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Treatment Outcome with High versus low-to-moderate Dosing of Corticosteroids in Early vis-a-vis Late-onset Hypoxic Cases of COVID-19: A Multicentric Retrospective Cohort Study

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Highlights

- Selecting a proper corticosteroid regime in terms of dosage and duration is crucial
- Survival benefit analysed between high vs. low-moderate dose steroid recipients
- Lesser mortality benefits seen with higher doses of steroids in early-onset hypoxia
- Statistically insignificant when therapy is initiated late in course of the disease
- NLR, a marker of the immune response varied between treatment groups

ABSTRACT

Background: Corticosteroid dosing in COVID-19 cases associated with early-onset and late-onset hypoxia have not been separately explored.

Methods: In this retrospective cohort study, we divided hypoxic COVID-19 cases into groups based on timing of initiation of corticosteroids relative to onset of symptoms; Group-A (≤6th day), Group-B (7th-9th day) and Group-C (≥10th day), each group being sub-grouped into high and low-to-moderate dose corticosteroid recipients. Cox regression with propensity-scoring was used to compare 28 days-mortality between high and low-to-moderate dose recipients separately in Group-A, Group-B, Group-C.

Results: Among 505 patients included, propensity-score matched Cox regression showed greater risk of all-cause mortality among high dose recipients in Group-A [HR= 7.35, 95%CI 3.36-16.11, p-value<0·01, N=114] and Group-B [HR=3.17, 95%CI 1.65-6.07, p-value<0·01, N=251]. In Group-C, mortality was lowest [12.8% (18/140)] with no significant difference between sub-groups [HR=2.52, 95%CI 0.22-29.15, p-value=0.459,

N=140]. Kruskal-Wallis Test between Group-A, Group-B and Group-C for six pre-defined exposure variables showed significant differences for Neutrophil:Lymphocyte Ratio (NLR).

Conclusion: When steroids were initiated early (owing to an earlier onset of hypoxic symptoms), a high dose of corticosteroid was associated with greater overall 28 days-mortality compared to a low-to-moderate dose. NLR, a marker for individual immune response, varied between treatment groups.

Keywords: COVID-19, Hypoxia, Early-onset, Late-onset, Corticosteroids, Mortality

INTRODUCTION

Corticosteroids are found to have mortality benefits in hypoxic COVID-19 cases. These benefits have recently been established in large trials like the Recovery trial (RECOVERY Collaborative Group, Horby P, Lim WS, 2021) and a large meta-analysis (Sterne et al., 2020) that pooled the result of seven Randomized Clinical Trials (RCTs). There is some consensus between globally accepted guidelines (thebmj, 2020), (IDSA, 2022), (WHO, 2021) regarding the dosing and duration of corticosteroid therapy in hypoxic COVID-19 cases, but these guidelines are not clear as to whether the dosing and regimen of corticosteroid therapy should vary between cases presenting with early-onset and late-onset hypoxia. In this study, we tried to separately evaluate the impact of different doses of corticosteroids in three different groups (based on the day of onset of symptoms when steroids were initiated) of hypoxic COVID-19 patients.

METHODS

Study Design and Setting

A multicentric, institution-based retrospective cohort study was conducted among hypoxic COVID-19 patients admitted and treated between Feb-Aug 2021 during second wave of COVID-19 pandemic in India. This study was conducted across two tertiary-care super-specialty hospitals in Eastern India, Rampurhat Government Medical College & Hospital and AMRI Hospitals, Mukundapur, Kolkata. The study population included hospital-admitted hypoxic COVID-19 patients who received corticosteroid therapy and other supportive medications.

Study Participants

Hypoxic (SpO2≤94%) COVID-19 RT-PCR positive adult (age>18 years) patients initiated on corticosteroids within 24 hours of hospital admission and continued so for at least three days, were included. Cases receiving corticosteroids due to concomitant autoimmune /immunosuppressive disease (Inflammatory Bowel Disease, Rheumatoid Arthritis, Post-Renal Transplant, etc.) or those receiving so in the last seven days (as available from past medication records), $SpO_2 \geq 95\%$ and those receiving tocilizumab, antibody-cocktail, baricitininb or any other immunomodulatory therapy for the present illness, were excluded. We also excluded patients with inadequately evidenced clinical history regarding onset of symptoms and those with co-existing bacterial sepsis (as seen from high pro-calcitonin levels or positive culture reports).

Data Sources

Hospital-based records from either institution were filled into pre-designed data extraction forms and codified into MS Excel. Treatment history was reviewed including medications

received, dosage and preparation of corticosteroids used and day of symptom when corticosteroids were started (day 1 being the 1st day of symptom onset). We analyzed the entire study population in three separate groups based on the day of symptom when corticosteroids were initiated. The patients were divided into three groups. In Group-A, patients had received steroids on or before day 6 of onset of symptoms. Group-B included patients initiated on corticosteroids between days 7-9. Group-C patients received steroids on or after day 10 of symptom onset. [COVID-19 illness is known to exhibit three grades of increasing severity with correspondingly different clinical findings, response to therapy, and clinical outcome. Timelines for grouping the cohort were selected arbitrarily (i.e. ≤6 days, 7-9 days and ≥10 days) keeping in mind, the 3 corresponding distinct stages of disease (Siddiqi and Mehra, 2020) and accordingly different immune responses by the host cell (Sette and Crotty, 2021)].

Each group was subdivided into two subgroups based on whether they received a high-dose (>40 mg prednisolone or 6 mg dexamethasone equivalent /day) or low-to-moderate dose (≤40 mg prednisolone or 6 mg dexamethasone equivalent /day) corticosteroids within 24 hours of hospital admission. This dose cut-off of 40 mg prednisolone was selected based on a few trials (Maskin et al., 2022), (Munch et al., 2021) that considered this dose as a low dose. A major trial by Recovery Group used equivalent dose ranges in their study population (RECOVERY Collaborative Group, Horby P, Lim WS, 2021). A standard steroid-conversion calculator ascertained equivalent doses of corticosteroids.

Study Variables

The baseline study variables included the following:

a) *Demographic parameters* [Age (Petrilli et al., 2020); Sex; Body Mass Index (BMI) (Palaiodimos et al., 2020); Charlson Comorbidity Index (CCI) (Tuty Kuswardhani et al., 2020); Vaccination Status]

b) C*linical parameters* [Quick COVID-19 Severity Index (qCSI, comprising of Respiratory Rate, SpO2, Oxygen Demand) (Rodriguez-Nava et al., 2021); Pulse Rate; Systolic and Diastolic Blood Pressure (SBP and DBP); SOFA Score; Treatment with Remdesivir]

c) *Laboratory parameters* [White Blood Count (WBC); Hemoglobin in gm/dl (Hb%); Neutrophil:Lymphocyte ratio (NLR) (Alkhatip et al., 2021); serum Alanine Transferase (ALT); serum Creatinine; Serum C-Reactive Protein (CRP) (Stringer et al., 2021); serum D-dimer levels]

Outcome measures

The primary outcome measure in this study was all-cause mortality over 28 days post-hospital admission. Secondary outcome measures included length of hospital stay, percentage of ICU admissions, and the percentage receiving oxygen through face masks /cannula, through invasive or non-invasive ventilation. We compared primary and secondary outcomes between high-dose and low-to-moderate dose recipient sub-groups in each of Group-A, Group-B and Group-C.

Additionally, from the before-mentioned baseline variables, we selected six variables (Age, BMI, CCI, qCSI, CRP, NLR) that could potentially impact treatment outcomes, based on literature review of similar studies. We intended to look for differences in these variables between the study groups, Group-A, Group-B and Group-C.

