Steroids in severe COVID-19 patients: A retrospective analysis on the first pandemics in Lombardy

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Abstract

The pathogenesis of COVID-19 appears to be characterized by a dysregulated immune response. During the first pandemic wave in Lombardy, we started to administer glucocorticoids to some patients with severe respiratory failure requiring support with Continuous Positive Airway Pressure (CPAP) therapy. We retrospectively collected data to identify the effect of glucocorticoids in this COVID-19 particular population. With a multidisciplinary consensus, we administered to selected patients with severe COVID-19 disease (PaO_2/FiO_2 159±71 mmHg) 0,91 mg/kg/die of methylprednisolone equivalent dose after a median of 8 days of hospitalization. In our study we compared 57 patients from the steroid group with 123 from the control group: the event of invasive mechanical ventilation or death was reduced by 43% between steroid group and control group (19.3 % vs. 34.1 % respectively, p=0.001) and mortality was reduced by about 31% between steroid and usual care alone (15.8 % *vs.* 22.8 % respectively, p=0.011). Corticosteroids in selected COVID-19 patients may have a relevant impact on outcome, better profiling of the heterogeneity of this disease may be essential to guarantee the best treatment choices.

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Informed consent: Patients' consent was waived.

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Introduction

The pathogenesis of COVID-19 appears to be characterized by a dysregulated immune response which causes systemic and pulmonary inflammation, along with endothelial injury, hyper-coagulability and thrombosis.[1-3] Recent findings support the use of glucocorticoids to modulate the immune response aiming to decrease the effects of hyperinflammation.[2-9] The beneficial effect of glucocorticoid therapy has been described in ICU patients, while the evidence for patients requiring ventilatory support outside and/or before the ICU is not univocal, also due to the lack of data in this population.

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial[5] found the greater benefit from steroids in invasive ventilated patients and, to a lesser degree, among those receiving oxygen without invasive Mechanical Ventilation (MV); unfortunately, a stratification for different respiratory support levels between simple oxygen supplementation and ventilatory support systems was not reported in that paper.

The following WHO meta-analysis,[6] reviewing 1703 critically ill patients, confirmed the beneficial effect of glucocorticoids administration; interestingly the strongest signal was founded among non-invasively ventilated patients, which accounted just for 8.5% of the cases (144 patients).

Many retrospective cohort and case-series studies have yielded conflicting results on the efficacy of glucocorticoids for the treatment of COVID-19. Since different severity of illness and different steroid dosage and timing of administration where reported,[10-14] better profiling and targeting of COVID-19 patients is desired; thus, several RCTs are ongoing.[15-17]

During the first pandemic wave, in our third level hospital in Lombardy, on the basis of a multidisciplinary collaboration between intensivists, hematologists, rheumatologists and infectivologists we started to immunomodulate some patients with severe respiratory failure, still not requiring MV.

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In this paper we report the results of our experience during the first wave of pandemics.

Materials and Methods

From February 2020, in San Gerardo Hospital, a large tertiary teaching hospital, based upon increasing pathophysiological knowledges and clinical early experience, systemic glucocorticoids were administered to selected patients with severe COVID-19 who were not mechanically ventilated, opening the opportunity to assess their contribution to manage this disease.

All patients have been managed using the best supportive treatment following the indications available at the time at the judgment of the physician.

Relying on early experience and the limited but increasing physio-pathological knowledge, our multidisciplinary group began prescribing systemic glucocorticoids to patients with COVID-19 referred to MET. Each case was discussed daily and therapeutic strategy choice was made taking into account medical history and clinical course: steroid therapy was usually administered to patients that didn't show improvement after about one week of standard therapy. No specific algorithm for steroid administration was produced at the time since they were relatively contraindicated.[14,18,19]

We took advantage of this change in practice to investigate the association between glucocorticoids use and mortality and the rate of MV in hospitalized COVID-19 patients.

We retrospectively reviewed medical records of COVID-19 patients referred to MET (Medical Emergency Team) who received Continuous Positive Airway Pressure Therapy (CPAP)support in the ED and/or medical ward.

For this observational, single center study data were collected in a local online registry as part of the STORM study (Spallanzani Institute approval number 84/2020; NCT04424992). Patients' consent was waived.

