between patients belonging to the first and second waves of the SARS-CoV-2 pandemic, the virus triggering coronavirus disease 2019 (COVID-19). In this retrospective observational study, we analyzed the clinical characteristics and the short-term outcomes of two groups of laboratory-confirmed COVID-19 patients with moderate-to-severe acute respiratory distress syndrome (ARDS) belonging to two different waves of the pandemic.

Methods: We analyzed 97 consecutive patients from 11 March 2020 to 31 May 2020 and 52 consecutive patients from 28 August 2020 to 15 October 2020.

Results: Patients belonging to the second wave were younger, had a lower number of concomitant chronic conditions (multimorbidity), and had a milder clinical phenotype. Medical treatments and respiratory support use have changed during the COVID-19 pandemic, based on different laboratory results and disease clinical features. Patients in the second wave had better short-term clinical outcomes, with lower death rates and more step-down transfers to a general ward.

Conclusion: The present findings show a clear phenotypic difference in patients hospitalized at different stages of the COVID-19 pandemic in Italy. These results can help to stratify clinical risk and to better tailor medical treatments and respiratory support for patients with ARDS and COVID-19 pneumonia.

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Critical care; assisted ventilation; intermediate RICU; survival; pandemic; Italy

1. INTRODUCTION

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 2019 (COVID-19), represents a major hurdle for global health systems to overcome. COVID-19 patients may develop acute respiratory distress syndrome (ARDS), requiring respiratory support [1] and possible hospitalization in the Intensive Care Unit (ICU). The 'first wave' of infection, which began in Italy in March 2020, decreased during the summer of the same year. Since the end of August 2020, however, there has been a substantial increase in infections from SARS-CoV-2. Furthermore, in mid-October 2020, the COVID-19 pandemic showed a new increase in infections and deaths throughout Europe. During the first wave of the pandemic, an evolution of clinical characteristics of COVID-19 was highlighted in patients who had undergone hospitalization [2]. In fact, with decreasing viral diffusion, at hospital presentation, the severity of the respiratory tract involvement and the inflammatory status were less pronounced [2]. It is also known that COVID-19 pneumonia can present itself with different clinical phenotypes identified by computed tomography (CT) scan and driven by different pathophysiological mechanisms [3]. Furthermore, also cluster analysis of clinical features has been recognized as an important tool to predict COVID-19 outcomes in hospitalized patients [4]. The two waves of COVID-19 pandemic seem to show different evolutions in terms of clinical course and short-term outcomes, at least, for a comparison including the first part of the second wave. However, to the best of our knowledge, there are no clinical data available comparing COVID-19 patients hospitalized between the first and second waves of the COVID-19 pandemic. This confrontation can highlight useful information to improve our clinical management of patients with COVID-19 pneumonia and ARDS. In the present study, we analyzed the different clinical characteristics and the short-term outcomes of these two different periods of the pandemic for laboratory-confirmed COVID-19 patients with moderate-to-severe ARDS admitted to our intermediate Respiratory Intensive Care Unit

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ARTICLE HIGHLIGHTS

- Since the beginning of the pandemic, the study of phenotypic manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus triggering coronavirus disease 2019 (COVID-19), has aroused great interest. Different 'waves' of the spread of the virus can be recognized, with phases of intense viral diffusion alternating with phases of reduction of infections. Nevertheless, there are no comparison studies between patients belonging to the first and second waves. In the present study, we analyzed the different demographic, clinical, and prognostic characteristics of laboratory-confirmed COVID-19 patients with moderate-to-severe acute respiratory distress syndrome (ARDS) admitted to our intermediate Respiratory Intensive Care Unit (RICU) during these two different periods of the pandemic.
- We analyzed the different clinical characteristics and the short-term outcomes of 97 consecutive patients from 11 March 2020 to 31 May 2020 and 52 consecutive patients from 28 August 2020 to 15 October 2020. Laboratory-confirmed COVID-19 patients with moderate-to-severe ARDS belonging to the second wave were younger, had a lower number of concomitant chronic conditions (multimorbidity), and a milder clinical phenotype. Furthermore, medical treatments and respiratory support use have changed during the COVID-19 pandemic, according to different laboratory results and clinical features of the disease. Finally, patients in the second wave had better short-term clinical outcomes, with a lower death rate and more step-down transfers to GW.
- In the Italian intermediate RICU, there was a clear phenotypic difference in patients hospitalized at different stages of the COVID-19 pandemic in Italy. The present findings can help to stratify clinical risk and to better tailor medical treatments and respiratory support for patients with ARDS and COVID-19 pneumonia.

