Remdesivir plus dexamethasone versus dexamethasone alone for the treatment of COVID-19 patients requiring supplemental O_2 therapy: a prospective controlled non-randomized study

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Summary: Treatment with remdesevir plus dexamethasone in COVID-19 patients requiring supplemental O_2 therapy compared to dexamethasone alone showed higher 30-day survival, faster viral clearance, shorter length of hospital stay, and faster reduction of inflammatory markers and improvement of respiratory function.

Abstract

Background. Remdesivir is an antiviral used to treat COVID-19 which improves some clinical outcomes. Dexamethasone has been shown to be effective in reducing mortality. It has been hypothesized that combination of these two drugs can improve mortality. We evaluated the effect of combination on mortality of COVID-19 patients requiring O_2 therapy.

Methods. A prospective quasi-experimental study, including two independent, sequential controlled cohorts, one received remdesivir-dexamethasone and the other dexamethasone alone, was designed. All COVID-19 patients requiring supplemental O_2 therapy were enrolled consecutively. The sample size to power mortality was *a priori* calculated. The primary endpoints were 30-day mortality and viral clearance differences. Secondary endpoints were differences in hospitalization times, improvement in respiratory failure (PO_2/FiO_2) and inflammatory indices (fibrinogen, CRP, neutrophil/lymphocyte ratio, D-Dimer). Kaplan-Meier curves and the log-rank test were used to evaluate significant differences in mortality between groups.

Results. 151 COVID-19 patients were enrolled (remdesivir/dexamethasone group, 76 and dexamethasone alone,75). No differences in demographic, clinical and laboratory characteristics were observed between the two groups at baseline. Faster viral clearance occurred in the remdesivir/dexamethasone group compared to dexamethasone alone (median 6 vs 16 days; $p<0.001$). 30-days mortality in the remdesivir/dexamethasone group was 1.3%, while in dexamethasone alone was 16% ($p<0.005$). In the remdesivir/dexamethasone group compared to dexamethasone alone there was a reduction in hospitalization days ($p<0.0001$) and a faster improvement in both respiratory function and inflammatory markers.

Conclusions. Remdesivir/dexamethasone treatment is associated with significant reduction in mortality, length of hospitalization, and faster SARS-CoV-2 clearance, compared to dexamethasone alone

Key words: COVID-19, Remdesivir, Dexamethasone. Survival, viral clearance

Introduction

COVID-19, despite vaccines, continues to be a public health problem and we do not yet have an effective antiviral therapy. [1, 2] Remdesivir is a RNA-dependent RNA polymerase inhibitor effective against SARS-CoV-2 [3, 4]. The drug, currently, is the only antiviral authorized by the FDA for COVID-19 emergency based on data demonstrating its efficacy in reducing recovery time from disease which results in shorter hospitalization time [5], although, recently the WHO does not recommend the use of remdesivir alone as there is no evidence that the drug can reduce mortality and disease progression [6].

SARS-CoV-2 infection is characterized by a local and systemic inflammatory response that correlates with disease severity [7]. The anti-inflammatory effects of glucocorticoids, such as dexamethasone, have been evaluated in the treatment of COVID-19. The RECOVERY study demonstrated that dexamethasone significantly reduced mortality in COVID-19 patients requiring supplemental O2-therapy [8]. Further studies evaluated the efficacy of dexamethasone, recommending a low-dose approach to treating COVID-19 [9-10].

In agreement with other investigators [7], we assume that a prognostic improvement in COVID-19 patients requiring supplemental O_2 supportive care can be achieved by combining, in an early phase, an antiviral treatment, e.g., remdesivir, with an anti-inflammatory treatment, e.g., dexamethasone. A Bayesian re-analysis of randomized controlled trials of remdesivir and corticosteroids highlights a possible benefit in reducing mortality in COVID-19 patients requiring supplemental oxygen and suggests rapid evaluation in a targeted controlled prospective study [11]. In addition, a hypothetical study of cost/benefit analysis supports the possible use of remdesivir and dexamethasone as proven to be cost-effective and would save costs and lives [12].

