Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

High dose corticosteroids in patients hospitalized for COVID-19 pneumonia: an observational study of comparative effectiveness

Annette Langer-Gould MDPhD , Stanley Xu PhDMS , Laura C. Myers MDMPH , Aiyu Chen MPH , John D. Greene MA , Beth Creekmur MA , Katia Bruxvoort PhDMPH , John L. Adams PhD , Vincent Liu MDMSc , Michael K. Gould MDMS

PII: S1201-9712(22)00562-8
DOI: https://doi.org/10.1016/j.ijid.2022.10.023
Reference: IJID 6460

To appear in: *International Journal of Infectious Diseases*

Received date: 1 July 2022
Revised date: 13 October 2022
Accepted date: 17 October 2022

Please cite this article as: Annette Langer-Gould MDPhD , Stanley Xu PhDMS , Laura C. Myers MDMPH , Aiyu Chen MPH , John D. Greene MA , Beth Creekmur MA , Katia Bruxvoort PhDMPH , John L. Adams PhD , Vincent Liu MDMSc , Michael K. Gould MDMS , High dose corticosteroids in patients hospitalized for COVID-19 pneumonia: an observational study of comparative effectiveness, *International Journal of Infectious Diseases* (2022), doi: https://doi.org/10.1016/j.ijid.2022.10.023

High dose corticosteroids in patients hospitalized for COVID-19 pneumonia: an observational study of comparative effectiveness

Annette Langer-Gould, MD, PhD[a,b]

Stanley Xu, PhD, MS[c]

Laura C. Myers, MD, MPH[d]

Aiyu Chen, MPH[c]

John D. Greene, MA[d]

Beth Creekmur, MA[c]

Katia Bruxvoort, PhD, MPH[c]

John L. Adams, PhD[e,f]

Vincent Liu, MD, MSc[f]

Michael K. Gould, MD, MS[f]

[a]Southern California Permanente Medical Group, Neurology Department, Kaiser Permanente Southern California, 1505 N Edgemont, 5th Floor, Los Angeles, California 90027, USA

[b]Department of Clinical Science, Kaiser Permanente Bernard J. Tyson School of Medicine, 98 S Los Robles, Pasadena, California 91101, USA

[c]Department of Research and Evaluation, Kaiser Permanente Southern California, 100 S Los Robles, Pasadena, California, 91101, USA

[d]Division of Research and The Permanente Medical Group, Kaiser Permanente Northern California, 2000 Broadway, Oakland, California 94612, USA

[e]Kaiser Permanente Center for Effectiveness and Safety Research, 100 S Los Robles, Pasadena, California 91101, USA

[f]Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, 98 S Los Robles, Pasadena, California 91101, USA

Corresponding Author Contact Information:

Annette Langer-Gould, MD PhD

Southern California Permanente Medical Group

Neurology Department, Los Angeles Medical Center

1505 N Edgemont, 5th Floor

Los Angeles, CA 90027

Email: Annette.M.Langer-Gould@kp.org

Abstract

Objective: To assess whether high- compared to low-dose corticosteroids started upon hospitalization reduce mortality in patients with severe coronavirus disease 2019 (COVID-19) pneumonia or in subgroups stratified by severity of respiratory impairment on admission.

Methods: We conducted a retrospective cohort study of patients with confirmed severe acute respiratory syndrome coronoavirus-2 (SARS-CoV-2) infection who required oxygen supplementation upon hospitalization between 3/1- 12/31/2020. In-hospital death was analyzed using logistic regression with inverse probability of treatment weighting of receiving low- or high-dose corticosteroid (dexamethasone 6-10mg daily or >10-20mg daily or other corticosteroid equivalent).

Results: We analyzed 13,366 patients who received low-dose and 948 who received high-dose corticosteroids, of whom 31.3% and 40.4% had severe respiratory impairment (>15L/min of oxygen or mechanical ventilation) upon admission, respectively. There were no differences in the propensity score-adjusted odds of death (odds ratio [OR] 1.17, 95% CI 0.72-1.90) or infections (OR 0.70, 95% CI 0.44-1.11) for patients who received high-dose compared with low-dose corticosteroids beginning on the day of admission. No significant differences in subgroups stratified by severity of respiratory impairment were found.

Conclusion: Initiating high-dose compared to low-dose corticosteroids among newly hospitalized patients with COVID-19 pneumonia did not improve survival. However, benefit of high-dose corticosteroids in specific subgroups cannot be excluded.

Keywords: corticosteroids; anakinra; COVID-19; mortality; infections

Introduction

The optimal dose of corticosteroids in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection is uncertain, particularly among patients with severe respiratory impairment (The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, 2020), and practice remains varied. Recent randomized controlled trials (RCT) that compared high (12mg) to low (6mg) doses of dexamethasone in patients hospitalized for severe coronavirus disease 2019 (COVID-19) pneumonia found no difference in mortality (Bouadma et al., 2022) or were inconclusive (The COVID STEROID 2 Trial Group, 2021). The inconclusive study reported a statistically non-significant lower 28-day mortality in the high- compared to the low-dose groups (27.1% vs 32.3%, adjusted relative risk, 0.86 [99% CI, 0.68-1.08]), but a high likelihood of benefit in the pre-planned Bayesian analyses across multiple endpoints (Granholm et al., 2022).