Inclusion criteria

For this observational, retrospective, single center study we considered eligible adult patients (age ≥18 years) admitted to San Gerardo hospital, between February 27th and April 30th 2020, confirmed to be positive for SARS-CoV-2 by reverse transcription-polymerase chain reaction of pooled nasal and pharyngeal swabs.

Only patients referred to the MET for more than 24 hours by the ED or medical wards with a confirmed diagnosis of COVID-19-related severe pneumonia were included.

Exclusion criteria

We excluded patients treated with steroids for less than 48 hours before death or start of MV; equally, those treated for other reasons or with chronic steroid therapy were considered not eligible.

Moreover, patients were excluded if they were transferred from an out-of-system hospital without complete medical records, if considered moribund on the basis of clinical judgment or died within 24 hours since the presentation to the ED.

Analysis focus

Since steroid therapy was administered after a few days of hospitalization, to adjust our results for immortal time bias (*i.e.* patients must survive long enough to receive the intervention of interest) leading to a potential incorrect overestimation of a positive treatment effect, we excluded from the primary analysis those who died, were intubated or de-escalated CPAP before the median time of steroid beginning since the hospital admission. Data and analysis regarding the whole population that met inclusion and exclusion criteria is also reported in this manuscript.

Data collection

Data were collected from electronic patient records and entered, anonymously, into a securely stored database.

We collected demographics, Charlson Comorbidity Index (CCI) as a performance status indicator, Sequential Organ Failure Assessment (SOFA) score, timing of symptoms onset, hospital admission and MET referral.

We focused on five significant events in the course of the disease: hospital admission, onset of O2 administration, onset of CPAP support, initiation of steroid administration (if available) and the final multiple event defined as de-escalation of O2 support (to FiO_2 < 40%, no more need of CPAP support and PaO_2/FiO_2 > 300) OR tracheal intubation and ICU admission OR withdrawal of treatment.

Outcomes

The primary outcome was a composite of in-hospital mortality or MV.

Secondary outcome was in-hospital all causes mortality rate.

The independent variable of interest was treatment with glucocorticoids.

Statistical analysis

Statistical analysis and graphs were performed with IBM SPSS Statistic v. 27.

Continuous variables are summarized as mean values with standard deviations or median values and interquartile range for normal and non-normal distribution respectively. Categorical variables were summarized as counts and percentages.

Population characteristic comparison between the control group and the steroid group was performed with an independent-sample T-test for continuous variables and Chi-Square statistic for categorical variables.

Paired sample T-test was performed for comparison of variation of CRP (between hospital admission and initiation of steroids) and of PaO_2/FiO_2 (between onset of CPAP support and initiation of steroids).

For the primary composite outcome of invasive MV or death a multinomial logistic regression (with multivariate analysis for steroid therapy, age, CRP and PaO_2/FiO_2, CCI and SOFA score) was used to estimate the odds ratio.

For the secondary outcome (in hospital mortality) we performed a multinomial logistic regression (with multivariate analysis for steroid therapy, age, CRP and PaO_2/FiO_2) due to the low number of exitus.

Interaction between steroid therapy and age, CRP, PaO_2/FiO_2 and CCI were also analyzed in the multivariate analysis.

Results

Population characteristic

In our hospital between February 27th and April 30th, 2020 we admitted 1026 COVID-19 patients and more than an half were reviewed by the MET at least once; 471 patients were strictly followed by the MET service for at least 2 days or more receiving helmet CPAP in a non-intensive care setting. Thirty patients were

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excluded because they were referred to the MET for less than 24 hours. 70 patients met other exclusion criteria. Hence the analysis included 371 patients (305 in control group, 66 in steroid group). Whole population characteristics are summarized in Supplemental Table 2. Patients from control group were younger (65 *vs.* 69 years old) and had generally more severe systemic disease (SOFA 3.9 *vs.* 3.4) compared to the steroid group. However, no difference in respiratory failure severity categorized as PaO_2/FiO_2, neither in comorbidity (Charlson Comorbidity Index), neither in grade of inflammation (C-Reactive Protein) were evident. CPAP were started after a median of 1 day after hospital admission in both groups, however on average the steroid group received this support 1 day later (p=0.021; Figure 1).