Statistical Analysis

To compare the primary outcome, i.e., 28 days-mortality between the high-dose and low-to-moderate dose corticosteroid recipients in each of Group-A, Group-B and Group-C, survival analysis was done using the following methods:

a. Cox regression adjusting for baseline covariates [Age, Sex, BMI, CCI, qCSI, Pulse Rate, Body Temperature (in Dégrée-Fahrenheit), SBP, DBP, NLR, serum D-Dimer values, CRP, WBC, Hb%, ALT, Creatinine, Remdesivir Status, SOFA score and Vaccination status]

b. Cox regression with propensity-score adjustment along with adjusted baseline covariates.

c. Cox regression with IPTW with adjusted baseline covariates.

d. Cox regression in propensity-score matched data set with adjusted baseline covariates.

The proportional hazard assumption of the Cox model was tested by the log(-log(survival)) graph versus the length of a hospital stay along with the global Schoenfeld residual. In every group (Group-A, Group-B, Group-C), three different propensity-scoring methods (covariate adjustment using propensity-score, inverse probability of treatment weighting (IPTW) using propensity-score and propensity-score matching) were used to minimize selection bias and confounding (Ali et al., 2019) while estimating the effect of the intervention on outcomes.

Based on a thorough literature review and clinical evidence, the potential confounders identified were Age, BMI, qCSI, CCI, CRP, and NLR. Propensity-scoring was done by binary logistic regression for these potential confounders. Matching was done separately within each of Group-A, Group-B and Group-C between high-dose and low-to-moderate dose corticosteroid recipients. For propensity-scoring, a separate model was developed

for each group. Initially, nearest neighbour score matching (1:1) with 0·2 calipers without replacement yielded poor balance in standardized mean difference (SMD>0·1). Therefore, optimal matching (1:1) was tried using the Optmatch package, which showed SMD<0·1, indicating adequate balance (Zhang et al., 2019). In addition to Cox proportional hazard regression, the Kaplan-Meier survival plot was used to compare the mortality over time in propensity-score-matched cohorts in each group.

To compare the secondary outcome parameters between the high-dose and low-to-moderate dose recipient sub-groups in each of Groups Group-A, Group-B and Group-C, an unpaired t-test was done. The normality of data was calculated using One-Sample Kolmogorov-Smirnov testing. A p-value ≤0·05 with a confidence interval (CI) of 95% was considered statistically significant. All tests were two-sided. Baseline variables among three groups of high-dose and low-to-moderate dose corticosteroid recipients were expressed as mean with standard deviation (SD) and median with interquartile ranges (IQR) for numerical variables and frequencies with percentages for categorical variables.

Kruskal-Wallis test followed by post-hoc Dunn's test was done to compare the six pre-defined baseline variables between Group-A, Group-B and Group-C. Post-hoc Bonferroni-adjusted significance tests for pairwise comparisons were done for those variables that rejected the null hypothesis in the independent Kruskal-Wallis test.

Missing data were addressed as per Rubin's typology (Rubin, 1976). The null hypothesis for Little's MCAR test was "data missing completely at random". Missing data were calculated by the multiple imputation method from five imputed data sets. Data were

codified and calculated with the help of statistical software SPSS (version 26·0) and R (version R-4.1.2).

RESULTS

A total of 1102 case records of hypoxic COVID-19 patients treated between February to August ’21, were screened for this study. 597 patients were excluded and 505 patients meeting all inclusion criteria were selected [Figure-1]. All were hospital inpatients and received IV corticosteroids as per physician choice, guided mainly by the existing national guideline (AIIMS/ ICMR-COVID-19 National Task Force/ Joint Monitoring Group (Dte.GHS), 2022) or Recovery Protocol (RECOVERY Collaborative Group, Horby P, Lim WS, 2021). Patients having a prolonged hospital course were seen to receive corticosteroids for 7-10 days generally as per ICMR guidelines (AIIMS/ ICMR-COVID-19 National Task Force/ Joint Monitoring Group (Dte.GHS), 2022) and for those who recovered within a few days of therapy, corticosteroids were stopped as hypoxia got corrected.

The entire study population was subdivided into three groups: Group-A had 114 (22.57%) patients, Group-B had 251 (49.70%) patients, and Group-C had 140 (27.72%) patients. We conducted propensity-score based 1:1 optimal matching with six pre-defined exposure variables (demographic characteristics, clinical parameters and laboratory values) for the entire study population [Supplementary Appendix; Figure-S.1]. The SMD for these variables were calculated between matched and unmatched cohorts besides the p-value. SMD of all the six variables of the matched cohort was <0·1. [Table-1] The proportional hazard assumption tested with Global Schoenfeld residual held valid for

Group-A and Group-B (p>0·05) but not for Group-C (p<0·05). [Supplementary Appendix; Table-S.1] The log(-log(survival)) graph versus the length of a hospital stay seemed to be parallel in Group-A and Group-B but not in Group-C. [Supplementary Appendix; Figure-S.2]

Group-A showed overall mortality of 64% (n=73, N=114) [Table-2]. Cox regression analysis adjusted with all the baselines covariates showed a higher risk of post-admission death in patients receiving high-dose corticosteroids in this group [Adjusted Hazard Ratio (HR) 5·036, 95% CI 2·461-10·302, p<0·001]. Propensity-score adjusted Cox regression, IPTW regression and Cox regression with propensity-score optimal matching (1:1) adjusted with the same covariates showed similar results [Figure-2].

Group-B had a mortality of 38·2% (n=96, N=251) [Table-2]. We repeated the same statistical methods for survival analysis as above and found a higher risk of mortality at day 28 among high-dose recipients than low-to-moderate dose recipients in this group. [Adjusted HR: 3·375, CI 1·91-5·94, p<0·001] [Figure-2].

The mortality rate in Group-C was the lowest at 12.8% (n=18, N=140) [Table-2] using the same analytical methods as before. There was no statistically significant (p>0·05) mortality difference between high-dose and low-to-moderate dose recipients in this group. [Figure-2 & Figure-4]

Kaplan-Meier survival curves between high-dose versus low-to-moderate dose corticosteroids in unmatched data in each of Group-A, Group-B and Group-C are depicted in Figure-4.

The results of the comparison in secondary outcome parameters between high-dose and low-to-moderate dose recipient sub-groups in each of Group-A, Group-B and Group-C have been depicted in Table-3.

Kruskal-Wallis Test was done in-between Group-A, Group-B and Group-C for the six exposure variables (age, BMI, CCI, qCSI, NLR, CRP). Two of the variables (BMI and CCI) showed no significant differences ($p>0{\cdot}05$) [Supplementary Appendix; Table-S.2]. In contrast, the rest of the four variables (age, qCSI, NLR, CRP) showed significant differences ($p<0{\cdot}05$) between high-dose and low-to-moderate dose subgroups, in at least one of the groups, Group-A, Group-B or Group-C. Statistically significant difference was seen between Group-A & Group-B (Bonferroni adjusted $p=0{\cdot}001$) and between Group-B & Group-C (Bonferroni adjusted $p=0{\cdot}003$) only for the NLR [Figure-3], among these four variables [Supplementary Appendix; Table-S.3]. Missing values for each of the variables in either Group-A, Group-B or Group-C did not exceed 10% and have been detailed in Supplementary Appendix [Table-S.6]. As such, most received dexamethasone some received methylprednisolone. Types and relative percentages of corticosteroids received are shown in Supplementary Appendix [Table-S.8].

DISCUSSION

This multicentric retrospective study was carried out across two tertiary care referral hospitals in India, where most of the population was of Asian-Indian ethnicity. Data were collected from hospital records of cases affected during the second wave of the COVID-19 pandemic, where the Delta strain B.1.617.2 (pango-designation, n.d.) was

predominant and the major portion of the population was not fully vaccinated. A surveillance study on COVID-19 strain done on a cohort in the same population showed absolute B.1.617.2 predominance.