Accordingly, the aim of this study was to prospectively evaluate the safety and efficacy of remdesivir plus dexamethasone versus dexamethasone alone in improving prognostic outcomes in COVID-19 patients who require supplemental non-invasive O_2-therapy.

Methods

Study design and sample size.

This prospective study was conducted between January 15 and May 15, 2021 at the Internal Medicine COVID CENTER, University of Campania "Luigi Vanvitelli". A quasi-experimental study, including two independent, sequential controlled cohorts, one received remdesivir-dexamethasone and the other dexamethasone alone, was designed. In the first two months of the enrollment period, we were not prescribers for remdesivir, and therefore all patients eligible for the study were treated consecutively with dexamethasone alone; in the following 2 months, having become prescribers of remdesivir, we used it consecutively in combination with dexamethasone in all eligible patients.

The sample size of the study was *a priori* calculated on the basis of our previous data as well as the Italian data which showed an in-hospital mortality around 23%, and on the data of the RECOVERY study showing that dexamethasone reduced mortality by 6-8%. [8,13]. Using the above data, we estimated that in-hospital mortality in the dexamethasone group could be 17%, while in the remdesivir/dexamethasone group it could be 3%. We set an α-error of 0.05 and β-error of 0.2, and a power of 0.8. The two tails sample size calculated for an adequate power was 71 patients for each group to be enrolled. The study was conducted in accordance with the principles of good clinical practice guidelines and all patients signed informed consent. The study was approved by the local Ethics Committee.

Eligibility criteria and therapeutic protocol. In accordance with NIH COVID-19 treatment guidelines [2] and Italian Drug Agency (AIFA) [14], all adult COVID-19 patients requiring non-invasive supplemental O_2-therapy were eligible for treatment with remdesivir and dexamethasone. Patients eligible for remdesivir treatment were also required to have a COVID-19 symptom duration of no more than 10 days. Patients with transaminase elevations greater than 5-fold and those with an eGFR lower than 30 mL/min were excluded from remdesivir treatment.

Remdesivir was administered i.v., at a dose of 200 mg on the first day and then 100 mg for a total of 5 days. Dexamethasone was administered at a dose of 6 mg/day for 10 days. The two drugs of the combination group were started on the same day. All patients received the same supportive standard of care. In particular, a prophylaxis with low molecular weight heparin was made and if necessary used at therapeutic dosage. Specific antibiotic therapy was done in the presence of bacterial infection or empirically when an infection was suspected. All active comorbidities were treated according to their respective guidelines.

Based on the degree of hypoxemia, patients received O_2-therapy via nasal cannula, venturi mask, high-flow nasal cannula, or non-invasive ventilation (NIV).

Diagnostic, clinical and laboratory parameters

The diagnosis of SARS-CoV-2 was assessed by nasal/throat swabs by RT-PCR amplifying ORF1ab, N gene and E gene of SARS-COV-2 in LC480 II Roche.

Patients evaluation, on admission, included a medical history to assess the onset of symptoms referable to COVID-19, physical examination, and evaluation of the respiratory and cardiovascular functions, and of comorbidities. All patients, during hospitalization, were monitored 24 hours a day by telemetry for respiratory and cardiovascular function.

At hospitalization, patients underwent a CT scan of the chest and lung damage was quantified with a score of 0-20; in addition, they underwent an ultrasound of the chest with quantification of the

damage with a score (LUS) 0-36. Through blood gas analysis (EGA) the respiratory exchanges were assessed and the PaO_2/FiO_2 ratio estimated. In accordance with the ARDS Berlin definition, a value of PaO_2/FiO_2 >300 was considered normal. [15]

Laboratory tests for hematological and renal functions were evaluated by red and white blood cells, hemoglobin and platelet counts, creatinine, BUN, eGFR; liver function with AST, ALT, bilirubin, albumin, gamma-globulin. Moreover, serum levels of CRP, fibrinogen and D-Dimer were evaluated.