Using the first COVID-19 patient's date of access to our hospital as the reference, the steroid group was admitted 7 days later (95% CI: 4-10) than the usual care group (Figure 2). The time of hospital admission does not modify the outcomes in the multivariate analysis.

Considering the steroid group, the mean administered steroid dose was 0.91 (SD ±0,26) mg/kg/die of prednisone equivalent dose (largely methylprednisolone, exceptionally dexamethasone). At steroid therapy beginning these patients had PaO_2/FiO_2 of 159±71 mmHg. The mean duration of steroid therapy was 14.5 days (IQR 9-30).

The median number of days between hospital admission and steroid administration was 8 (IQR 5-14). To adjust our results for immortal time bias, we excluded patients who met the composite outcome before that date. After applying this filter, the statistical analysis was performed on 180 patients (123 control and 57 steroid, Figure 1); population characteristics are summarized in Table 1.

Age was significantly higher by 4.5 years (95% CI: 1.1-8.0) in the steroid group. CRP at hospital admission was 2.4 mg/L higher in the steroid group (p=0.046), while the same values at first CPAP trial did not reach the level of significance (p=0.051). No difference in comorbidity, illness severity, days of symptom before hospital access and days between admission and first CPAP trial were found between the two groups.

Primary outcome

The event of invasive MV or death was significantly lower in the steroid group than in the usual care group according to the multivariate analysis for steroid therapy, age, CRP and PaO_2/FiO_2 (OR 0.196; 95% CI 0.078-0.497; Table 2).

The event of invasive MV or death was 43% lower in the steroid group compared to control group (19.3 % *vs.* 34.1 % respectively, p=0.001).

Age, CRP recorded at hospital admission and SOFA score were independent predictors of bad outcome, while no effect of CCI and PaO_2/FiO_2 at first CPAP trial was evident.

The interactions between steroid therapy and age, CRP and PaO_2/FiO_2 on primary outcome are graphically summarized in Figure 3. The event MV or death: i) was more frequent in older patients who did not undergo steroid treatment (p<0.001) while no relation was seen in those with steroid therapy (p=0.378; Panel A); ii) was more likely in patients with higher CRPs with no steroid therapy (p=0.021) while no association was seen in steroid therapy group (p=0.236; Panel B); iii) had no statistically significant

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Table 1. Population baseline comparison between usual care alone and usual care + steroid.

	Treatment Control group (N=123)	Steroids group (N=57)	P-value
Age - Years	64±11	68±10	0.010*
Female - no. (%)	29 (24)	17 (30)	0.371
Days of symptoms before admission	7±6	7±5	0.438
Days between admission and CPAP therapy	3±3	3±4	0.355
CCI	3.5±2.0	3.9±1.3	0.170
SOFA score	3.3±1.5	3.4±1.2	0.847
CRP ‡ – mg/L	9.7±6.8	12.1±8.3	0.046*
CRP † - mg/L	11.6±7.3	14.0±7.5	0.051
PaO_2/FiO_2 † - mmHg	247±116	217±114	0.114
Admission time since first patient entrance - days	23±9	30±10	<0.001*

CCI: Charlson Comorbidity Index; SOFA: Sequential Organ Failure Assessment; CRP: C-Reactive protein; *: p<0.05; ‡: Value recorded at hospital admission; †: Value recorded at first CPAP trial.

Table 2. Multivariate analysis for primary outcome and relative Odds Ratio.

Effect of steroid treatment – Main results Primary outcome: mechanical ventilation or death	Adjusted Odds Ratio (95% CI)
Steroid therapy	0.198 (0.073-0.536)*
Age - years	1.168 (1.010-1.128)*
PaO_2/FiO_2 † - mmHg	0.999 (0.995-1.003)
CRP ‡ - mg/L	1.069 (1.010-1.131)*
CCI	1.130 (0.835-1.530)
SOFA score	2.006 (1.433-2.808)*

Missed data for primary and secondary outcome: 171 cases of 180 (53/57 in steroid group, 118/123 in standard care alone group). CRP: C-Reactive protein; CCI: Charlson Comorbidity Index; SOFA: Sequential Organ Failure Assessment. *: p < 0.05; ‡: Value recorded at hospital admission; †: Value recorded at first CPAP trial; ‡: Value recorded at hospital admission

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relation with PaO_2/FiO_2 in both control and steroid groups, even if the higher rates of MV or death in patients with PaO_2/FiO_2 < 200 mmHg was shown (Panel C).