(RICU), a model of care designed for monitoring and treating respiratory patients whose illness is at a level of severity that is intermediate between that which requires ICU facilities and that which can be managed on a conventional ward [5,6].

2. METHODS

We performed a single-center, observational, retrospective study, enrolling patients with moderate-to-severe ARDS due to COVID-19 pneumonia [6,7] according to the Berlin definition, i.e., a respiratory failure characterized by arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO_2/FiO_2) <300 mmHg despite positive end-expiratory pressure (PEEP) >5 cmH_2O, associated to bilateral chest opacities (not fully explained by effusions, lobar/lung collapse, or nodules) with an acute onset, within 1 week of a known clinical insult or new or worsening respiratory symptoms [8]. Our enrollment was carried out during the period from 11 March 2020 to 31 May 2020 and from 28 August 2020 to 15 October 2020 in our intermediate RICU, Policlinico Hospital, Bari, Italy. We identified the patients belonging to the first enrollment period as 'First Wave Group (FWG)' and those belonging to the initial part of the second period as 'Second Wave Group (SWG)'. The present study adhered to the 'Standards for Reporting Diagnostic Accuracy Studies' (STARD) guidelines (http://www.stard-statement.org/), the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines (https://www.strobe-statement.org/), and was conducted in accordance with the Helsinki Declaration of 1975. The present study was approved by the Policlinico Hospital of the University of Bari 'Aldo Moro' institutional review board and informed consent was obtained from all subjects involved in the present analysis.

In the FWG, 97 consecutive patients were enrolled, while 52 consecutive patients were enrolled in the SWG. COVID-19 patients who showed moderate-to-severe ARDS requiring therapy with noninvasive ventilation (NIV) or high-flow oxygen therapy (HFOT) were admitted to our intermediate RICU from the emergency department. For NIV, in these laboratory-confirmed COVID-19 patients, apart from moderate-to-severe hypercapnic patients, who clearly needed the bilevel positive airway pressure (BPAP) respiratory support rather than continuous positive airway pressure (CPAP) respiratory support, our choice was driven by patient's clinical evaluation. After a CPAP trial with a progressive pressure rise of up to 12–15 cmH_2O (when needed), if the respiratory rate was still >30, we decided to switch from CPAP to BPAP. The high respiratory rate in ARDS patients is an indicator of respiratory fatigue, and BPAP can reduce the work of breathing, giving relief in these patients [9]. Laboratory-confirmed COVID-19 patients affected by severe ARDS, not responding to NIV, in which endotracheal intubation and ICU transfer would not modify their outcome according to resuscitator counseling, remained in our intermediate RICU. Patients requiring endotracheal intubation and invasive mechanical ventilation (IMV) were transferred in step up to the ICU of our hospital. Therefore, all patients who did not respond to the NIV were asked for resuscitator counseling, whose opinion determined the possibility of an ICU transfer or not. In particular, since our ward was deputed to manage patients requiring NIV, ICU admission was allowed only for patients requiring endotracheal intubation or extracorporeal membrane oxygenation (ECMO). Endotracheal intubation was considered with PaO_2/FiO_2 < 100 in the presence of signs of respiratory distress (dyspnea, tachypnea, use of intercostal and neck respiratory muscles). Despite these criteria, personal clinical judgment (age, comorbidities, chest CT alterations) of every resuscitator influenced endotracheal intubation decisions, according to the risk/benefit ratio of the procedure. For the first wave, the number of COVID-19 patients in this medical area were 181 (97 in intermediate RICU plus 84 in ICU), while for the second wave, it was 82 (52 in intermediate RICU plus 30 in ICU). Patients permanently weaned from HFOT or NIV were transferred in step down to a general ward (GW).