Primary and secondary outcomes evaluated.

The primary end point of the study was represented by difference of mortality, assessed at 30 days from admission, in the two groups evaluated.

Another primary end point was SARS-CoV-2 clearance time in the two treated groups, defined as the median number of days from start of treatment until nasopharyngeal swab turned negative. Viral clearance was assessed by PCR on nasal swabs at the end of remdesivir treatment, i.e. 6 days after starting treatment and every 3-6 days thereafter. Swabs, in the dexamethasone alone group, were made at the same time points as the remdesivir group.

The secondary outcomes evaluated were: a) the difference in the number of hospitalization days between the two groups; b) the difference in the reduction of the levels of inflammatory markers such as CRP, fibrinogen, neutrophil/lymphocyte ratio and D-Dimer at the end of each treatment and at discharge c) the difference in the variation or normalization of PaO_2/FiO_2 at the end of the treatments and at discharge between the two study groups.

Statistical analysis

The results of the study are expressed as median and interquartile range (IQR). The Mann-Whitney U test was used to evaluate differences of death between the two groups. The chi-square test with Yates correction was used to evaluate difference between categorical variable of the two groups.

The differences in mortality between groups was evaluated by Kaplan-Meier curves and the Mentel-Cox log rank test was used for individuate significant differences between groups. A $p < 0.05$ was assumed to denote significance.

Results

General characteristics of the enrolled patients.

Figure 1 shows the flow chart of all patients evaluated and included in the study. One hundred and fifty-one consecutive COVID-19 patients requiring supplemental non-invasive oxygen therapy were enrolled in the study, 76 in the remdesivir plus dexamethasone group and 75 in the dexamethasone only group. Analysis of basal patient characteristics in both groups, reported in table 1, did not show significant differences between the remdesivir/dexamethasone group and dexamethasone group in terms of onset of symptoms (7.5 vs 7 days, respectively), median age (64 vs 66 yrs, respectively), sex (male: 63.2% vs 64%, respectively), number of comorbidities (median 2 vs 2, respectively), diabetes (19.5% vs 21.3%, respectively), hypertension (54% vs 60%, respectively), obesity (24.7 vs 24%, respectively), renal failure (18.4% vs 22.6%, respectively), chronic liver disease (9.2 % vs 12%, respectively), cardiopathy (18.4% vs 26.6, respectively), vasculopathy (19.7% vs 20% respectively) and active neoplasia (3.9% vs 4.0%, respectively). In addition, respiratory failure and initial respiratory support required were not different between the two groups (median PaO_2/FiO_2 was 231 and 242, respectively). Moreover, both the CT score and the LUS score and laboratory analysis were not significantly different between the two groups (Table 1). The initial ventilatory supports and the other therapeutic interventions were similar in the two groups. Furthermore, during the study period there was no change in hospital capacity in terms of occupancy of beds or staffed beds in both ordinary hospitalizations and in sub-intensive/intensive care and there was no overcrowding or overwhelming since the number of beds was fixed and the number of hospitalized corresponded to the number of pre-established beds.

The data demonstrated that the demographic, clinical and laboratory characteristics of the two groups were not significantly different and, therefore, the statistical analysis of the outcomes stated could be done with great confidence.

Primary and secondary outcomes

Viral clearance occurred within a median of 6 days (IQR: 6-8) after initiation of remdesivir/dexamethasone therapy, while in the dexamethasone alone group it occurred in a median of 16 days (IQR: 13-19; p <0.001, table 2)**.** Specifically, at 6 days of starting treatment, 69% of patients in the remdesivir/dexamethasone group, while only 20% in the dexamethasone group had cleared the virus (p <0.001).

The end point powered in this study was the 30-day mortality assessment starting from the first day of hospitalization. As shown in table 2 in the remdesivir/dexamethasone group one patient died (1.3%), while in the dexamethasone alone group 12 patients died (16%; p <0.005, table 2). Figure 2 shows the Kaplan-Meier survival curve of the two groups and the log rank test shows that the observed difference was significant (p <0.003).