The interaction between steroid therapy and CCI on primary outcome is graphically summarized in Figure 4. The event MV or death had no statistically significant relation with PaO_2/FiO_2 in both control and steroid groups.

Secondary outcome

In hospital mortality was significantly lower in the steroid group compared with standard care alone group according to the multivariate analysis for steroid therapy, age, CRP and PaO_2/FiO_2 (OR 0.269; 95% CI 0.097-0.743). Multivariate analysis for the secondary outcome is reported in Appendix Table 1. The in-hospital mortality was reduced by about 31% between steroid and usual care alone (15.8% vs. 22.8% respectively, p=0.011).

Age and CRP recorded at hospital admission were an independent predictor of mortality, while non effect of PaO_2/FiO_2 at first CPAP trial was evident.

Supplemental data

Other analysis on CRP and PaO_2/FiO_2 recorded at steroid therapy administration, as well as data regarding patients a-posteriori excluded from analysis, are available in the appendix.

Discussion

The main findings of this study can be summarized as follows: i) patients with severe COVID-19 respiratory failure needing CPAP support and hospitalized from at least 1 week may have strong benefits from steroid therapy adjusted on body weight in

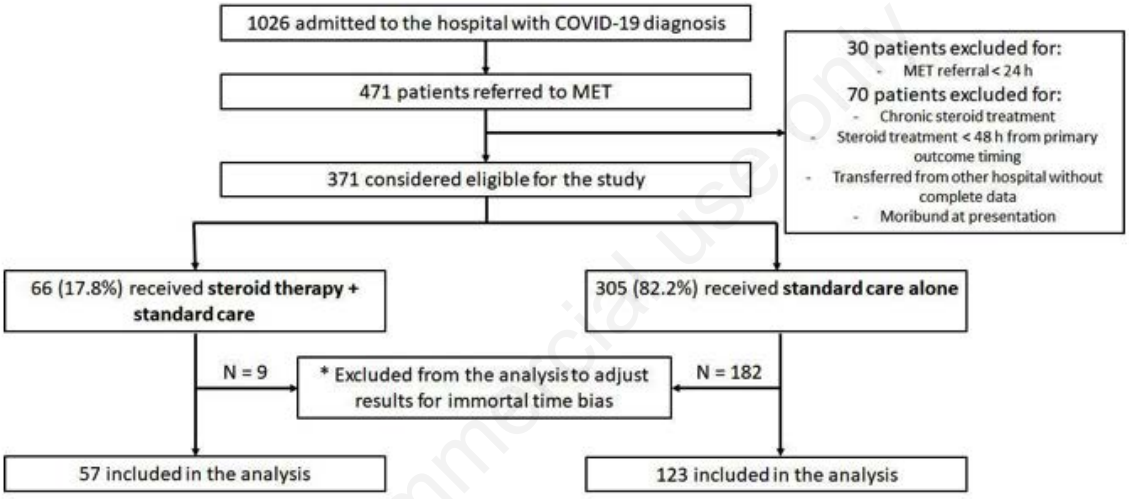

Figure 1. Enrollment, exclusion and patients distribution in the primary analysis. *Since steroid therapy was administered after a median of 8 days of hospitalization, we excluded those who died, were intubated or de-escalated CPAP before 8 days since the admission.