2.1. Statistical analysis

Data were reported as median and standard deviation. A comparison between the two groups was performed using 2-tailed T tests for independent samples; Pearson's chi-squared or Fisher's exact test were used for the analysis of distribution frequencies. P value <0.05 was considered statistically significant. We used GraphPad program for the statistical analysis.

3. RESULTS

3.1. Patient characteristics

Sociodemographic features, clinical, laboratory, respiratory support data, and short-term clinical outcomes are shown in Table 1. Regarding the sociodemographic characteristics, there are no differences in the percentages of males and females in the two groups (males: 72% *vs*. 73%). The mean age of the FWG was significantly higher than that of the SWG (69.65 ± 14 *vs*. 64.23 ± 12.04 years). In the same way, the mean age of the females of the FWG was higher than that of the SWG (74.70 ± 12.2 *vs*. 65.29 ± 14.6 years). Despite this finding and contrary to data found in the first wave, there are no differences between mean age of males and females in the second wave. On the other hand, no significant difference was found in the percentage of current smokers of the two groups (4% *vs*. 5.7%). For multimorbidity, patients hospitalized in the first wave had at least one chronic condition more frequently than those in the second wave (91% *vs*. 71.1%). There was also a higher percentage of patients with two or more chronic conditions (60% *vs*. 36.5%) and a higher frequency of hospitalizations for patients with more than three chronic conditions (47.4% *vs*.13.4%). The most frequent chronic conditions in the first wave were hypertension (64.5% *vs*.5.7%), chronic heart failure (16.5% *vs*.0%), chronic renal failure (44.3% *vs*.9.6%), and neurological diseases (18.5% *vs*.3.8%). We did not find any difference in the presence of chronic obstructive pulmonary disease and asthma, confirming the low frequency of chronic respiratory diseases also in the second wave. As regards the first wave, the mean duration of length of stay in hospital was 11.3 ± 8.7 days, while for the second wave, it was 10.8 ± 7.9 ($p = 0.7$).

3.2. Disease severity

The analysis of symptoms did not show significant differences in the presence of fever, cough, dyspnea, or diarrhea. On the contrary, a lower frequency of dysgeusia and ageusia was highlighted in the second wave compared to the first wave (13.4% *vs*. 1.9%). We also considered the percentage of patients who presented 'early dyspnea' or respiratory fatigue within the first 5 days from the onset of symptoms, highlighting a higher frequency of early dyspnea in the first wave (65.38% *vs*. 36.8%). At the admission, the mean D-dimer values were higher in the first wave (2347 ± 3600 *vs*. 1103 ± 1265 ng/mL), with a higher percentage of patients with D-dimer more than sixfolds of upper limit (19.6% *vs*. 5.7%). Despite this, no statistical differences were found in inflammatory indices (C-reactive protein and lactate dehydrogenase). The mean values of 25-hydroxyvitamin D were instead lower in the first wave compared to the patients of the second wave (18.64 ± 12.08 *vs*. 35.62 ± 17.38 ng/mL). At admission to our intermediate RICU, drug history showed a significant difference in the intake of angiotensin-converting enzyme (ACE) inhibitors between the two groups (26.8% *vs*. 5.7%). The comparison between PaO_2/FiO_2 at admission and at discharge in the two groups, on the contrary, was not statistically significant.