Table 2 shows a significant reduction in hospitalization in the remdesivir/dexamethasone group compared to those treated with dexamethasone alone (median: 13 days, IQR, 10-15 vs 17 days, IQR, 12-19, respectively; p <0.0001). Additionally, when disease duration was assessed, patients treated with remdesivir/dexamethasone had significantly shorter disease durations than those treated with dexamethasone alone (median: 16 days vs 22 days, respectively, p <0.0001, table 2).

As reported in Table 3, a rapid significant decrease in CRP was observed at the end of treatment in patients in the remdesivir/dexamethasone group, while it was not observed in the dexamethasone alone group. A significant reduction in the fibrinogen and neutrophil/lymphocyte ratio was observed in the two groups at the end of treatment (Table 3), but it should be noted that the Δ% difference for both variables was significantly greater in the remdesivir/dexamethasone group than that

observed in the group treated with dexamethasone alone (Table 3). In addition, at the end of treatment, among patients with altered fibrinogen values, 27% had normalized the fibrinogen value (<400 mg/dl) in the remdesivir/dexamethasone group, while in the group treated with dexamethasone alone the normalization of the values occurred in 8% ($p< 0.05$). Similarly, normalization of fibrinogen values occurred in 50% and 26% ($p<0.05$) in the remdesivir/dexamethasone group and in the dexamethasone alone group, respectively, at the end of treatment.

In the group of patients treated with remdesivir/dexamethasone, no significant increase in D-Dimer values was observed at the end of treatment (Δ= +11.3%), while a reduction in Δ of -9% was observed at the time of discharge (table 3). In contrast, in patients treated with dexamethasone alone, a significant increase in D-Dimer (Δ= +43%; $p <0.05$; table 3) was observed at the end of treatment and at discharge patients continued to have an increase in D-dimer compared to baseline with a Δ of +5.2% (table 3).

The effects of the two treatments on respiratory function, estimated by PaO_2/FiO_2 ratio are show in figure 3. PaO_2/FiO_2 ratio assessed on the sixth and tenth day of treatment with remdesivir/ dexamethasone demonstrate a rapid and significant improvement ($p <0.0001$) compared to those treated with dexamethasone alone. At the end of remdesivir/dexamethasone treatment, 50.6% of patients had normal respiratory function, while in the dexamethasone group only 22.9% had normal respiratory function ($p<0.0005$) and at hospital discharge the respiratory function was normal in 70% of patients treated with remdesivir/dexamethasone and in 37% of patients treated with dexamethasone alone ($p<0.003$).

Side effects.

All patients completed the treatments and no serious events were observed. In the remdesivir group, 6 (7.9%) patients had elevated transaminases of which 2 had an increase greater than 5 times the normal value at the end of treatment. Transaminases turned normal in the weeks following drug withdrawal. A moderate increase in serum bilirubin values was observed in 15 (20%) of remdesivir-treated patients who became normal in the days following treatment discontinuation.

Discussion

This prospective controlled study was powered to test the hypothesis that the remdesivir/dexamethasone combination could reduce the mortality of COVID-19 patients requiring supplemental oxygen therapy. The data show that treatment with remdesivir plus dexamethasone significantly reduces mortality at 30 days of these patients in comparison to treatment with dexamethasone alone (Table 2, Figure 2). Furthermore, this is the first clinical study that has targeted and demonstrated that remdesivir treatment induces rapid elimination of SARS-CoV-2, already at the end of treatment in 69% of cases, with a median clearance of 6 days compared to 16 days observed in the dexamethasone-only group (Table 2).

The result of our study on mortality reduction in the remdesivir/dexamethasone group is in concert with the data of two recently large studies that retrospectively assessed the efficacy of the combined use of corticosteroids and remdesivir demonstrating a significant reduction in mortality at 30 days compared with corticosteroids alone treatment (12.6% vs 19.7%) [16-17]. In addition, these studies reported that a clinical improvement was observed in the remdesivir/corticosteroids group over a significantly shorter time interval as well as a reduction in days of hospitalization [17].