Prior to this study, a relatively small, open label, RCT of high-dose dexamethasone (mean daily dose 15mg) in COVID-19 patients with moderate or severe acute respiratory distress syndrome (ARDS) (Tomazini et al., 2020) reported a statistically significant increased number of days alive and free from invasive mechanical ventilation (IMV) over 28 days and a statistically non-significant lower 28-day mortality compared to standard care (56.3% and 61.5%, respectively). Subsequently a large, open label RCT of low-dose corticosteroids (6mg daily) compared to usual care showed lower 28-day mortality in hospitalized patients requiring oxygen (23.3% vs 26.2%), even more so in those requiring IMV (29.3% vs 41.4%) but favored usual care in those who did not require respiratory support (17.8% vs 14.0%) (The RECOVERY Collaborative Group, 2021).

The two real-world studies comparing the effectiveness and safety of corticosteroid dose groups in relatively small samples of patients (n=1379) (Kumar et al., 2022), 573 (Monreal et al., 2021)), both reported significantly *increased* mortality in high- compared to low-dose treated patients. But methodological limitations that increase the potential for unmeasured confounding make these findings difficult to interpret, such as excluding patients who died or were discharged within 7 days after admission (Kumar et al., 2022) and defining dose-group by last-used rather than first-started (Monreal et al., 2021). In addition, neither study reported results stratified by the degree of respiratory impairment.

The purpose of this study was to compare the effectiveness and safety of high- and low-dose corticosteroids upon admission for COVID-19 pneumonia stratified by severity of respiratory impairment. We hypothesized that high-dose corticosteroids would be associated with lower in-hospital mortality only in the sickest patients and may increase the risk of infections in patients with mild or moderate respiratory impairment. Using granular electronic health record data, we performed a retrospective, observational study to generate real-world evidence to address these clinically important questions.

Study Design and Methods

We performed this large, population-based, retrospective cohort study after receiving approval from the Kaiser Permanente Southern California (KPSC) Institutional Review Board (#12396).

Study Population. KPSC and Kaiser Permanente Northern California (KPNC) provide care for >9 million members and operate 36 medical centers across California. To assemble the study cohorts, we identified adults (aged ≥18 years) admitted between 3/1/2020-12/31/2020 with positive SARS-CoV-2 polymerase chain reaction result in the 3 weeks before admission or during the hospitalization who required oxygen supplementation (a proxy for COVID-19 pneumonia) within 24 hours of admission. We excluded patients who were admitted for labor and delivery; did not receive corticosteroid treatment or oxygen supplementation within 24 hours of admission; received corticosteroid doses less than 6mg or greater than 20mg of dexamethasone or equivalent, and patients with "do not intubate" (DNI) orders, comfort care status or unknown gender (**Figure 1**).

Data collection. We retrieved data from the KPSC and the KPNC electronic medical records on exposures, outcomes and covariates of interest, the latter of which included patient demographic characteristics, comorbidity burden as reflected by the Elixhauser comorbidity score, corticosteroid use in the 12 months prior to admission, body mass index (BMI), inpatient, outpatient and emergency department utilization in the year prior to admission, other inpatient treatments (including anakinra, tocilizumab, convalescent plasma and hemodialysis) and selected inflammatory markers, including D-dimer and c-reactive protein values. We also calculated values for the Epic Deterioration Index (DI), a score based on inpatient vital signs and

laboratory values that has been shown to predict hospital mortality in hospitalized patients with and without COVID-19 (Singh et al., 2021).

We categorized patients according to their respiratory status, defined by the intensity of respiratory support. The categories included four tiers: mild impairment (>0-<6 L/min via nasal cannula or <40% FiO2 via face mask), moderate (6-15 L/min via nasal cannula or 40-60% FiO2 via mask), severe (>15 L/min via nasal cannula or high flow system, >60% FiO2 via mask or non-invasive ventilation), or very severe (invasive mechanical ventilation).

Corticosteroid Groups. Low-dose corticosteroid use was defined as a total daily dose of 6-10mg of dexamethasone or equivalent doses of other corticosteroids. High-dose corticosteroid use was defined as a total daily dose of >10 up to 20 mg of dexamethasone or equivalent doses of other corticosteroids. We did not distinguish between oral or intravenous administration or whether doses were divided into twice or more daily doses. Corticosteroid group assignment was based on as the highest prescribed corticosteroid dose (e.g., dexamethasone 6mg once a day for 10 days) within 24 hours of admission. All analyses followed the intention-to-treat principle with patients remaining in their day 1 group assignment even if corticosteroid doses were subsequently increased or decreased.

Outcomes. The primary outcome was in-hospital death. Secondary outcomes were hospital length of stay, proportion of patients subsequently requiring mechanical ventilation after day 1, duration of mechanical ventilation among those patients who required it, and infectious complications. We assessed the frequency of all hospital acquired infections as well specific infections (bloodstream, urinary tract, soft tissue and pulmonary infections other than COVID)

by using the ICD-10 codes (**Appendix Table 1**) entered by professional medical coders on discharge.