3.3. Disease management

Regarding the therapy used in our intermediate RICU, anticoagulant therapy with low molecular weight heparin (LMWH) had greater prominence in the second wave (83% *vs*. 98%), especially at prophylactic dosage (22.5% *vs*. 48%). During the first wave, the use of corticosteroids was not standardized. Consequently, various forms and dosages have been used. The most commonly administered were methylprednisolone 20 mg b.i.d. e.v. or prednisone 25 mg o.d. per os for at least 5 days. Corticosteroid therapy was also widely used in the second wave (26% *vs*. 86.5%). During the second wave, following new scientific evidences, we opted for dexamethasone 6 mg o.d. e.v. for 10 days. In both cases, after the starting dose, a slow steroid tapering was performed. None of the patients in the second group received therapy with lopinavir/ritonavir or with hydroxychloroquine. No significant difference was highlighted regrading antibiotic therapy and in particular for the use of azithromycin (67% *vs*. 63.5%). Since tocilizumab was used only in clinical trials during the first wave of the COVID-19 pandemic, we administered it for compassionate use only. Unfortunately, of the nine patients receiving tocilizumab, 55.5% died. We dosed serum interleukin-6 in four patients with a mean value of 134.3 ± 95 pg/mL. Considering the small sample of patients who were treated with tocilizumab, we did not perform a specific statistical analysis with other clinical or laboratory findings. Finally, for respiratory supports used, patients of the second group needed BPAP (38% *vs*. 11,6%) less frequently; instead, more HFOT was provided (3% *vs*. 19.2%), without differences in the use of low-flow oxygen therapy (11% *vs*. 19.2%) or CPAP (40% *vs*. 50%). Finally, statistically significant differences were found regarding patients transferred to GW (51% *vs*. 77%) without differences in ICU admissions from our intermediate RICU (30% *vs*. 22.98%). The overall deaths (43.3% *vs*. 11.5%) and deaths in our intermediate RICU (19% *vs*. 0.02%) showed a clear difference between the two groups.

4. DISCUSSION

The present study, to the best of our knowledge, is the first report comparing clinical characteristics and outcomes of patients from two different waves of the COVID-19 pandemic in Italy. In particular, patients belonging to the second wave were younger, had a lower number of concomitant chronic conditions (multimorbidity), a milder clinical phenotype, and better short-term clinical outcomes, with a lower death rate and more step-down transfers to GW.

Demographic data showed that patients belonging to the SWG were younger, especially the female population. This result is in contrast to the findings on our hospitalized sample on the first wave of the COVID-19 pandemic, where the difference in mean age values between men and women was statistically significant [10]. Moreover, after the first wave, the loss of the containment measures for the COVID-19 spread and the social events related to the summer season led to an increase in the percentage of infections, especially in younger people [11]. A large retrospective review of SARS-CoV-2 molecular testing suggested that the greater percentage of infected young subjects could refer only to non-hospitalized

Table 1. Sociodemographic and clinical characteristics, respiratory support data, therapeutic approaches, and short-term clinical outcomes of COVID-19 patients hospitalized in an intermediate Respiratory Intensive Care Unit (RICU) subdivided in two groups according the two different waves of the pandemic in Italy, i.e., First Wave Group (FWG) from 11 March 2020 to 31 May 2020 and Second Wave Group (SWG) from 28 August 2020 to 15 October 2020.