Our study had the evaluation of clinical improvement and hospitalization days as secondary end points. Similar to what has been observed in retrospective studies [16-17], a clinical improvement, defined as an increase in PaO_2/FiO_2 ratio greater than 300, was observed in 50.6% of patients at the

end of remdesivir/dexamethasone treatment compared with 22.9% of patients treated with dexamethasone ($p<0.0005$), and the ratio was further improved at discharge (70.1% vs 40%, respectively; $p<0.0002$); in addition, it was found that patients treated with remdesivir/dexamethasone had a significant reduction in the duration of hospitalization compared to those in the dexamethasone group (13 days, IQR, 10-15 vs 17 days, IQR, 12-19, respectively $p<0.0001$).

Another interesting finding observed in our study, as a secondary end point, was that patients treated with remdesivir/dexamethasone showed a greater significant reduction in inflammatory markers at the end of remdesivir treatment and at discharge compared to patients treated with dexamethasone alone. In particular, the group of patients treated with the combination showed an earlier and profound significant reduction in the neutrophil/lymphocyte ratio, D-Dimer, CRP and fibrinogen (Table 3).

From the overall analysis of the results of our study it can be inferred that the observed improvements in the outcomes are due to the combined additive action at various levels of remdesivir and dexamethasone leading to a significant reduction of inflammatory reaction. The first step appears to be related to the action of remdesivir which eliminates or reduces viral replication early and this could mitigate the proinflammatory cytokine storm seen in SARS-CoV-2 infection, the extent of which is related to the severity of the disease [7]. However, the elimination of the virus alone, in an advanced stage of the disease, in which an important inflammatory reaction has already established, although having a positive impact by improving the clinical condition, does not seem to be sufficient to improve also the mortality in these patients [18]. Thus, the anti-inflammatory effect of dexamethasone appears to be important in blocking or permanently eliminating the residual and possibly self-sustaining inflammatory reaction. The data from our study support the above concept as they demonstrate a significant reduction in inflammatory markers in the remdesivir/dexamethasone group compared to dexamethasone alone and this seems to suggest

that the early reduction or clearance of viral load by the antiviral, eliminating the inflammatory trigger, favors the action of dexamethasone in the definitive elimination of inflammation and thus the therapeutic association translates into a winning strategy that reduces mortality in COVID-19 patients who require supplementary oxygen therapy.

Treatment was overall well tolerated and safe, with no significant adverse events occurring and no treatment interruption was required in any patient.

A potential limitation to our study is due to the non-randomization for treatment assignment to the patients included in the study. However, we believe that the results of our study can be viewed with confidence as the study was prospective, controlled a priori, the enrollment of patients was consecutive and took place in a very short period of time, and moreover, of greater importance, was the analysis of the demographic and clinical characteristics which showed that the two groups were superimposable in all the examined parameters, and in particular the duration of onset of symptoms, the stratification for the severity of the disease, the stage of ARDS, the distribution and severity of the comorbidities and the uniformity of treatments were also similar in the two groups studied.

A further conceivable limitation could be represented by changes in circulating SARS-CoV-2 variants occurring over the study time. However, epidemiological analysis by 'Istituto Superiore di Sanità' reported a prevalence of the B.1.1.7 strain up to 89% of circulating SARS-CoV-2 variant throughout the study period in our region of Campania [19]. In addition, an in vitro study suggests that the efficacy of remdesivir is not affected by known SARS-CoV-2 variants [20].

New antivirals such as molnupiravir and paxlovid are on the horizon. However, these drugs are expected to be used for home therapy, and there is currently no evidence that they work in patients requiring O_2 therapy.

In conclusion, the data demonstrate that early combined treatment with remdesivir plus dexamethasone, e.g. within 10 days of symptom onset, in COVID-19 patients requiring supplemental oxygen therapy, induces a rapid SARS-CoV-2 clearance, reduces the risk of 30-days mortality, prevents clinical progression of the disease, and shortens the length of hospitalization of these patients.