Statistical analysis. We described continuous and categorical variables using means and standard deviations and counts and percentages, respectively. To reduce imbalance in demographic and clinical characteristics among the treatment groups, we fit propensity score models using logistic regression to estimate the probability of receiving each treatment as a function of predictor variables that were plausibly associated with both exposure and outcome (Imbens GW, 2000). Covariates included the continuous variables inpatient and emergency department utilization in the year prior to admission, age, Elixhauser comorbidity score, Epic DI upon admission; and categorical variables, sex, race and ethnicity, smoking, body mass index (BMI), respiratory status (mild, moderate, severe and very severe), treatment with remdesivir (yes/no), anakinra (yes/no), dialysis (yes/no) or convalescent plasma (yes/no) and medical center on day 1 of admission; and month of admission. Tocilizumab use on day 1 of admission and oral corticosteroid prescriptions in the year prior to admission were not included in the propensity score because they were associated with corticosteroid treatment group but not with the primary outcome in our dataset (Brookhart et al., 2006).

We analyzed in-hospital mortality by fitting logistic regression models with inverse probability of treatment weights based on propensity scores. We used robust sandwich estimators to obtain appropriate standard errors of treatment effects, because the weighting induced a within-subject correlation in outcomes and an inflated sample size (Hernan, Brumback, & Robins, 2000; van der Wal WM, 2011; Xu et al., 2010). Propensity score adjusted odds ratios (OR) were reported with low-dose corticosteroids as the reference group. To

examine heterogeneity of treatment effect, we performed pre-specified subgroup analyses, comparing treatment groups stratified by age, sex, body mass index, CRP levels, and respiratory status. We displayed these subgroup results as forest plots.

All analyses were conducted using SAS 9.4 (Cary, NC). Two-tailed tests were used with the threshold of 0.05 for statistical significance.

Results

Among 28,035 patients admitted between 3/1/2020-12/31/2020, 13,721 were excluded for a final study population of 14,314, of whom 8,985 were from KPSC and 5,329 were from KPNC. The main reasons for exclusion were initial daily dexamethasone or corticosteroid equivalent dose of 0 to less than 6mg or >20mg, no supplemental oxygen requirements within 24 hours of admission, or DNI/comfort measures only (**Figure 1**).

Most of the included patients (n=13,366, 93.4%) received low-dose corticosteroids, while 948 (6.6%) patients received high-dose corticosteroids within 24 hours of admission (**Table 1**). The median daily dose of dexamethasone or equivalent was 6 mg (interquartile range, IQR 6-6mg) in the low-dose group and 15mg (IQR 7.5-15mg) in the high-dose group. Of the patients started on low-dose corticosteroids, 12.1% (n=1620) were switched to high-dose corticosteroids after a median of 2.2 days. The median duration of corticosteroid treatment was 6 days (IQR 4-10) in the low-dose group and 6 days (IQR 4-10) in the high-dose group.

Patients started on high-dose corticosteroids were more often of Hispanic ethnicity, more likely to receive anakinra, had slightly higher CRP values and had more severe respiratory impairment (>15L/min of oxygen or mechanical ventilation) upon admission compared with patients who received low-dose corticosteroids (40.4% and 31.3%, respectively) (**Table 1**). High- and low-dose groups were similar in age, gender, BMI, smoking behavior, Elixhauser comorbidity indices, inpatient ED and urgent care utilizations in the 12 months prior to admission and d-dimer levels and Epic DI scores upon admission. Treatment on day 1 with remdesivir was common while tocilizumab treatment was rare and neither differed significantly between groups.

Crude in-hospital mortality was higher among patients who received high-dose corticosteroids (18.8%, 95% CI 16.3-21.3%) compared with the low-dose group (14.8%, 95% CI-14.2-15.4%) but this difference was not significant in the propensity score-adjusted model (OR= 1.17, 95% CI 0.72-1.90) (**Table 2**). Similarly, there was no significant difference in length of hospital stay, duration of mechanical ventilation, total or specific types of hospital acquired infections between groups in adjusted models although crude rates were somewhat higher in the high-dose group (**Table 2**).

In subgroup analyses stratified by severity of respiratory impairment upon admission, the unadjusted frequencies of both mortality and hospital acquired infections increased with increasing severity of impairment (**Table 3**). However, adjusted models showed no significant difference between the high- and low-dose corticosteroid treated groups in either mortality or hospital-acquired infections, regardless of severity of respiratory impairment (**Figure 2, Panels A and B**). Among patients receiving mechanical ventilation upon admission (n=532), the crude mortality rate was lower among patients treated with high- compared to low-dose corticosteroids (49.4% and 55.8% respectively, **Table 3**). However, this difference was not statistically significant after propensity-score adjustment (adjusted OR 0.97, 95%CI 0.54 -1.77; **Figure 2, Panel A**). In the mild and moderate respiratory impairment groups, the crude mortality and hospital-acquired infection rates were almost identical among patients treated with high- or low-dose corticosteroids (**Table 3**) and adjusted analyses showed no significant differences (**Figure 2, Panels A and B**).

Treatment with high-dose corticosteroids also showed no significant association with mortality in subgroups stratified by gender, age, BMI or CRP values in either crude or adjusted analyses compared to the low-dose treated group (**Figure 3**).