While the overall mortality was found to be high in Group-A and Group-B, the lowest was in Group-C. High-dose corticosteroid therapy in Group-A and Group-B was seen to be associated with greater mortality when compared to low-to-moderate dose therapy. The overall mortality in low-to-moderate dose corticosteroid sub-groups in Group-B and Group-C (those who received corticosteroids after 6 days of onset of symptoms) was seen to be 42/145 (28%). [Table-2] This finding is similar to that of the mortality seen in the Recovery trial (23% and 29%) in hypoxic cases. On the contrary, no statistically significant difference in 28 days-mortality was observed in Group-C between the two corticosteroid receiving subgroups similar to the Covid-Steroid 2 Trial. We found the overall mortality to be less in Group-C (12·8%) where Ana Fernandez Cruz et al. (Fernández-Cruz et al., 2020) showed similar findings in in-hospital mortality (13·9%) among corticosteroids treated patients, where patients received corticosteroid therapy for a median of 10 days after the onset of symptoms, and in-hospital mortality was not different between the two corticosteroid recipients groups.

When comparing the secondary outcomes among treatment subgroups in Group-A, Group-B and Group-C, high-dose recipients in Group-A showed a significantly greater need for invasive and non-invasive ventilation oxygen requirements as compared to the low-to-moderate dose subgroup. No such difference was seen in Group-C. These findings partially corroborate our study findings related to the primary outcome.

While steroids are proven to be beneficial in COVID-19, eventually multiple recommending bodies including the British Medical Journal (thebmj, 2020), WHO (WHO, 2021) and IDSA (IDSA, 2022) advocated for use of a low-dose steroid in hospitalized hypoxic patients. We searched for available evidence with high-dose corticosteroids. Few recently published RCTs that have used different dosing of corticosteroids have concluded differing opinions**.** Manuel Taboad et al. (Taboada et al., 2021) in their RCT showed high-dose dexamethasone to reduce clinical worsening in hypoxic COVID-19 patients. Another three-arm RCT by Toroghi N et al. (Toroghi et al., 2022) showed higher doses of dexamethasone increased the adverse events and worsened survival in hospitalized patients compared to low-dose dexamethasone. Again, Maskin, Luis Patricio et al**.** (Maskin et al., 2022) in a multicenter, open-label RCT showed, 28 days after randomization, there was no difference in ventilation-free days between high and low-dose dexamethasone groups. The large comparative COVID STEROID 2 (Munch et al., 2021) trial showed that 12 mg/day of dexamethasone compared with 6 mg/day did not result in statistically significantly more days alive without life support at 28 days.

Though there are limitations in the above-mentioned RCTs, e.g., not fulfilling power, receiving steroids before the intervention, and using other immunomodulators (IL-6 antagonist) in their course, these studies have thrown some light on the effects of different dose ranges of steroid therapy among hypoxic patients. The findings in the above-mentioned RCTs varied one from the other. It is now known that in COVID-19 infection, the nature of the immune response in persons developing early-onset hypoxia and late-onset hypoxia is not the same, a variation in responses to corticosteroids is therefore scientifically plausible. One of the possibilities for the conflicting opinions

could be arising from bias due to differences in the day of onset of symptoms when corticosteroids were initiated.

Amongst quite many studies conducted to explore the appropriate dose and duration of corticosteroids in COVID-19, very few considered the day of symptom onset when deciding the dosage of corticosteroids on initiation. Bahl et al. (Bahl et al., 2021) concluded corticosteroids are initiated more than 7 days after onset of symptoms and may be considered during 48-72 hours post-admission, and should be initiated if patients remain hospitalized at 72 hours. The host immune response, which varies from person to person, and day to day, is known to play a significant role in COVID-19 infection pathophysiology. Immune status is often clinically reflected by the onset and severity of symptoms (Sette and Crotty, 2021) and a variation in the hematologic profile. A marker for such is the NLR (Zeng et al., 2021), (Sette and Crotty, 2021). As consistent across many studies, an abnormal innate-immune response characterized by an unduly excessive cytokine/chemokine signature predominates the immuno-pathogenesis in moderate-to-severe COVID-19 infection. A high neutrophil percentage (the most important cell marker for natural immunity) is seen in blood (Kuri-Cervantes et al., 2020) and lungs. Severe COVID-19 presents with hyper-inflammation, immune paralysis and massive vascular inflammation, frequently triggering ARDS (Wiersinga et al., 2020). In contrast, the end-stage disease is generally not associated with preferential T-cell abundance in the lung tissues (Liao et al., 2020). In COVID-19 infection, an initial innate immune response is followed by an adaptive immune response (Sette and Crotty, 2021). In the initial phases of the disease, viral load increases in the upper respiratory tract with viral evasion of the lungs. If the adaptive immune response starts late, the outcome may be fatal because without substantive adaptive immunity, the viral burden may

become high (Sette and Crotty, 2021). Corticosteroids are immunomodulators, causing lymphopenia, reducing CD4+/CD8+ T-cells, and NK cells, and promoting neutrophilia (Marté et al., 2020). With the degree of lymphocyte-suppression being dose-dependent (Fleishaker et al., 2016), it is feasible that in high-dose corticosteroid recipients in the early course of the disease, an attempt to stop viral replication by the body's adaptive immunity may be attenuated by corticosteroid therapy itself. This may boost viral replication leading to greater chances of cytokine storm, disease worsening, longer duration of hospital stay, enhancing chances of hospital-acquired infections (Grasselli et al., 2021) and secondary sepsis.

In a similar line to these assumptions, the results of a meta-analysis on the use of corticosteroids in influenza state that corticosteroids might alter the immune reactions leading to prolonged viremia and delayed viral clearance, ultimately increasing the risk of mortality (Ni et al., 2019). In studies on MERS (Arabi et al., 2018) and earlier SARS infections, corticosteroids were seen to prolong viral replication (Hui, 2018), and their beneficial role was questioned. The Recovery group found no mortality benefit during the early days of corticosteroid therapy in non-hypoxic COVID-19 patients (RECOVERY Collaborative Group, Horby P, Lim WS, 2021). This could be attributed, at least in part, to prolonged viral replication.

Among the six pre-defined baseline covariates in the three study groups, the NLR was the only marker significantly different across all groups and the mean NLR value was found to be highest in Group-A and lowest in Group-C. Similarly, overall mortality was also seen to be highest in Group-A and lowest in Group-C. A prospective cohort study (Zeng et al., 2021) showed NLR to be greater in patients with deterioration than

in those without deterioration and higher in patients with serious clinical outcomes (shock, death) than in patients without so.

Patients in Group-A and Group-B (having an overall higher NLR), receiving low-to-moderate dose corticosteroids showed lower mortality. Lymphopenia by corticosteroid being dose-dependent (Fleishaker et al., 2016), lymphocyte suppression may have been optimal, creating a balance between cytokine suppression and viral replication. In Group-C, the mortality difference between the high-dose and low-to-moderate corticosteroid recipients was not statistically significant. Since these patients presented on or after day 10, probably viral replication was no longer an essential driving factor and adaptive immunity (lower NLR, higher lymphocyte percentage) may have taken over.

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In this study, the groups showing greater mortality (Group-A & Group-B) showed a higher NLR, such findings are exciting and raise a question, as to whether tailoring corticosteroid therapy based on individual immune response may yield better outcomes, and whether the prior assessment of immune response using markers like NLR or others could serve in determining the appropriate dosage of corticosteroid therapy.

Our study is unique in the sense that we have conducted it in a predominantly unvaccinated population, and that we have considered not only various dose ranges of corticosteroid but also the timing of initiation of corticosteroid therapy relative to the day of symptom onset. We have included patients receiving the first dose of corticosteroid within 24 hours of hospital admission and those on other immunomodulators have been excluded.

Our study had certain limitations, to our perception. Steroid-related ADRs were not well-documented in a subset of patients while they were documented in others. A causality assessment was also not available for some of the documented ADRs. As such, we could not include ADR assessment in our study design. The study population received mainly two types of corticosteroids, methylprednisolone and dexamethasone. We duly converted both types of corticosteroids into an equivalent dose of prednisolone, but the glucocorticoid or mineralocorticoid activity of these two steroids are not the same and this could have affected the outcome. Due to a small observed effect size in Group-C, a greater sample size could have increased the power of the study in this group. As per the study protocol and the terms of permission from the institutional ethics committee, we followed up on all the cases up to day 28 of symptoms. For those surviving on day 28, the outcomes beyond day 28 (including mortality, ICU transfer, use of high flow oxygen, non-invasive mechanical ventilation or invasive mechanical ventilation) were not taken into consideration. Radiological assessments are done at admission routinely at the study sites but were inadequately documented for some of the patients. Hence, we could not include radiological data in this study.