Notes

Author contribution. Conceived and design: L.E.A., A.M., R.N., A.S. Acquired data: C.A, M.X.P.S., C.R., G.C., S.I., L.R., K.G., A.P., R.R., C.R., L.MA.M., M.A., F.C., C.C. Analyzed and interpretation of data: L.E.A., A.M., R.N. First drafting: A.M., L.E.A., Critical revision of the manuscript: D.C., C.P.R., R.N., A.S. All authors have read and approved the final version of the manuscript.

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Table 1. Baseline demographic and clinical characteristics of the enrolled patients.

Characteristic	**Remdesivir + Dexamethasone**	**Dexamethasone**	
	(N= 76)	(N=75)	P-Value
Onset of symptoms/start of treatment, days (IQR)	7.5 (6-9)	7 (5-10)	0.984
Age – median (IQR)	64 (55-74)	66 (55-75)	0.077
Sex, male n (%)	48 (63.2)	48 (64)	0.950
Number of comorbidities, median (IQR)	2 (0-3)	2 (1-4)	0.089
Smoker	36 (46.8)	37 (49.3)	0.937
Type 2 diabetes mellitus, n (%)	15 (19.5)	16 (21.3)	0.967
Hypertension, n (%)	41 (54.0)	45 (60.0)	0.557
Obesity, n (%)	19 (24.7)	18 (24.0)	0.953
Chronic Kidney Disease, n (%)	14 (18.4)	17 (22.6)	0.656
eGFR, median (IQR)	89 (76-100)	84 (57-98)	
Hepatopathy, n (%)	7 (9.2)	9 (12.0)	0.769
COPD, n (%)	13 (17.1)	15 (20.0)	0.803
Vasculopathy, n (%)	15 (19.7)	15 (20.0)	0.870
Active neoplasia, n (%)	3 (3.9)	3 (4.0)	0.689
Cardiopathy, n (%)	14 (18.4)	20 (26.6)	0.308
Clinical characteristic:			
PO_2/FiO_2, median (IQR)	231 (168-280)	242 (149-305)	0.603
ARDS:			
none, n (%)	15 (19.8)	18 (24.0)	0.693
mild, n (%)	33 (43.4)	26 (34.7)	0.349
moderate, n (%)	28 (36.8)	29 (38.7)	0.949

severe, n (%)	0	2 (2.6)	0.792
LUS score on admission, median (IQR)	15 (10-19)	15(10-20)	0.841
CT score on admission, median (IQR)	9 (7-12)	10 (7-13)	0.183
Laboratory characteristic:			
ALT, n: increased (%)	23 (30.2)	24 (32)	0.956
GGT, n: increased (%)	18 (23.7)	17 (22.6)	0.964
Bilirubin, n: increased (%)	6 (7.9)	8 (10.6)	0.759
Neutrophil/lymphocyte ratio (IQR)	7.5 (3.86-12.1)	7.9 (3.62-14.2)	0.928
Fibrinogen, median (IQR)	597 (493-750)	546 (445-698)	0.841
CRP, median (IQR)	6.11 (2.65-10.25)	6.5 (2.47-12.67)	0.303
D-Dimer, median (IQR)	638 (327-880)	720 (314-1518)	0.432
Initial respiratory support:			
Venturi mask, n (%)	22 (28.9)	20 (26.7)	0.895
High flux, n (%)	50 (65.9)	48 (64.0)	0.952
cPAP, n (%)	4 (5.2)	7 (9.3)	0.516

Abbreviations: n, number; IQR, interquartile range; ns, not significant; eGFR, estimated glomerular filtration rate; PO_2/FiO_2, partial pressure of arterial oxygen/ fractioned inspiratory oxygen ratio; ARDS, acute respiratory distress syndrome; LUS, lung ultrasound; CT, computed tomography; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; CRP, C-reactive protein; cPAP, continuous positive airway pressure.