Discussion

In this large observational comparative effectiveness study of hospitalized patients with COVID-19 pneumonia, we found that high-dose corticosteroid use upon admission was not associated with reduced in-hospital mortality or increased hospital-acquired infections compared to low-dose corticosteroid use. As expected, the risk of in-hospital mortality and hospital-acquired infections increased with increasing severity of respiratory impairment upon admission. However, high- compared to low-dose corticosteroids did not significantly reduce mortality in any subgroup of respiratory impairment, although in patients with very severe impairment requiring IMV, the crude but not adjusted mortality rate was lower in the high-dose treated group. Among the patients with mild or moderate respiratory impairment upon admission, mortality and infection rates were low and very similar in patients treated with high- or low-dose corticosteroids. However, because switching from low- to high- and even more so from high- to low-dose corticosteroids after admission occurred rather frequently, this study cannot exclude the possibility of a benefit of high-dose corticosteroids in a specific subgroup.

Our findings are consistent with a recent RCT that compared 12mg to 6mg of dexamethasone, in addition to oxygen support strategies, and found no difference in mortality between treatment groups regardless of severity of respiratory status at randomization (Bouadma et al., 2022). Our findings in patients requiring IMV upon admission in the high-dose treated group are also consistent, strictly speaking, with the open-label RCT that compared

high-dose dexamethasone (20mg daily for 5 days followed by 10mg daily for 5 days) to standard care in COVID-19 patients with moderate or severe ARDS and found no significant difference in 28-day mortality between groups (Tomazini et al., 2020).

However, the possibility of benefit of high-dose corticosteroids particularly in the severe respiratory or IMV groups remains. The RCT in COVID-19 ARDS patients did observe a lower 28-day mortality in the high-dose group compared to standard care (56.3% and 61.5%, respectively) although this was not statistically significant (Tomazini et al., 2020). In addition, the pre-planned Bayesian analyses of the RCT that compared 12mg to 6mg of dexamethasone in patients hospitalized for severe COVID-19 pneumonia found a high probability of benefit across all outcome measures (Granholm et al., 2022). This leaves open the possibility that both studies were under-powered. Furthermore, the RCT comparing 12mg to 6mg of dexamethasone has not yet reported treatment effects stratified by respiratory impairment (The COVID STEROID 2 Trial Group, 2021); thus, it is unclear whether the trend toward beneficial effect of high-dose corticosteroids was seen across multiple subgroups or only in the 22% of who required IMV at the time of corticosteroid initiation. Should post-hoc analyses show a potentially beneficial effect in the IMV group, this would bolster the rationale for repeating a low- versus high-dose corticosteroid RCT in patients with very severe respiratory impairment from COVID-19 pneumonia.

Interestingly, long term (180 day) follow-up of COVID STEROID 2 RCT population, found that fewer patients in the 12mg group had died compared to the 6mg group (33.7% versus 38.6%, respectively) and quality of life scores were higher, although neither finding reached statistical significance (Granholm et al., 2022). The higher quality of life scores are consistent

with the RCT's primary endpoint, days alive without life support, which also favored the high-dose group but did not reach statistical significance (adjusted mean difference, 1.3 days [95% CI, 0-2.6 days]; P = .07) (The COVID STEROID 2 Trial Group, 2021). This suggests that an under-explored benefit of high-dose corticosteroids may be in lowering the risk of post-acute COVID-19 syndrome.

This study has several limitations. First, residual confounding by indication could explain the null result of high-dose corticosteroids in the IMV subgroup despite lower unadjusted in-hospital mortality. High-dose corticosteroid treated patients had more respiratory impairment and higher Epic DI scores upon admission. This coupled with unmeasured practice trends including timing of IMV could have obscured a potentially beneficial effect in patients with the most severe respiratory impairment upon admission. During the course of the study, some clinicians questioned whether patients with COVID-19 pneumonia were being intubated too early, contributing to poor outcomes, and shifted towards high flow nasal cannula respiratory support rather than early intubation (Papoutsi et al., 2021). While we incorporated month of admission in the propensity score models, it is unlikely to have completely captured this practice trend. Second, assigning corticosteroid-dosing group upon admission when 12.1% in the low-dose group switched to high-dose and over 25% in the high-dose group switched to the low-dose group, may have obscured a potential benefit of high-dose corticosteroids in a specific subgroup and/or a potentially increased risk of hospital acquired infections in patients with severe respiratory impairment or IMV where the crude infection rate was higher. Other limitations are the relatively small number of high-dose treated IMV patients and combining various preparations and dosing regimens of corticosteroids into 2 groups. Corticosteroids vary

in their anti-inflammatory and mineralocorticoid potency which could theoretically have different effects on COVID-19 patients, although evidence to support this is lacking. Lastly, whether these results can be extrapolated to vaccinated populations where far fewer patients experience severe respiratory impairment or to the omicron variant, or any future strain is uncertain.

Strengths of this study include the importance of the question, the very large number of patients, particularly those treated with low-dose corticosteroids, and restricting the analysis to corticosteroids started on day 1. Upon release of the RECOVERY trial results, starting patients with COVID pneumonia requiring oxygen support on 6mg of dexamethasone (or higher) upon admission rapidly became standard of care in our hospitals. Prior to this, the risks and benefits were debated and if corticosteroids were started, it was often not until a patient's respiratory status had declined. In the cohort included in these analyses, the dose chosen in patients especially in those with mild or moderate respiratory impairment appears to be largely driven by clinician-preference, as there was sufficient uncertainty whether doses higher than 6mg of dexamethasone could further reduce mortality.