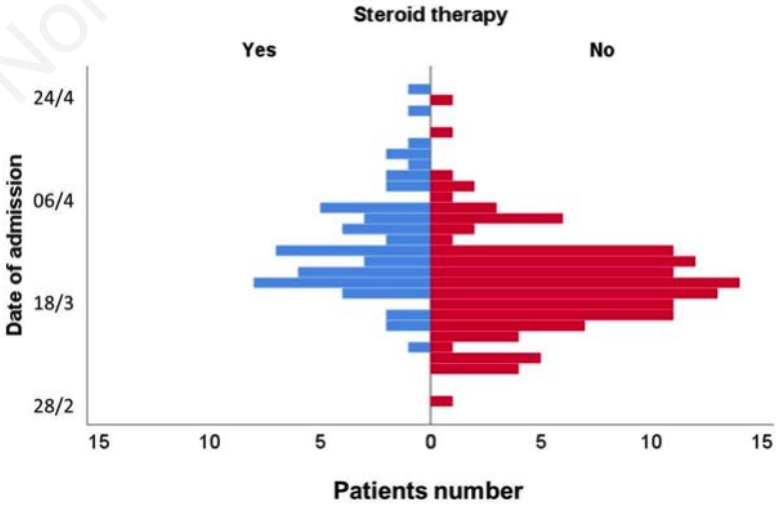

Figure 2. The steroid group vs. usual care group time of hospital admission since first COVID-19 patient admission (February 28th, 2020).an of 8 days of hospitalization, we excluded those who died, were intubated or de-escalated CPAP before 8 days since the admission.

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terms of hospital mortality and rate of MV; ii) steroid therapy seems to mitigate age and CRP effects on mortality and rate of MV.

During the so called first wave in Lombardy, as a consequence of limited ICU resources due to the overwhelming number of patients needing respiratory assistance, many critical patients were treated outside the ICU setting.[20,21] In our hospital this was facilitated by our experience with MET which was initially introduced to avoid inappropriate ICU admissions and to start prompt intensive treatment. It evolved over the years introducing the possibility of receiving helmet CPAP, amine support and other intensive treatments in non-intensive wards. This organization was discovered precious during the pandemic when crisis management systems and logistic support became essential.[22]

Patients with severe COVID-19 can develop a systemic inflammatory response leading to lung injury and multisystem organ dysfunction.[1,3,7,23-25] Based on the pathogenesis of COVID-19, approaches that modulate the immune response may have greater impact in the later phases of the disease.[5,12,25-27] Relying on early experience and the limited but increasing physio-pathological knowledge, our multidisciplinary group began prescribing systemic glucocorticoids to patients with COVID-19.

Slightly after, evidences in favor of glucocorticoids rapidly raised and their ability to prevent or mitigate the deleterious effects of inflammatory activation[1,7] and even to reduce mortality in COVID-19, especially in more severe groups of patients, was clear.[5-7]

RECOVERY trial demonstrated that dexamethasone (6mg daily for 10 days) in hospitalized patients with COVID-19 reduced 28-days mortality, duration of hospitalization and progression to invasive MV. The greater benefit on survival was observed in the invasive ventilated patient subgroup.[5]

Since our study is retrospective, a comparison with RECOVERY trial would not be appropriate, however clear differences in methodological structure are evident. Particularly, in our study dosage was adjusted for the weight (on average 1 mg/kg/die of methylprednisolone equivalent dose). It is reasonable that administering the same dosage (6 mg of dexamethasone) to all the patients without any adjustment could have some limitations. In addition, it has been demonstrated in different clinical settings that rapid clearance and high level of dilution of glucocorticoids