Table 2. Viral clearance, duration of the disease and mortality in the two groups of treatment.

Outcomes	Remdesivir + Dexamethasone	Dexamethasone	P <
Initial symptoms/discharge COVID free, median days, (IQR)	16 (15-20)	22 (19-26)	0.0001
Viral clearance from beginning of treatment, median days (IQR)	6 (6-8)	16 (13-19)	0.001
Hospitalization, median days, (IQR)	13 (10-15)	17 (12-19)	0.0001
30-days Mortality, n (%)	1 (1.3%)	12 (16%)	0.005

Table 3. Behavior of the inflammatory indices during the two different treatments.

	Remdesivir + Dexamethasone						Dexamethasone					
	Baseline	End of treatment	Δ%	Discharge	Δ %	p<	Baseline	End of treatment	Δ%	Discharge	Δ%	p<
D-Dimer mg/dl, median (IQR)	638 (327-880)	710 (475-1110)	+11	580 (330-905	-9	ns	720 (314-1518)	1090 (625-1845)	+43	800 (455-1615)	+5.2	*0.05
Fibrinogen, mg/dl, median (IQR)	597 (493-750)	435 (368-561)	-27	378 (324-570)	-37	0.00001	546 (445-698)	462 (326-566)	-15	400 (339-550)	-27	0.001
CRP, mg/dl, median, (IQR)	6.11 (2.65-10.25	0.87 (0.5-2.6)	-86	0.62 (0.3-1.69)	-90	0.00001	6.5 (2.47-12.67)	4.95 (0.25-5.21)	-24	1.6 (0.64-4.68)	-75	0.001**
Neutrophil/lymphocyte ratio, median (IQR)	7.55 (3.86-12.1)	3.24 (2.37-6.24)	-56	3.22 (2.34-4.63)	-59	0.00001	7.95 (3.62.14.2)	4,50 (2.27-8.31)	-43	3.84 (2.63-6.46)	-51	0.05

Abbreviations: ns, not significant.

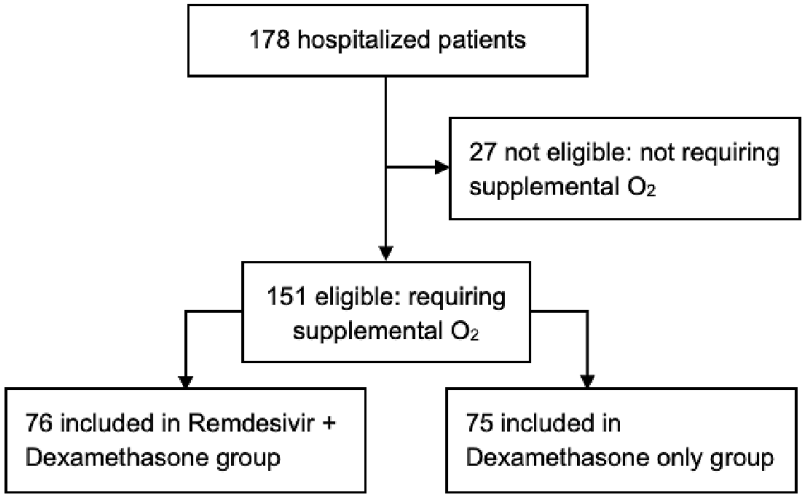
* end of treatment vs baseline; ** discharge vs baseline; no asterisk indicates significance between previous groups

NOTES

Figure 1. Flow chart of all patients hospitalized evaluated and included in the study.

Figure 2. Kaplan-Meier curves estimated mortality of patients with COVID-19 in the two groups of treatment: line a, patients treated with remdesivir plus dexamethasone, line b, patients treated with dexamethasone alone. Log-rank test: p<0.003

Figure 3. Box plot representing variation of PO_2/FiO_2 ratio in patients treated with remdesivir/dexamethasone and dexamethasone alone at baseline, end of treatment and at hospital discharge.