Interpretation

Our findings are consistent with a recently published RCT (Bouadma et al., 2022) which do not support the use of high-dose corticosteroids in patients with mild (Swaminathan et al., 2022), moderate, or severe respiratory impairment from COVID-19 pneumonia. However, due to the observational study design and the frequency of switching dose groups in our population, our findings do not exclude the possibility that high-dose corticosteroids in patients with severe respiratory impairment particularly those requiring IMV upon admission, or other specific

subgroup, provides a small mortality benefit or reduced risk of post-acute COVID-19 syndrome. These questions should be addressed in future studies.

Conflicts of Interest: KB has received research support unrelated to this study from Moderna/Pfizer. LCM has received research support unrelated to this study from Boehringer Ingelheim. The other authors have no conflict of interest.

Funding: This work was funded by the Sidney Garfield Memorial Fund, Kaiser Foundation Hospitals, Inc., the Southern California Permanente Medical Group, Inc., and The Permanente Medical Group, Inc. VXL was funded in part by NIH R35GM128672. The funders were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethical Approval Statement: We performed this retrospective cohort study after receiving approval from the KPSC Institutional Review Board (#12396).

Acknowledgements

The authors wish to thank Fernando Barreda (Project Manager, Kaiser Permanente Northern California) for facilitating the data transfer agreement and IRB approval and Jessica B. Smith (Research Associate IV, Kaiser Permanente Southern California) with manuscript preparation.

References

Bouadma, L., Mekontso-Dessap, A., Burdet, C., Merdji, H., Poissy, J., Dupuis, C., . . . Timsit, J. F. (2022). High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure: The COVIDICUS Randomized Clinical Trial. *JAMA Intern Med, 182*(9), 906-916. doi:10.1001/jamainternmed.2022.2168

Brookhart, M. A., Schneeweiss, S., Rothman, K. J., Glynn, R. J., Avorn, J., & Sturmer, T. (2006). Variable selection for propensity score models. *Am J Epidemiol, 163*(12), 1149-1156. doi:10.1093/aje/kwj149

Granholm, A., Munch, M. W., Myatra, S. N., Vijayaraghavan, B. K. T., Cronhjort, M., Wahlin, R. R., . . . Perner, A. (2022). Dexamethasone 12 mg versus 6 mg for patients with COVID-19 and severe hypoxaemia: a pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial. *Intensive Care Med, 48*(1), 45-55. doi:10.1007/s00134-021-06573-1

Hernan, M. A., Brumback, B., & Robins, J. M. (2000). Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology, 11*(5), 561-570. doi:10.1097/00001648-200009000-00012

Imbens GW. (2000). The role of the propensity score in estimating dose-response functions. *Biometrika, 87*(3), 706-710.

Kumar, G., Patel, D., Hererra, M., Jefferies, D., Sakhuja, A., Meersman, M., . . . Guddati, A. K. (2022). Do high-dose corticosteroids improve outcomes in hospitalized COVID-19 patients? *J Med Virol, 94*(1), 372-379. doi:10.1002/jmv.27357

Monreal, E., Sainz de la Maza, S., Natera-Villalba, E., Beltran-Corbellini, A., Rodriguez-Jorge, F., Fernandez-Velasco, J. I., . . . group, C.-H. (2021). High versus standard doses of corticosteroids in severe COVID-19: a retrospective cohort study. *Eur J Clin Microbiol Infect Dis, 40*(4), 761-769. doi:10.1007/s10096-020-04078-1

Papoutsi, E., Giannakoulis, V. G., Xourgia, E., Routsi, C., Kotanidou, A., & Siempos, II. (2021). Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. *Crit Care, 25*(1), 121. doi:10.1186/s13054-021-03540-6

Singh, K., Valley, T. S., Tang, S., Li, B. Y., Kamran, F., Sjoding, M. W., . . . Nallamothu, B. K. (2021). Evaluating a Widely Implemented Proprietary Deterioration Index Model among Hospitalized Patients with COVID-19. *Ann Am Thorac Soc, 18*(7), 1129-1137. doi:10.1513/AnnalsATS.202006-698OC

Swaminathan, L., Kaatz, S., Chubb, H., Tae, K., Ramesh, M. S., Fadel, R., . . . Prescott, H. C. (2022). Impact of Early Corticosteroids on Preventing Clinical Deterioration in Non-critically Ill Patients Hospitalized with COVID-19: A Multi-hospital Cohort Study. *Infect Dis Ther, 11*(2), 887-898. doi:10.1007/s40121-022-00615-x

The COVID STEROID 2 Trial Group. (2021). Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. *JAMA, 326*(18), 1807-1817. doi:10.1001/jama.2021.18295

The RECOVERY Collaborative Group. (2021). Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med, 384*(8), 693-704. doi:10.1056/NEJMoa2021436

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. (2020). Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA, 324*(13), 1330-1341. doi:10.1001/jama.2020.17023

Tomazini, B. M., Maia, I. S., Cavalcanti, A. B., Berwanger, O., Rosa, R. G., Veiga, V. C., . . . Investigators, C. C.-B. I. (2020). Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *JAMA, 324*(13), 1307-1316. doi:10.1001/jama.2020.17021

van der Wal WM, G. R. (2011). ipw: An R Package for Inverse Probability Weighting. *Journal of Statistical Software, 43*(13), 1-23.