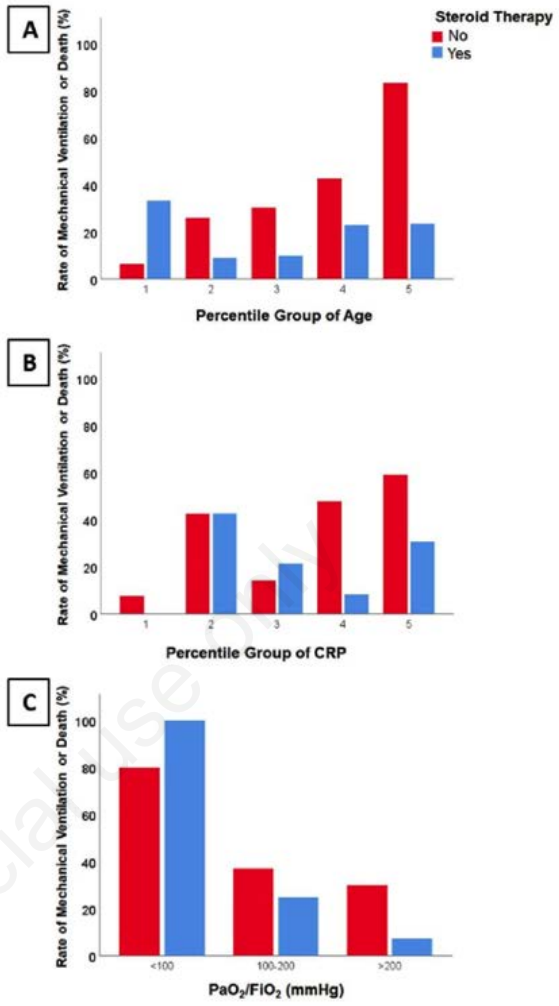

Figure 3. The Steroid vs. control groups rate of mechanical ventilation or death in relation to Age quintiles (Panel A), hospital admission CRP quintiles (Panel B), and PaO_2/FiO_2 at CPAP positioning main division (Panel C). CRP: C-Reactive Protein.

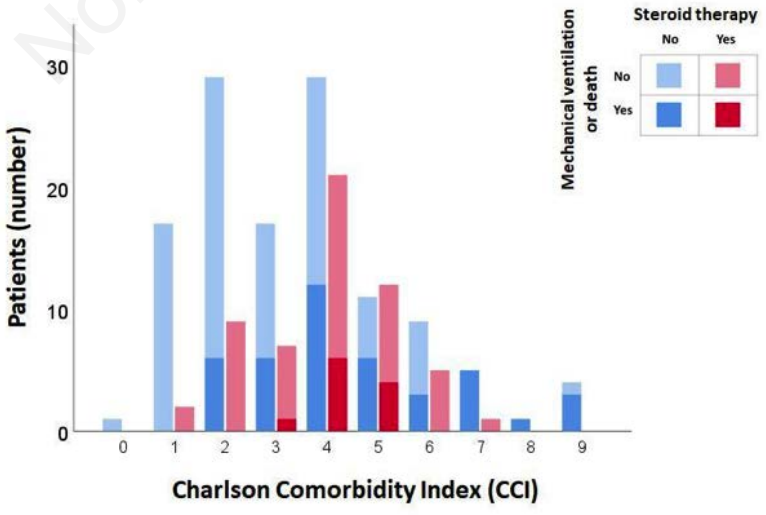

Figure 4. The Steroid vs. control groups patients distribution for CCI score. In vivid colors are highlighted patients who met the composite outcome invasive mechanical ventilation or death. CCI: Charlson Comorbidity Index.

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among obese patients may contribute to persistent inflammation and their suboptimal response to systemic glucocorticoids.[28,29]

Moreover, at the time of steroid administration, our patients were already hospitalized for 8 days, were symptomatic for 15 days on average and had a significant respiratory failure even with the maximization of CPAP assistance (PaO2/FiO2 159±71 mmHg). In Recovery trial dexamethasone was generally administered in an earlier and milder stage of the disease according to the staging proposed by Siddiqi *et al*.[26] and subsequently suggested elsewhere.[9,25]

Indeed, evidence from the RECOVERY also suggests that benefit from corticosteroids is clear only after more than 7 days since symptoms onset, supporting our thesis. Also, no stratification was made for different respiratory support levels between simple oxygen supplementation and ventilatory support systems as helmet CPAP, HFNC or NIMV, even if during the pandemic these systems have been largely used in medical wards[20,21] consequently to the decreased accessibility of intensive care beds. Finally, authors themself admitted a possible harm of steroid therapy in the subgroup of patients not receiving oxygen support.

Interestingly, our patients requiring CPAP support and hospitalized for slightly more than one week represent a particular sub-group of the disease variety: excluding patients with hyperacute respiratory failure who needed immediate intensive treatment or rapidly died and those who had a favorable evolution, we had to face those who were not improving after 8 days of hospitalization and 6 after CPAP support (15 days from illness onset). Only at this point we considered steroids, and our results on this population are encouraging: steroids were effective in reducing the event MV or death from 34.1 to 19.3% (p=0.001) and mortality from 22.8 to 15.8% (p=0.011) despite the steroids group was 4 years older than the control group.