To summarize, we studied the effect of high-dose vs low-to-moderate dose steroids at 28 days since hospital admission in hypoxic COVID-19 patients, stratified by the time between the onset of symptoms and initiation of treatment by steroids. We found that a high dose of corticosteroid initiated early since the onset of the disease is associated with lesser mortality benefits as compared to low-to-moderate dose therapy. We also found that this distinction in mortality benefit between high dose low-to-moderate dose of corticosteroids is not statistically significant when the therapy is initiated late in the course of the disease. NLR, a marker of the immune response, was seen to vary

between treatment groups. Our study findings incite the need for prospective research to explore factors needing to be considered when selecting the dosage of corticosteroids in COVID-19, for optimal patient benefit.

Conflicts of Interest

This study is a non-sponsored investigator-initiated academic study. The author(s) received no financial support for this research, authorship, and /or publication of this article. All the researchers declare that they do not have any conflict of interest related to the conduct or publication of this research work.

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Ethical Approval Statement

Permission to conduct the study was duly obtained from the Institutional Clinical Research Ethics Committees of both institutes. Following ethics committee approval, data were accessed from all subsequent medical records fulfilling the study criteria.

Contributors

AKS led the study conceptualisation and the development of the research question, supported by AM, DG, RC, MM, SBI, DNG, SS and SKT. A literature search was done by AKS, AM, DG, SBI, and SK. AKS, SD, BS, and SBA were responsible for data collection. AKS, SD and DB accessed and verified the data, developed the statistical analysis plan and performed the analyses. AKS, SD, BS, and RR wrote the first draft of the paper. Review and editing were done by SKT, SS, MM, SD, and DNG. All authors contributed to the interpretation and discussion of the results, critically revised the manuscript for intellectual content, and approved the final and revised versions and manuscript submission. The corresponding author had the final responsibility regarding the decision to submit the article for publication.

Data Sharing

Individual participants' data (de-identified), as available from case records, will remain archived for five years after the publication of the research but are not freely available. Upon reasonable request directed to the corresponding author at arpitsaha21@gmail.com, anonymized data will be shared with researchers who provide a methodologically sound proposal.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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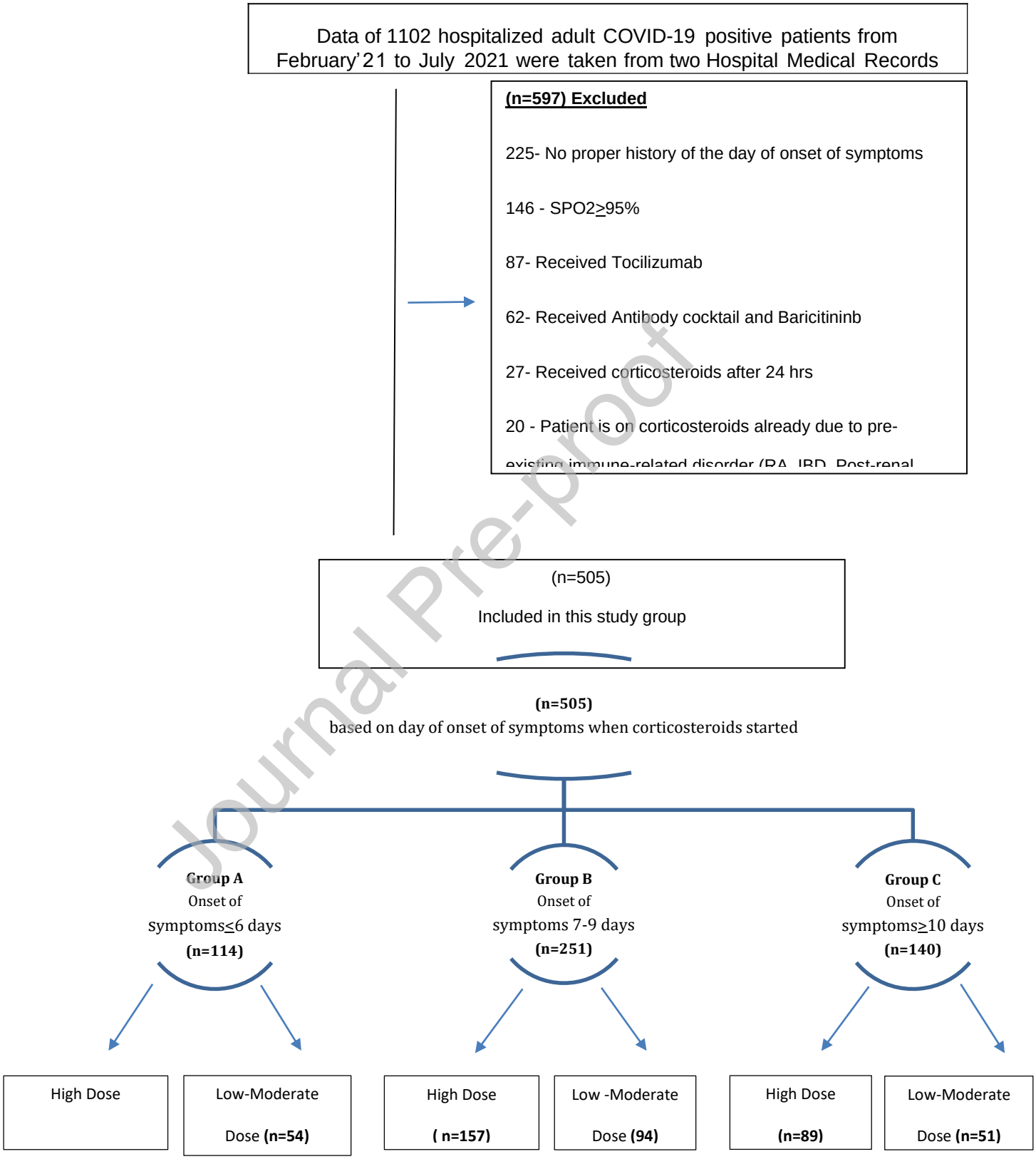
Figure -1: Study flow Diagram



- Low to moderate dose of corticosteroid has been defined as an equivalent dose of ≤ 40mg prednisolone or 6mg Dexamethasone.
- High dose of corticosteroid has been defined as an equivalent dose of > 40mg prednisolone or 6mg Dexamethasone.