Xu, S., Ross, C., Raebel, M. A., Shetterly, S., Blanchette, C., & Smith, D. (2010). Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health, 13*(2), 273-277. doi:10.1111/j.1524-4733.2009.00671.x

Figure Legends

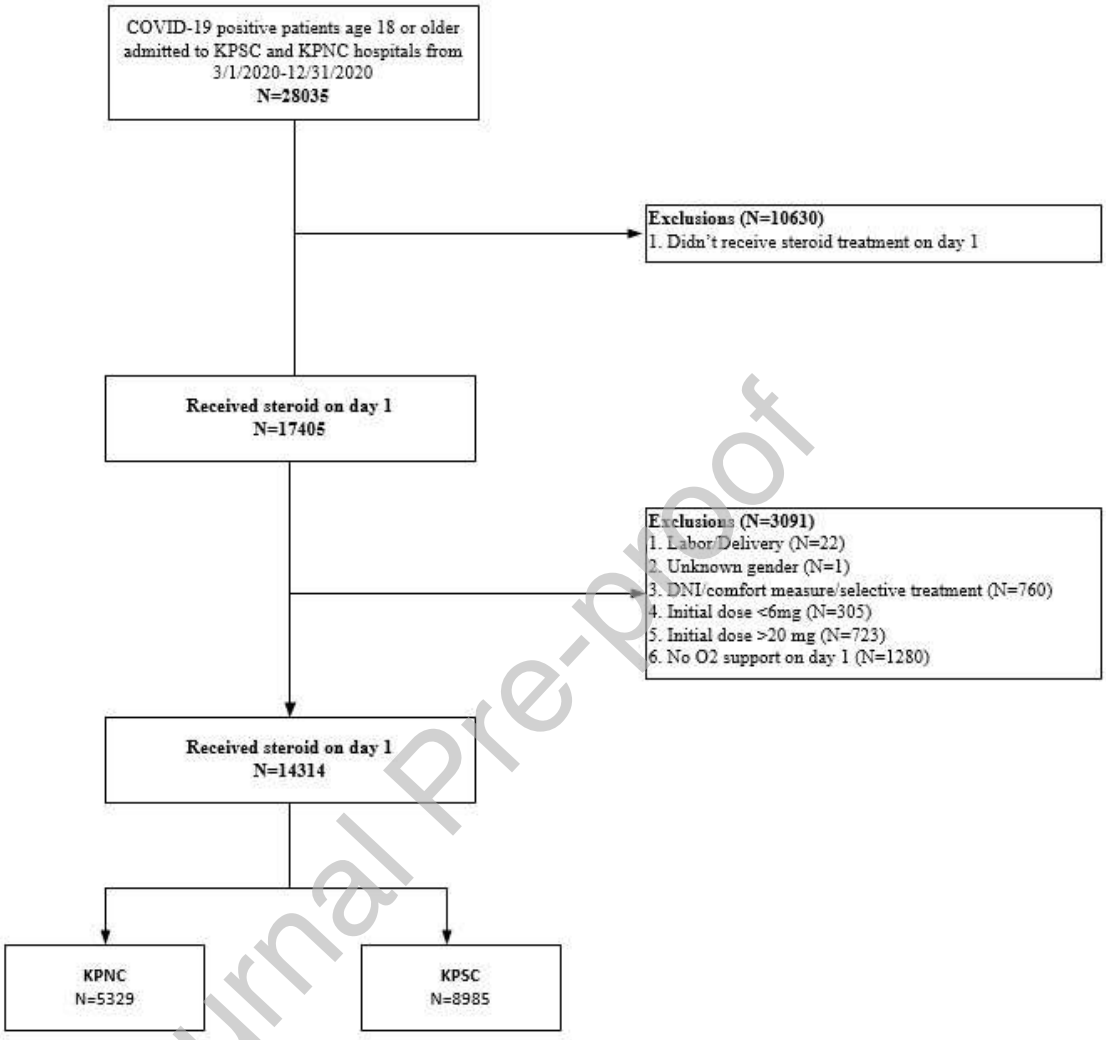

Figure 1. Consort diagram of cohort derivation

Abbreviations: COVID-19=coronavirus disease 19, KPSC=Kaiser Permanente Southern California, KPNC=Kaiser Permanente Northern California, DNI=do not intubate, AC=anticoagulation