	FWG N. 97	**SWG** N. 52	P-value
Age (years, mean ± SD)	69.65 ± 14	64.23 ± 12.04	P = 0.02†
• Males	67.64 ± 14	63.84 ± 11.15	P = 0.15†
• Females	74.70 ± 12.2	65.29 ± 14.6	P = 0.03†
Sex (M/F, %)	72%/28% (70/97)	73%/27% (38/52)	P > 0.9‡
Smoking habits (%)	96% (93/97)	94.3% (49/52)	P = 0.69‡
Non-.smokers (or ex-smokers from 15 years)	4%	5.7%	
Current smokers			
Symptoms			
• Dyspnea	80.4% (78/97)	73% (38/52)	P = 0.31‡
• Early dyspnea	65.38 (51/78)	36.8% (14/38)	P = 0.031‡
• Fever	70% (68/97)	63.4% (33/52)	P = 0.46‡
• Cough	25.74% (25/97)	28.8% (15/52)	P = 0.7‡
• Diarrhea	4% (4/97)	7.7% (4/52)	P = 0.45‡
• Dysgeusia/Ageusia	13.4% (13/97)	1.9% (1/52)	P = 0.035‡
Patients with at least 1 chronic condition (%)			
• Hypertension	91% (89/97)	71.1% (37/52)	P = 0.0016‡
• Chronic heart failure	64.5% (63/97)	5.7% (3/52)	P < 0.0001‡
• Atrial fibrillation	16.5% (16/97)	0%	P = 0.0013‡
• Diabetes mellitus type II	13.4% (13/97)	51.9% (27/52)	P < 0.0001‡
• COPD	30.5% (30/97)	26.9% (14/52)	P = 0.70‡
• Asthma	17.5% (17/97)	7.7% (4/52)	P = 0.14‡
• Chronic kidney failure	3% (3/97)	5.7% (3/52)	P = 0.42‡
• Cerebrovascular disease	44.3% (43/97)	9.6% (5/52)	P < 0.0001‡
• Neurological disease	16.5% (16/97)	3.8% (2/52)	P = 0.03‡
• Cancer	18.5 (18/97)	3.8% (2/52)	P = 0.01‡
Patients with 2 chronic conditions (%)	14.4% (14/97)	11.5% (6/52)	P = 0.8‡
Patients with 3 or more chronic conditions (%)	60% (59/97)	36.5% (19/52)	P = 0.0059‡
	47.4% (46/97)	13.4 (7/52)	P < 0.0001‡
Home drug treatments (%)			
• ACE inhibitors	26.8% (26/97)	5.7% (30/52)	P = 0.0003‡
LDH at admission (mean ± SD, mU/mL)	335.5 ± 112.5	331.8 ± 102.1	P = 0.8†
CRP at admission (mean ± SD, mg/L)	99.6 ± 81.04	80.86 ± 62.42	P = 0.14†
D-dimer at admission (mean ± SD, ng/mL)	2347 ± 3600	1103 ± 1265	P = 0.017†
Patients with D-dimer >3000 ng/mL at admission (%)	19.6% (19/97)	5.7% (3/52)	P = 0.028‡
25-hydroxyvitamin D (mean ± SD, ng/mL)	18.64 ± 12.08	35.62 ± 17.38	P = 0.0002†
Mean PaO_2/FiO_2 admission (mean ± SD)	186 ± 80	172.7 ± 70.53	P = 0.29†
Mean PaO_2/FiO_2 discharged (mean ± SD)	202.1 ± 105.7	202.6 ± 92.14	P = 0.97†
Drug treatments			
• Anticoagulant therapy (%)	83% (80/97)	98% (51/52)	P = 0.0037‡
• Enoxaparin (prophylactic dose) (%)	22.5% (18/97)	48% (25/52)	P = 0.0003‡
• Enoxaparin (therapeutic dose) (%)	77.5% (75/97)	52% (27/52)	P = 0.0028‡
• Antibiotic therapy	81% (79/97)	90% (47/52)	P = 0.23‡
• Azythromycin (%)	67% (65/97)	63.5% (33/52)	P = 0.72‡
• Lopinavir/ritonavir (%s)	36% (35/97)	0%	P < 0.0001‡
• Hydroxychloroquine (%)	73% (71/97)	0%	P < 0.0001‡
• Tocilizumab (%)	6% (6/97)	0%	P = 0.09‡
• Corticosteroids (%)	26% (25/97)	86.5% (45/52)	P < 0.0001‡
Noninvasive respiratory support (%)			
• LFOT	11% (11/97)	19.2% (10/52)	P = 0.219‡
• HFOT	3% (3/97)	19.2% (10/52)	P = 0.0016‡
• CPAP	40% (39/97)	50% (26/52)	P = 0.29‡
• BPAP	38% (37/97)	11.6% (6/52)	P = 0.0006‡
Discharged (%)		77% (40/52)	P = 0.0017‡
• Lower intensity care (GW)	51% (49/97)	22.98% (11/52)	P = 0.33‡
• ICU	30% (29/97)		
Died (total)	43.3% (42/97)	11.5% (6/52)	P < 0.0001‡
Died in intermediate RICU (%)	19% (19/97)	0.02% (1/52)	P = 0.0019‡

† t-test for two independent samples
‡ Pearson's chi-squared or Fisher's exact test
§ Wilcoxon–Mann–Whitney U Test
Abbreviations: SD: standard deviation; COPD: chronic obstructive pulmonary disease; ACE: angiotensin-converting enzyme; LDH: lactate dehydrogenase; CRP: C-reactive protein; PaO_2/FiO_2: arterial oxygen partial pressure to fractional inspired oxygen ratio; LFOT: low-flow oxygen therapy; HFOT: high-flow oxygen therapy; CPAP: continuous positive airway pressure; BPAP: bilevel positive airway pressure; GW: general ward; ICU: intensive care unit

patients, due to a shift in health surveillance toward younger populations [12]. The present findings, on the contrary, underlined the age variation in hospitalized patients between the first and second waves in Italy, without bias related to different screening patterns in the population. Considering the trend of COVID-19 infections, young asymptomatic carriers of the virus may infect older subjects, confirming the new increase in mean age of hospitalized patients for COVID-19 pneumonia in Italy. These data explain our choice to consider only the first part of the second wave of the COVID-19 pandemic in Italy (from August to the first half of October 2020), with less severe clinical impact and prognosis.