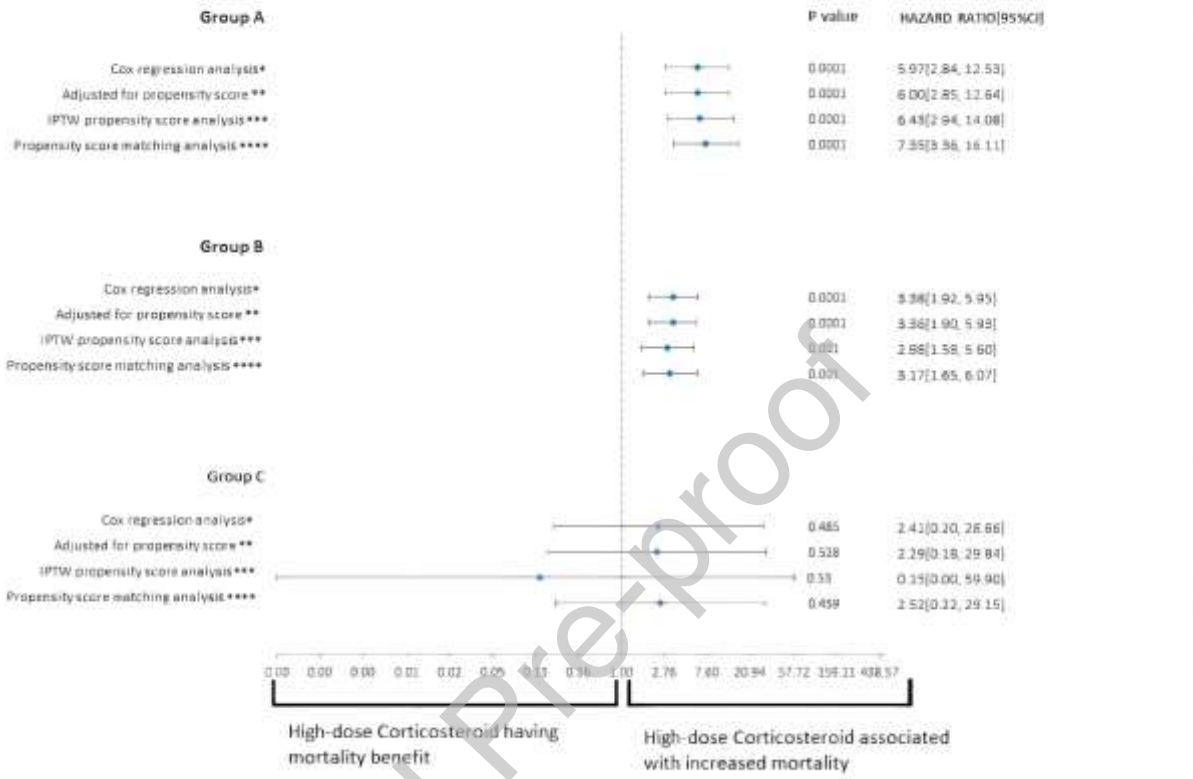


Figure-2: Forest plot comparing hazard ratios (HR) in Group A, Group B and Group C, CI=confidence interval

In each group (Gr A, Gr B, Gr C) Survival analysis was carried out between high dose vs low-moderate dose corticosteroid therapy recipients was analysed using the following methods-

*Cox regression with adjusted baseline covariates (*Age, Sex, BMI, Charlson Comorbidity Index (CCI), Quick Covid-19 Severity Index, Pulse, Body temperature -Dégrée Fahrenheit, SBP, DBP Neutrophil to Lymphocyte Ratio, D-Dimer, CRP, WBC count, Hb, ALT, Creatinine, and Remdesivir)*

[#SOFA SCORE & VACCINATION STATUS along with other existing covariables adjusted Cox regression showed on S.Table-9]

**Cox regression with propensity score adjustment along with adjusted baseline covariates

*** Cox regression with IPTW (*Inverse probability treatment weighting)* with adjusted baseline covariates

****Cox regression with adjusted baseline covariates in propensity score-matched data set

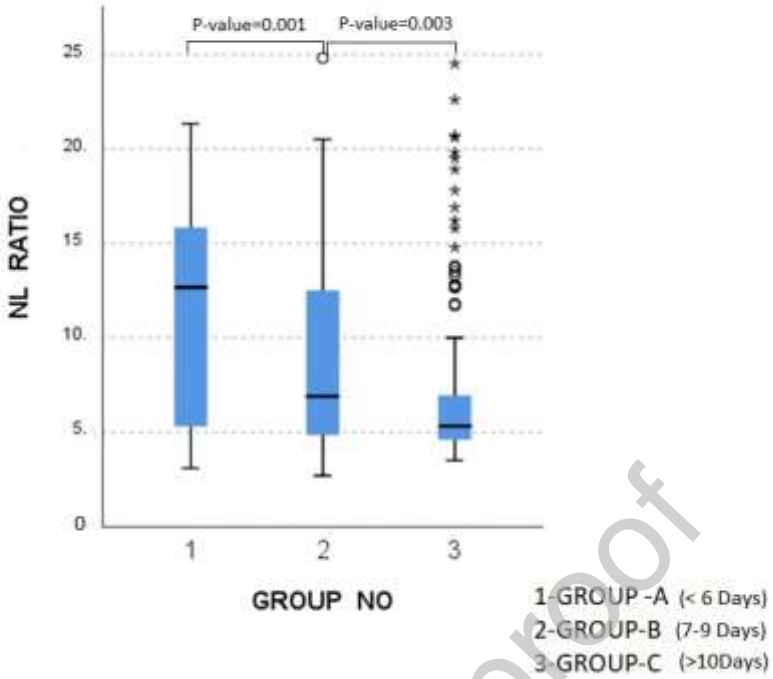
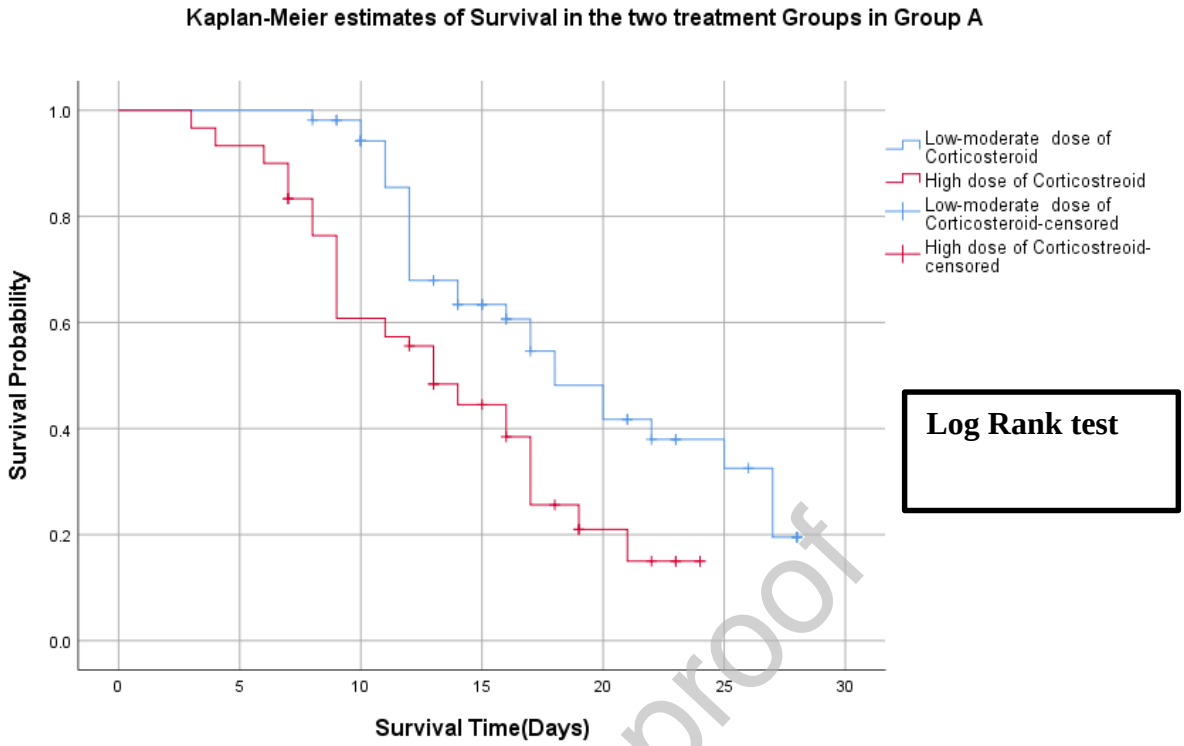


Figure 3: Box plot, Comparison of N/L ratio between three groups based on the day since onset of symptoms of Covid-19 when corticosteroids were initiated