Our results are consistent with those of the RECOVERY trial and, considering the absolute reduction in mortality and MV rate, underline a possible greater benefit in a specific phase and severity of COVID-19.

Moreover, different studies[2,8-10,14,25,27,30,31] suggest non benefit/possible harm of glucocorticoid administration in non-severe patients or in too early phases of the disease. This may explain the more beneficial effect on our population.

The WHO meta-analysis[7] compared the effect of steroids in severe COVID-19 patients, using data from seven randomized clinical trials, along with RECOVERY. The analysis was centered on mechanically ventilated patients (91,5%), however 144 critically ill patients (8.5%) were not on MV. On those 144 patients, the meta-analysis confirmed a decreased 28-day mortality in patients treated with glucocorticoids and interestingly, the analysis indicated that glucocorticoid use was of greater benefit in critically ill patients who did not undergo invasive MV, in accordance with our results.

The absence of clinical trials on steroid efficacy at the time of the first wave in Italy (with expert consensus expressing relative contraindication)[14,18,19,32] is the reason why a great number of patients in our study did not receive steroids and allow our comparison.

In our population younger patients (57±11 years old), with lower degree of respiratory failure (even if with PaO_2/FiO_2 265±81 mmHg with CPAP therapy), low CCI (2.4±1.8) and CRP (10.2±5.5 mg/L at hospital admission) had a good outcome just with supportive therapy. These results also suggest that a better profiling for glucocorticoid eligibility is needed.

Assessing the steroids effect on mechanically ventilated patients is not the core aim of our study since MET role is to triage and treat patients outside the ICU; moreover, we think that complex and conflicting interaction of steroids and ARDS[1,25,30-36] combined with COVID-19 pathophysiology, may need specific categorization.

In this study age and CRP recorded at hospital admission are independent predictors of both mortality and composite outcome MV or death. Interestingly, the interaction between age and CRP with steroids showed that the predicting value of age and CRP is evident only in the control group, while the Steroids outcomes appears not to be influenced by these 2 factors. (Figure 3, Panel A and B). These data are consistent with other studies that already underlined the importance of age and CRP in this disease. More importantly, the rationale for steroids therapy seems to be even stronger as CRP is widely considered a marker of severity of inflammation in COVID-19.[37-39]

Considering Panel A, the graphic representation suggests that steroids in younger patients may be harmful. However, due to the low number of patients included in the first quintile of age, we retained that a specific analysis on this group may be of poor statistical significance. These data may benefit from further investigations since the harmful effects of steroids in younger patients can't be excluded.

PaO_2/FiO_2 at the first CPAP trial seems not to be an independent predictor of bad outcome, however the 95% CI in the multivariate analysis for composite outcome and mortality touch the level of significance without reaching it (Table 2). Moreover, the graphical appearance of the relation between PaO_2/FiO_2 and MV or death rate shows a greater incidence of bad outcome in patients with PaO_2/FiO_2 < 100 mmHg (Figure 3, Panel C). According to these data, PaO_2/FiO_2 at CPAP must be considered a variable influenced by many conditions such as cardiac function or body positioning at the time it was measured;[40] prone position in awake patients in COVID-19 is associated with better oxygenation even if at this time no benefit of this procedure on outcome is evident.

In our additional analysis on a-posteriori excluded patients, wide population heterogeneity is evident: even if every patient needed CPAP support during the course of the disease, the evolution of the disease followed a different, sometimes opposite journey. Corticosteroids were marginally administered in this subgroup because of the clinical approach we adopted to prescribe this treatment. These patients may benefit or not of immunomodulating therapies; better profiling of this cohort is needed to manage the wide phenotypes variety of COVID-19.

Conclusions

Steroid therapy seems to be beneficial in severe respiratory failure COVID-19, reducing the mortality and the necessity of MV in our population.

Our results suggest a better profiling of COVID-19 patients for optimal rationales, timings, dosages of steroids since efficacy seems to differ broadly considering age, timing, disease severity and comorbidity.

CRP, age and SOFA are confirmed to be independent prognostic factors in COVID-19 in our population.

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