Multimorbidity findings showed that patients in the first wave were more frequently affected by multiple chronic diseases. In addition, we found a lower frequency of hypertension, chronic heart failure, chronic renal failure, and neurological diseases in the second wave of hospitalizations. Some studies suggested that patients with COVID-19 and hypertension had a greater risk of developing more severe pneumonia [13], with a more frequent unfavorable outcome. In addition, the simultaneous presence of hypertension and COVID-19 may be associated with an increased risk of ICU admission and all-cause mortality [14,15]. The mechanism by which hypertension is associated with worse outcomes in COVID-19 patients is still unknown, but the inflammatory response induced by the virus may be the link between the two diseases [16], although we did not find differences in inflammatory indices between the first and second waves of the pandemic. COVID-19 patients with chronic heart failure also showed higher mortality and a greater tendency to develop acute heart failure [17–19]. The presence of a smaller number of patients with hypertension and chronic heart failure in the second wave of the COVID-19 pandemic was in line with the prognostic data of the present study, confirming the role of this multimorbidity for the outcome of the infection.

Regarding symptoms, patients in the first wave showed more frequent early dyspnea and respiratory fatigue within the first 5 days of the disease onset. Despite this finding, no differences between the PaO_2/FiO_2 averages were found. This can be explained by considering that only patients with moderate-to-severe hypoxemia were hospitalized in our intermediate RICU, regardless of symptoms at the admission. Moreover, patients in the second wave were often hospitalized in the absence of dyspnea but with the evidence of a 'silent hypoxia'. In contrast, first wave patients showed similar hypoxemia when respiratory fatigue and tachypnea were already present. Dyspnea in COVID-19 patients is a marker of disease severity [20]. In fact, early dyspnea may often precede the sudden worsening of respiratory exchanges. In addition, late finding of the silent hypoxia can lead to worse prognosis in COVID-19 disease [21]. In these patients without dyspnea, early hospitalization allowed identifying silent hypoxia before a worsening of respiratory dynamics, with a positive impact on the course of the disease.

Among home drug treatments before admission to hospital, in the second wave, there was less frequent use of ACE inhibitors. The explanation lies in the ability of ACE inhibitors to increase the expression of the ACE2 protein, which is essential for the entry of the virus into the host cell [22]. Knowledge of the cellular entry mechanism of SARS-COV2 has presumably led many physicians to discontinue ACE inhibitor therapy, although currently there is no clinical study evaluating the outcome of patients treated with these drugs during COVID-19 infection [23].

For laboratory testing, there are no differences in inflammatory markers except for D-dimer. In fact, patients in the FWG had higher mean D-dimer values, with a significantly higher percentage of patients with D-dimer sixfolds of upper limit. Tang and colleagues demonstrated a reduction in mortality at 28 days with the use of LMWH in patients with severe COVID-19 and D-dimer > sixfolds of upper limit [24]. It is reasonable to hypothesize that microvascular involvement affected COVID-19 pneumonia more often during the first wave rather than the second wave. Differences in D-dimer serum levels also explain why LMWH was used with therapeutic doses more often during the first wave, while prophylactic dosages were more frequently administered in the SWG. As regards 25-hydroxyvitamin D, mean values were also different between the two groups; patients hospitalized in the second wave had higher values of 25-hydroxyvitamin D, in relation to the sun exposure in the summer period [25]. This may represent a positive prognostic factor, as vitamin D deficiency was associated with a worse clinical outcome, especially in older population [26,27]. Another substantial difference between the two waves concerns the use of corticosteroids. The use of dexamethasone in SARS-COV2 infection has been shown to be effective in reducing 28-day mortality in patients undergoing NIV and oxygen therapy [28]. If during the first wave there were many doubts about the usefulness of an early use of steroid therapy, during the second wave, over 85% of our sample received treatment with dexamethasone 6 mg/day for at least 10 days. None of these patients, on the other hand, performed therapy with hydroxychloroquine or lopinavir/ritonavir, following new evidences and indications from Italian guidelines [29,30].