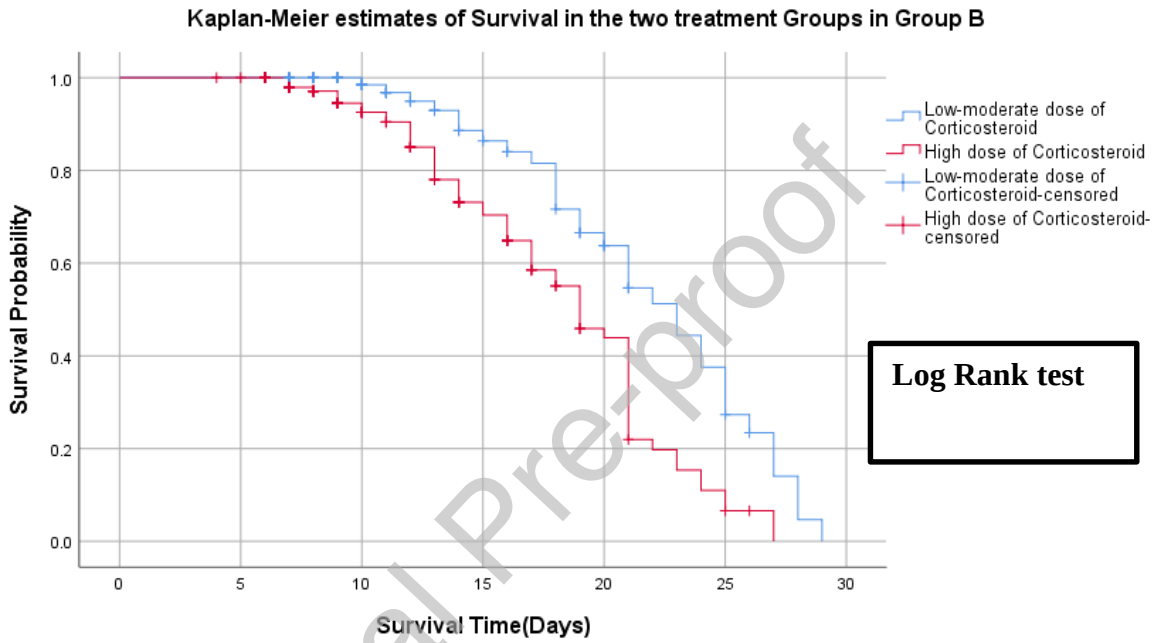
The horizontal line in each box plot shows the median, and the bottom and top of the box are located at the 25th and 75th percentiles, respectively. The whiskers represent values that are more than 1.5 times the interquartile range from the border of each box. Data points indicate outliers outside this range.



Log Rank test

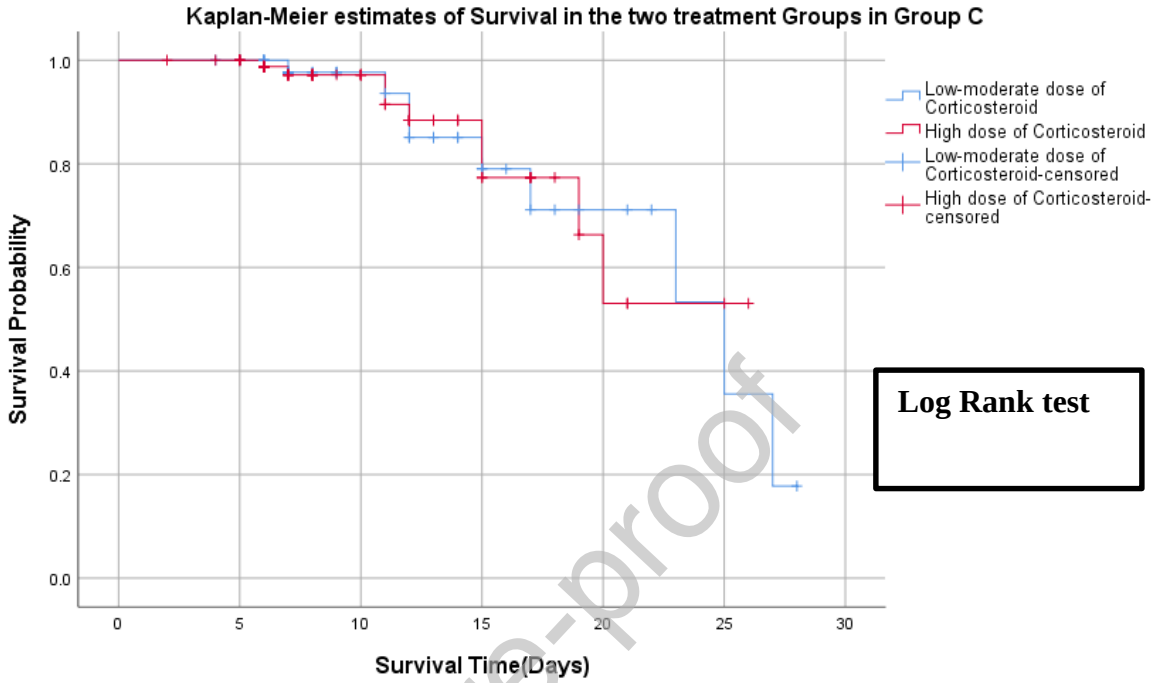
No at Risk

Low-moderate dose of corticosteroid	**54**	**54**	**50**	**26**	**15**	**7**
High dose of corticosteroid	**60**	**56**	**35**	**23**	**7**	**0**



No at Risk

Low-moderate dose of corticosteroid	**94**	**94**	**66**	**39**	**24**	**11**
High dose of corticosteroid	**157**	**156**	**98**	**53**	**23**	**5**



Log Rank test

No at Risk

Low-moderate dose of corticosteroid	**51**	**50**	**24**	**14**	**6**	**3**
High dose of corticosteroid	**89**	**87**	**39**	**16**	**5**	**2**

Figure 4. Kaplan Meier Survival estimates in High Dose corticosteroid vs Low to moderate dose recipients in Unmatched Groups(Gr-A, Gr-B, Gr-C)

Kaplan–Meier survival curves for 28-day since hospital admission: Cumulative Survival among the unmatched cohorts between High Dose corticosteroid and Low to moderate dose recipients in three separate groups;

(Group A) received steroids on or before day 6 of symptom-onset

(Group B) received steroids between 7- 9 days of symptom-onset

(Group C) received steroids on or after day 10 of symptom-onset.

The numbers below the figures denote the number of patients 'at risk' in each group.

Table 1: Demographic Table of Group A, Group B and Group C (unmatched and matched dataset)

				Unmatched Data				Matched Data			
Sl No	**Characteristics[a,c]**			**Low-to-moderate Dose Recipient**	**High Dose Recipient**	**p-Value**	**SMD**	**Low-to-moderate Dose Recipient**	**High Dose Recipient**	**p-Value**	**SMD**
DEMOGRAPHIC PROFILE											
1.	Age[b]		Group A (mean (SD))	57.30 (10.88)	59.87 (14.85)	0.299	0.197	57.30 (10.88)	58.44 (14.66)	0.645	0.089
			Group B (median [IQR])	54.00 [44.50, 63.75]	55.00 [44.00, 65.00]	0.615	0.057	54.00 [44.50, 63.75]	52.00 [42.25, 65.00]	0.937	0.024
			Group C (mean (SD))	56.86 (12.41)	54.42 (13.86)	0.299	0.186	56.86 (12.41)	56.02 (14.09)	0.749	0.064
2.	Sex	Group A	Male (%)	21 (38.9)	23 (38.3)	1.000	0.011	21 (38.9)	21 (38.9)	1.000	<0.001
			Female (%)	33 (61.1)	37 (61.7)			33 (61.1)	33 (61.1)		
		Group B	Male (%)	41 (43.6)	65 (41.4)	0.792	0.045	41 (43.6)	35 (37.2)	0.458	0.130
			Female (%)	53 (56.4)	92 (58.6)			53 (56.4)	59 (62.8)		
		Group C	Male (%)	22 (43.1)	33 (37.1)	0.59	0.124	22 (43.1)	19 (37.3)	0.687	0.120
			Female (%)	29 (56.9)	56 (62.9)			29 (56.9)	32 (62.7)		
3.	BMI[b]		Group A (mean (SD))	26.00 (3.01)	26.32 (3.65)	0.607	0.097	26.00 (3.01)	26.19 (3.63)	0.768	0.057
			Group B (median [IQR])	25.54 [23.60, 28.10]	24.80 [22.80, 27.70]	0.187	0.195	25.54 [23.60, 28.10]	25.45 [23.60, 28.56]	0.820	0.022
			Group C (mean (SD))	26.75 (3.56)	24.85 (3.67)	0.004	0.524	26.75 (3.56)	26.75 (3.06)	0.994	0.001
4.	**CHARLSON COMORBIDITY INDEX[b]**		Group A (median [IQR])	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.661	0.076	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.770	0.055
			Group B (median [IQR])	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.153	0.191	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.778	0.043
			Group C (median [IQR])	2.00 [1.00, 3.00]	2.00 [0.00, 3.00]	0.337	0.146	2.00 [1.00, 3.00]	2.00 [0.50, 3.50]	0.967	0.010