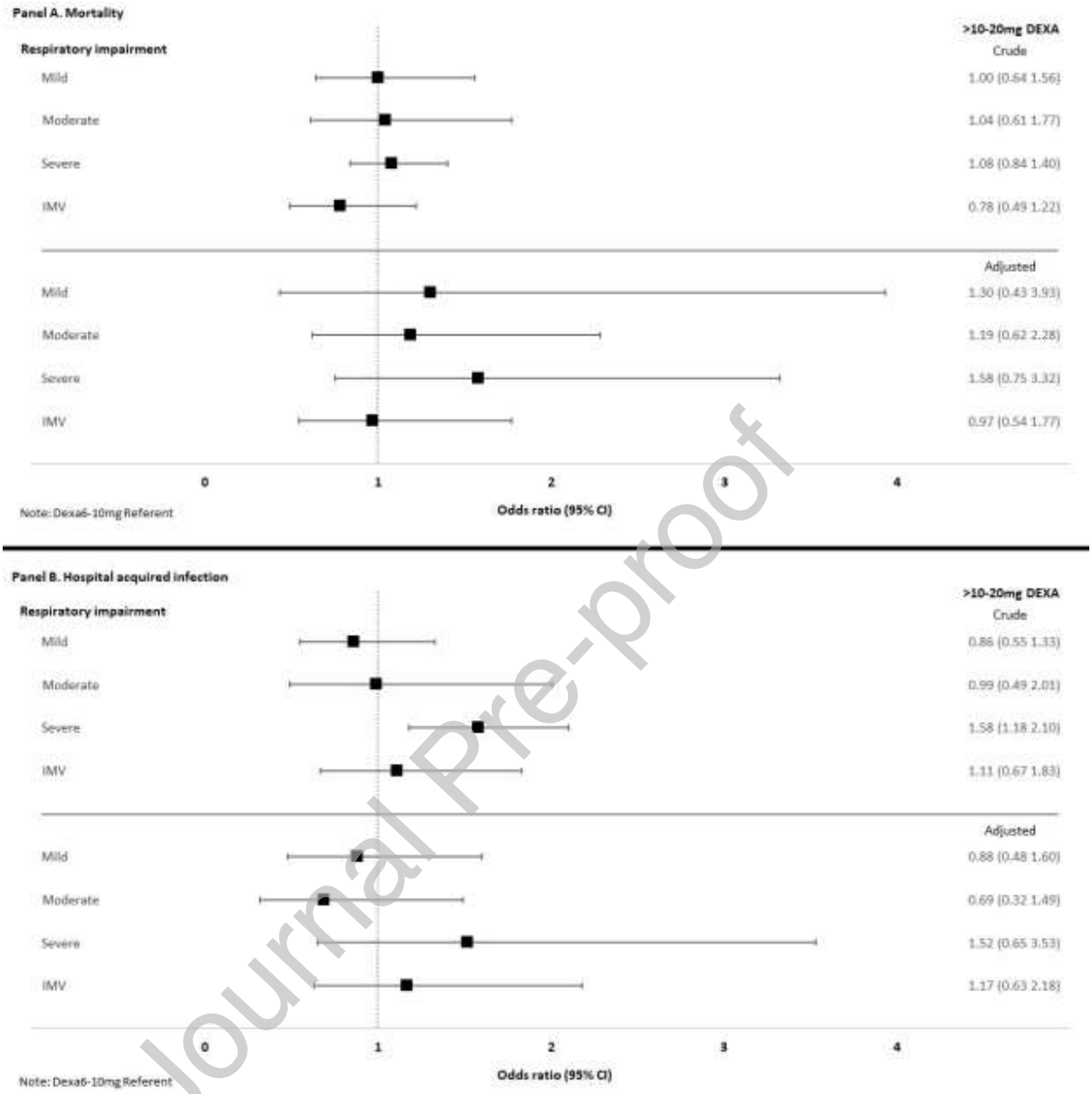

Figure 2. Severity of respiratory impairment, high-dose corticosteroids and odds ratios for death or hospital acquired infections

The forest plots depict the crude and adjusted odds ratios (squares) for in-hospital death (Panel A) or hospital-acquired infections (Panel B) in subgroups stratified by severity of respiratory impairment on day 1 of hospitalization comparing high-dose (10-20mg of dexamethasone or other corticosteroid equivalent, >10-20mg DEXA) to low-dose corticosteroids (6-10mg of

dexamethasone or equivalent). High-dose corticosteroids were not associated with increased or decreased odds of death or infection in any of these pre-specified subgroups in crude or adjusted analyses.

Abbreviations: IMV=invasive mechanical ventilation, CI=confidence interval

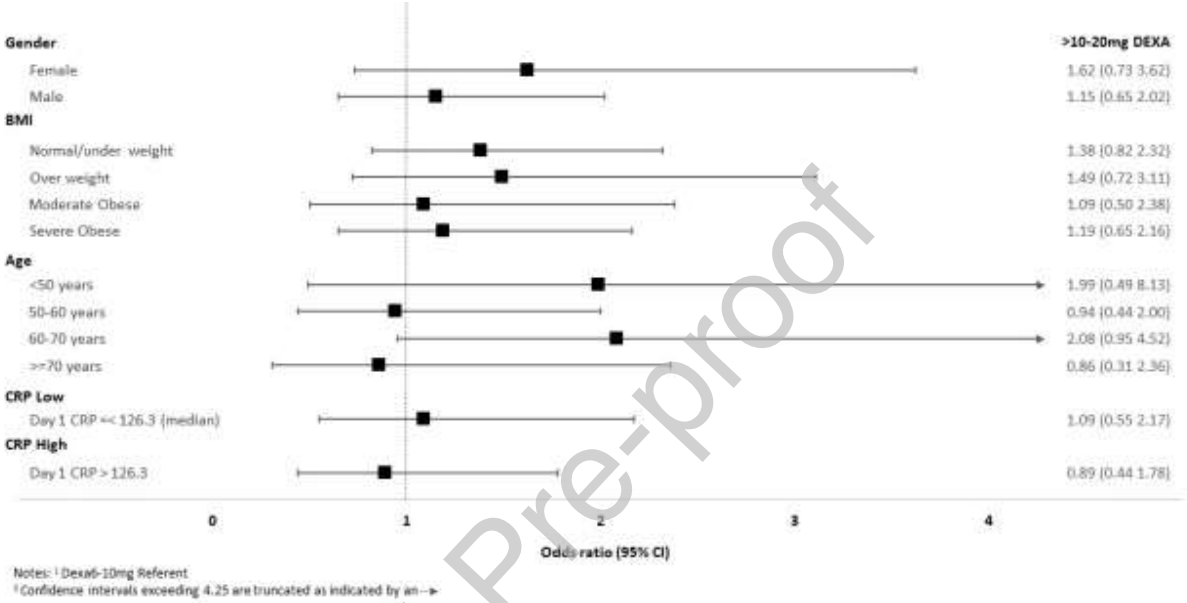

Figure 3. Age, gender, body mass index, high-dose corticosteroids and odds ratio for death or hospital acquired infections