For respiratory support, the patients in the second wave were characterized by a lower use of BPAP and a more frequent use of HFOT. For these patients, a treatment with HFOT or CPAP was sufficient in most cases to overcome the acute phase of ARDS. During the first wave, on the contrary, it was necessary to set up

BPAP more often, as the frequency of worsening of respiratory exchanges and dyspnea was higher, despite the use of other respiratory supports. Different clinical phenotypes identified by CT scan have been recently proposed, and COVID-19 pneumonia can be distinguished in Type L and Type H pneumonia [3]. Type L pneumonia is characterized by low elastance, low lung weight, and low recruitability. On the contrary, type H pneumonia fulfilled all the ARDS criteria, with high pulmonary elastance, high lung weight, and high recruitability. The transition from Type L to Type H pneumonia is considered to be a marker of COVID-19 disease progression [3]. In the present study, patients with silent hypoxia belonging to the second wave could be more prone to develop Type L pneumonia without changing phenotype toward Type H pneumonia. On the contrary, patients of the first wave could have an early shift of their phenotype toward Type H pneumonia, showing early dyspnea and often requiring NIV support to relieve respiratory fatigue and to improve gas exchanges.

Considering differences in age, multimorbidity, symptoms, and laboratory findings, we reasonably may suggest that lower mortality rates in SWG could have been related to a milder phenotype of COVID-19 pneumonia, requiring less aggressive ventilatory strategies. Furthermore, we cannot exclude a potential 'learning effect' of health-care professionals who, after the first wave of this pandemic, have improved their skills and level of care for these frail patients. If we also consider the possible role of new scientific evidences about the use of corticosteroids and LMWH on COVID-19 clinical management, we can suggest that all these factors could have a positive impact on prognosis.

The present study has some limitations. The first concerns the limited sample of the population taken into consideration. Second, no comparison data with CT scan was made, mainly due to the scarce possibility during the first wave to perform radiological examinations. Finally, the data on the SWG referred to patients in the first part of the second wave of the COVID-19 pandemic and it is not possible to exclude possible further differences with patients hospitalized later.

5. CONCLUSIONS

In conclusion, the present study demonstrated how patients hospitalized during the first wave and the initial part of the second wave of the COVID-19 pandemic in Italy had different characteristics and outcomes, an expression of the variability of clinical, demographic, and epidemiological aspects of the disease. The study of different clinical phenotypes allows us to identify patients at higher risk for the development of severe respiratory failure, choosing the most appropriate type of treatment and respiratory support according to the disease severity.

Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
COVID-19: coronavirus disease 2019
ARDS: acute respiratory distress syndrome
CT: computed tomography; RICU: Respiratory Intensive Care Unit
ICU: Intensive Care Unit
PaO_2/FiO_2: arterial oxygen partial pressure to fractional inspired oxygen ratio
FWG: First Wave Group
SWG: Second Wave Group; NIV: noninvasive ventilation
HFOT: high-flow oxygen therapy
BPAP: bilevel positive airway pressure
CPAP: continuous positive airway pressure
IMV: invasive mechanical ventilation
ACE: angiotensin-converting enzyme
LMWH: low molecular weight heparin

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Authors' Contributions

Conception and design of the study: A. Portacci, G.E. Carpagnano, V. Solfrizzi, F. Panza, and O. Resta. Collection of data: M.G. Tummolo, C. Ssantomasi, L. Palma, D. Fasano, and M. Lozupone. Analyzed the data: V. Solfrizzzi. Wrote the manuscript: A. Portacci, G.E. Carpagnano, F. Panza, and O. Resta. Final supervision and guarantee of the paper: G.E. Carpagnano, F. Panza, and O. Resta.

Ethics approval and consent to participate

Ethics approval was obtained through the Institutional Review Board and all patients provided consent to participate.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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