5	Vaccination _status-double dose (%)	Group A	2 (3.7)	4 (6.7)	0.682	0.134	2 (3.7)	3 (5.6)	1.000	0.088
		Group B	8 (8.5)	10 (6.4)	0.615	0.082	8 (8.5)	4 (4.3)	0.372	0.175
		Group C	5 (9.8)	12 (13.5)	0.6	0.115	5 (9.8)	5 (9.8)	1.000	<0.001
CLINICAL PARAMETERS										
6.	**Q COVID INDEX[b]**	Group A (median [IQR])	8.00 [7.00, 9.00]	8.00 [7.00, 9.00]	0.547	0.067	8.00 [7.00, 9.00]	8.00 [7.00, 9.00]	0.683	0.044
		Group B (median [IQR])	8.00 [7.00, 10.00]	9.00 [7.00, 10.00]	0.878	0.009	8.00 [7.00, 10.00]	9.00 [7.00, 10.00]	0.977	0.020
		Group C (median [IQR])	9.00 [7.50, 11.00]	8.00 [7.00, 11.00]	0.382	0.14	9.00 [7.50, 11.00]	8.00 [7.00, 11.00]	0.783	0.029
	a. SPO2	Group A (mean (SD))	90.00 [89.00, 91.00]	90.00 [89.00, 91.00]	0.762	0.052	90.00 [89.00, 91.00]	90.00 [89.00, 91.00]	0.726	0.090
		Group B (median [IQR])	89.00 [85.00, 90.00]	89.00 [86.00, 90.00]	0.969	0.015	89.00 [85.00, 90.00]	89.00 [85.00, 90.00]	0.634	0.110
		Group C (median [IQR])	88.00 [85.00, 90.00]	89.00 [86.00, 90.00]	0.336	0.153	88.00 [85.00, 90.00]	89.00 [85.50, 90.00]	0.734	0.041
	b. RESP RATE (/Min)	Group A (median [IQR])	24.00 [23.00, 29.00]	25.00 [23.00, 30.00]	0.477	0.116	24.00 [23.00, 29.00]	25.50 [23.00, 29.75]	0.435	0.133
		Group B (median [IQR])	26.00 [22.00, 31.00]	26.00 [22.00, 31.00]	0.959	0.005	26.00 [22.00, 31.00]	26.00 [23.00, 31.00]	0.699	0.067
		Group C (median [IQR])	25.00 [22.00, 28.50]	26.00 [23.00, 31.00]	0.408	0.159	25.00 [22.00, 28.50]	26.00 [23.00, 31.00]	0.483	0.158
	c. Oxygen Requirement (Lit/min)	Group A (median [IQR])	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.901	0.028	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.992	<0.001
		Group B (median [IQR])	4.00 [3.00, 6.00]	5.00 [3.00, 6.00]	0.266	0.156	4.00 [3.00, 6.00]	5.00 [3.00, 6.00]	0.469	0.118
		Group C (median [IQR])	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.616	0.083	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.928	0.017
7.	Pulse Rate (/min)	Group A (mean (SD))	94.40 (23.15)	93.30 (24.51)	0.806	0.046	94.40 (23.15)	94.11 (24.68)	0.949	0.012
		Group B (mean (SD))	105.51 (16.44)	107.53 (21.01)	0.426	0.107	105.51 (16.44)	107.53 (21.39)	0.468	0.106

		Group C (median [IQR])	101.00 [98.00, 113.98]	99.00 [90.00, 105.00]	0.041	0.363	101.00 [98.00, 113.98]	99.00 [90.00, 103.50]	0.020	0.543
8.	Temperature	Group A (median [IQR])	98.60 [98.53, 99.50]	98.60 [98.30, 98.77]	0.008	0.431	98.60 [98.53, 99.50]	98.60 [98.35, 98.79]	0.012	0.425
		Group B (median [IQR])	98.65 [98.40, 99.38]	98.60 [98.40, 99.27]	0.672	0.073	98.65 [98.40, 99.38]	98.60 [98.40, 98.94]	0.373	0.180
		Group C (median [IQR])	98.70 [98.50, 98.80]	98.60 [98.30, 98.70]	0.01	0.304	98.70 [98.50, 98.80]	98.60 [98.34, 98.70]	0.134	0.145
9.	SBP (mmHg)	Group A (median [IQR])	131.00 [120.00, 144.75]	130.00 [120.00, 140.00]	0.620	0.003	131.00 [120.00, 144.75]	130.00 [120.00, 139.25]	0.417	0.058
		Group B (median [IQR])	128.00 [120.00, 132.00]	130.00 [120.00, 140.00]	0.096	0.247	128.00 [120.00, 132.00]	130.00 [120.00, 140.00]	0.083	0.293
		Group C (median [IQR])	122.42 [118.00, 133.24]	120.00 [110.00, 129.00]	0.009	0.479	122.42 [118.00, 133.24]	120.06 [110.00, 130.00]	0.061	0.369
10.	DBP (mmHg)	Group A (median [IQR])	80.00 [72.00, 80.00]	78.50 [70.00, 80.00]	0.512	0.012	80.00 [72.00, 80.00]	78.50 [70.00, 80.00]	0.445	0.060
		Group B (median [IQR])	76.00 [70.00, 83.75]	74.00 [70.00, 80.00]	0.356	0.133	76.00 [70.00, 83.75]	74.00 [70.00, 81.50]	0.568	0.075
		Group C (median [IQR])	70.00 [70.00, 80.00]	70.00 [70.00, 80.00]	0.539	0.066	70.00 [70.00, 80.00]	70.00 [70.00, 71.50]	0.291	0.232
LAB PARAMETERS										
11.	SOFA Score	Group A (median [IQR])	4.00 [3.00, 5.00]	3.00 [3.00, 4.00]	0.072	0.234	4.00 [3.00, 5.00]	3.00 [3.00, 4.00]	0.143	0.179
		Group B (median [IQR])	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	0.444	0.048	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	0.384	0.062
		Group C (median [IQR])	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	0.368	0.162	3.00 [3.00, 4.00]	3.00 [3.00, 4.00]	0.368	0.162
12.	Haemoglobin (gm/dL)	Group A (mean (SD))	11.71 (1.76)	11.47 (1.81)	0.467	0.137	11.71 (1.76)	11.44 (1.79)	0.432	0.152