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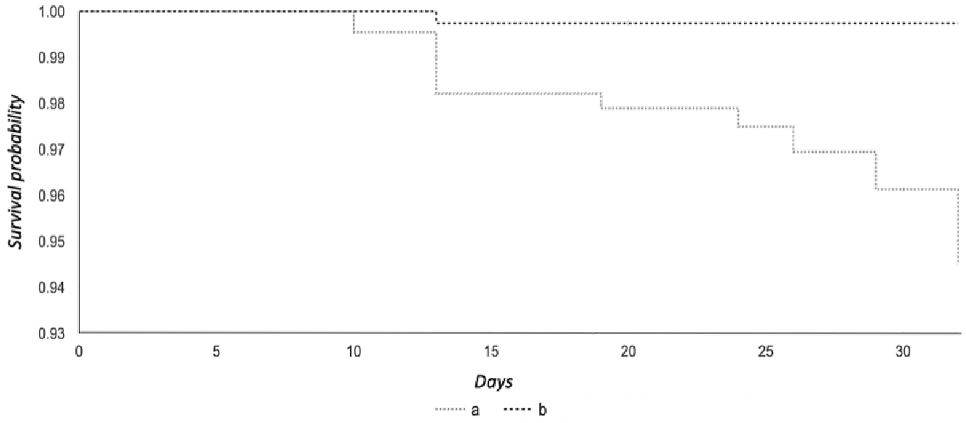
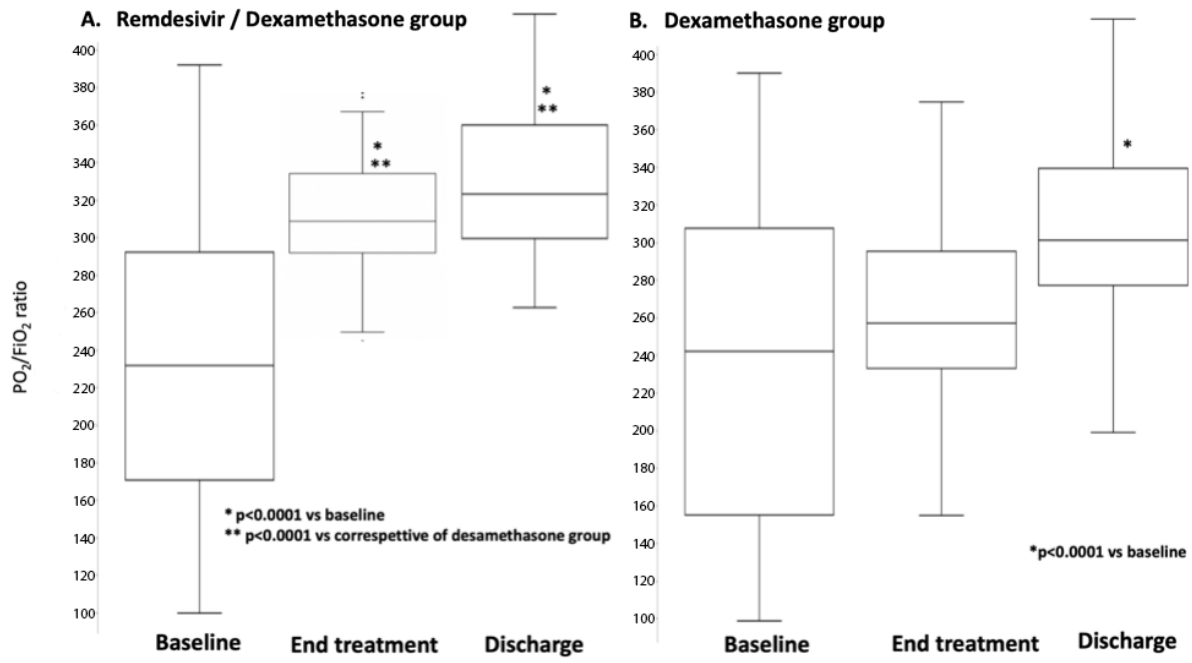


Figure 2.



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