		Group B (mean (SD))	11.76 (1.97)	12.00 (2.08)	0.371	0.118	11.76 (1.97)	12.35 (2.11)	0.051	0.286
		Group C (median [IQR])	11.50 [11.00, 12.40]	12.60 [10.40, 13.70]	0.081	0.174	11.50 [11.00, 12.40]	12.60 [10.40, 13.80]	0.153	0.201
13.	ALT (U/L)	Group A (median [IQR])	53.21 [41.50, 70.00]	52.00 [44.75, 68.25]	0.820	0.168	53.21 [41.50, 70.00]	52.00 [45.00, 68.75]	0.946	0.136
		Group B (median [IQR])	55.00 [44.25, 69.25]	54.50 [43.00, 70.00]	0.583	0.227	55.00 [44.25, 69.25]	54.50 [43.00, 70.00]	0.583	0.227
		Group C (median [IQR])	53.00 [43.50, 65.00]	50.00 [40.00, 75.00]	0.969	0.195	53.00 [43.50, 65.00]	49.00 [38.50, 76.50]	0.601	0.236
14.	White Blood Cell Count ($\times 10^9$/L)	Group A (median [IQR])	9.90 [8.51, 12.80]	13.08 [9.58, 17.56]	0.004	0.567	9.90 [8.51, 12.80]	12.83 [9.46, 17.26]	0.006	0.538
		Group B (median [IQR])	11.02 [8.25, 15.76]	10.11 [7.98, 13.79]	0.408	0.112	11.02 [8.25, 15.76]	10.73 [7.94, 14.55]	0.768	0.045
		Group C (median [IQR])	11.86 [8.56, 13.91]	9.23 [7.83, 13.50]	0.056	0.212	11.86 [8.56, 13.91]	9.36 [8.13, 14.55]	0.242	0.085
15.	Neutrophil: Lymphocyte Ratio[b]	Group A (median [IQR])	12.95 [5.29, 17.24]	12.60 [6.38, 15.19]	0.708	0.033	12.95 [5.29, 17.24]	12.40 [5.73, 15.24]	0.649	0.024
		Group B (median [IQR])	6.75 [5.10, 12.73]	7.18 [4.70, 12.10]	0.623	0.026	6.75 [5.10, 12.73]	7.40 [4.73, 11.93]	0.604	0.017
		Group C (median [IQR])	5.50 [4.96, 8.37]	5.24 [4.55, 6.78]	0.216	0.233	5.50 [4.96, 8.37]	5.70 [4.57, 7.90]	0.893	0.008
16.	Creatinine (mg/dL)	Group A (median [IQR])	1.05 [0.89, 1.23]	0.91 [0.73, 1.25]	0.042	0.330	1.05 [0.89, 1.23]	0.90 [0.73, 1.23]	0.037	0.332
		Group B (median [IQR])	0.90 [0.76, 1.19]	0.93 [0.79, 1.20]	0.456	0.034	0.90 [0.76, 1.19]	0.95 [0.79, 1.22]	0.323	0.006
		Group C	0.82 [0.60, 1.10]	0.98 [0.86, 1.18]	0.053	0.121	0.82 [0.60, 1.10]	0.88 [0.79, 1.10]	0.429	0.046
17.	C-Reactive Protein (mg/L)[b]	Group A (median [IQR])	55.90 [44.85, 77.50]	67.00 [50.00, 88.00]	0.112	0.180	55.90 [44.85, 77.50]	60.85 [49.62, 79.50]	0.373	0.022
		Group B (median [IQR])	85.45 [69.00, 124.75]	90.00 [70.00, 126.00]	0.538	0.053	85.45 [69.00, 124.75]	87.50 [67.20, 122.75]	0.955	0.014

		Group C (median [IQR])	86.00 [64.00, 127.00]	98.00 [65.00, 128.00]	0.64	0.018	86.00 [64.00, 127.00]	104.60 [60.50, 135.50]	0.508	0.065
18.	D-DIMER (ng/mL FEU)[d]	Group A (median [IQR])	565.00 [470.98, 695.00]	550.94 [442.50, 662.50]	0.566	0.072	565.00 [470.98, 695.00]	550.94 [427.50, 665.00]	0.651	0.043
		Group B (median [IQR])	915.00 [682.50, 2667.50]	780.00 [610.00, 1420.00]	0.007	0.399	915.00 [682.50, 2667.50]	770.00 [610.00, 1377.50]	0.007	0.394
		Group C (median [IQR])	1390.00 [925.00, 1825.00]	950.00 [860.00, 1570.00]	0.014	0.504	1390.00 [925.00, 1825.00]	960.00 [850.00, 1610.00]	0.058	0.470
ANTIVIRAL THERAPY										
19.	REMEDESIVIR THERAPY (%)	Group A	35 (64.8)	32 (53.3)	0.255	0.235	35 (64.8)	31 (57.4)	0.554	0.152
		Group B	42 (44.7)	84 (53.5)	0.194	0.177	42 (44.7)	47 (50.0)	0.559	0.107
		Group C	24 (47.1)	26 (29.2)	0.044	0.374	24 (47.1)	18 (35.3)	0.314	0.241

BMI body mass index, ALT alanine aminotransferase, SBP systolic blood pressure, DBP diastolic blood pressure, SMD standardized mean difference

[a]For normal distribution of continuous variables, means±standard deviation and for non-normal distribution medians (interquartile ranges, IQRs) were presented. For categorical variables, frequencies and percentages within parentheses were presented

[c]Missing data on demographic profile, vital signs, and laboratory tests were imputed from 5 imputed data sets for the entire cohort analysis and the propensity score matching analysis. Descriptive results from five imputed data sets were shown

[b]Only predefined six variables were considered in propensity score optimal (1:1) matching. The standardized mean difference of clinical characteristics was less than 10% to indicate the balance between high-dose corticosteroid and low to moderate dose corticosteroid groups.

[d]All the D dimer values of various units are converted into ng/mL

Table 2. 28 Days-Mortality and Relative Number of Remedesivir Recipients in Various Groups and Sub-Groups

Groups	High dose Corticosteroid Recipient		Low-Moderate dose Corticosteroid Recipient		Total	
	Overall Mortality	Number receiving Remedesivir	Overall Mortality	Number receiving Remedesivir	Overall Mortality	Number receiving Remedesivir
Group A	45/60 (75%)	32/60 (53%)	28/54 (51%)	35/54 (64%)	73/114 (64%)	67/114 (58%)
Group B	63/157 (40%)	84/157 (53%)	33/94 (35%)[a]	42/94 (44%)	96/251 (38.2%)	126/251 (49%)
Group C	9/89 (10%)	26/89 (29%)	9/51 (17%)[a]	24/51 (47%)	18/140 (12.8%)	50/140 (35%)

[a]The overall mortality in low-moderate dose corticosteroids of Group B and Group C (those who received corticosteroids> 6 days of onset of symptoms) was 28% (n= 42/145)

Table 3. Secondary outcome parameters in Group A, Group B and Group C

Secondary outcome parameters	High-dose Corticosteroid Recipient	Low-moderate dose Corticosteroid Recipient	p value
Group A			
Length of stay (median [IQR])	13.00 [8.00, 17.00]	14.00 [11.00, 20.00]	0.01
ICU admission (%)	57 (95.0)	45 (83.3)	0.0i65
Invasive Ventilation (%)	31 (51.7)	18 (33.3)	0.059
Non-Invasive ventilation (BIPAP/HFNO) (%)	30 (50.0)	33 (61.1)	0.262
Face mask/O2 cannula (%)	2 (3.3)	3 (5.6)	0.666
Group B			
Length of stay (median [IQR])	12.00 [8.00, 17.00]	13.00 [9.00, 19.75]	0.06
ICU admission (%)	125 (79.6)	69 (73.4)	0.278
Invasive Ventilation (%)	54 (34.4)	12 (12.8)	<0.001
Non-Invasive ventilation (BIPAP/HFNO) (%)	69 (43.9)	56 (59.6)	0.019
Face mask/O2 cannula (%)	34 (21.7)	25 (26.6)	0.442
Group C			
Length of stay (median [IQR])	8.00 [6.00, 12.00]	9.00 [7.00, 15.00]	0.193
ICU admission (%)	41 (46.1)	25 (49.0)	0.86
Invasive Ventilation (%)	5 (5.6)	5 (9.8)	0.497
Non-Invasive ventilation (BIPAP/HFNO) (%)	10 (11.2)	6 (11.8)	1
Face mask/O2 cannula (%)	50 (56.2)	26 (51.0)	0.599