The forest plots depict the adjusted odds ratios (squares) and 95% confidence intervals (CI, lines) for in-hospital death (Panel A) or hospital-acquired infections (Panel B) in pre-specified subgroups comparing high-dose (10-20mg of dexamethasone or other corticosteroid equivalent, >10-20mg DEXA) to low-dose corticosteroids (6-10mg of dexamethasone or equivalent). High-dose corticosteroids were not associated with an increased or decreased odds of death or infection in subgroups defined by gender, body mass index (BMI), age, or C-reactive protein (CRP) levels. Upper Confidence Interval is truncated at Odds Ratio of 4.5 for ease of presentation.

Table 1. Patient Characteristics on Day 1 of Hospital Admission

	6-10mg DEXA N=13,366	>10-20mg DEXA N=948	Total N=14,314
Age, mean (SD), y	59.6 (15.5)	59.7 (13.9)	59.6 (15.4)
Male gender, n (%)	7876 (58.9)	596 (62.9)	8472 (59.2)
Race and ethnicity, n (%)			
Asian	1562 (11.7%)	118 (12.4%)	1680 (11.7%)
Black	1015 (7.6%)	29 (3.1%)	1044 (7.3%)
Hispanic	7598 (56.8%)	661 (69.7%)	8259 (57.7%)
White	2512 (18.8%)	100 (10.5%)	2612 (18.2%)
Multiple	209 (1.6%)	4 (0.4%)	213 (1.5%)
Native American Alaskan	35 (0.3%)	2 (0.2%)	37 (0.3%)
Pacific Islander	210 (1.6%)	14 (1.5%)	224 (1.6%)
Other	61 (0.5%)	9 (0.9%)	70 (0.5%)
Unknown	164 (1.2%)	11 (1.2%)	175 (1.2%)
Body mass index categories, n (%)			
Underweight	109 (0.8%)	8 (0.8%)	117 (0.8%)
Normal	1421 (10.6%)	112 (11.8%)	1533 (10.7%)
Overweight	3705 (27.7%)	287 (30.3%)	3992 (27.9%)
Moderate Obese	5709 (42.7%)	403 (42.5%)	6112 (42.7%)
Severe Obese	2166 (16.2%)	130 (13.7%)	2296 (16.0%)
Unknown	256 (1.9%)	8 (0.8%)	264 (1.8%)
Smoking, n (%)			
Never/Passive	7584 (56.7%)	519 (54.7%)	8103 (56.6%)
Quit	3603 (27.0%)	237 (25.0%)	3840 (26.8%)
Active	326 (2.4%)	18 (1.9%)	344 (2.4%)
Unknown	1853 (13.9%)	174 (18.4%)	2027 (14.2%)
Oral corticosteroids in the past 12 months, n (%)	2229 (16.7%)	206 (21.7%)	2435 (17.0%)
Elixhauser comorbidities, median (IQR)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)
Healthcare utilizations in the past 12 months			
Inpatient visit count, n (%)			
0 visit	12,044 (90.1%)	852 (89.9%)	12,896 (90.1%)
1-2 visits	1127 (8.4%)	86 (9.1%)	1213 (8.5%)
3 or more visits	195 (1.5%)	10 (1.1%)	205 (1.4%)
Emergency department visit count, n (%)			
0 visit	8258 (61.8%)	658 (69.4%)	8916 (62.3%)
1-2 visits	4282 (32.0%)	244 (25.7%)	4526 (31.6%)
3 or more visits	826 (6.2%)	46 (4.9%)	872 (6.1%)

Urgent care visit count, n (%)			
0 visit	9923 (74.2%)	646 (68.1%)	10,569 (73.8%)
1-2 visits	2712 (20.3%)	227 (23.9%)	2939 (20.5%)
3 or more visits	731 (5.5%)	75 (7.9%)	806 (5.6%)
COVID severity on day 1 of hospital admission[a]			
Epic deterioration index, n	13,353	948	14,301
Median (IQR)	44.0 (36.9, 54.0)	45.5 (37.0, 57.0)	44.0 (36.9, 54.0)
Respiratory impairment, n (%)			
Mild (>0 and <6 l/min via N/C or 40% FiO2 via mask)	7749 (58.0%)	447 (47.2%)	8196 (57.3%)
Moderate (6-15 l/min via N/C or 40%-60% via mask)	1429 (10.7%)	118 (12.4%)	1547 (10.8%)
Severe (high flow, NIV, >15 l/min via N/C or >60% via mask)	3745 (28.0%)	294 (31.0%)	4039 (28.2%)
Invasive mechanical ventilation	443 (3.3%)	89 (9.4%)	532 (3.7%)
Other treatments started on day 1 of hospital admission			
Convalescent plasma, n (%)	618 (4.6%)	77 (8.1%)	695 (4.9%)
Tocilizumab, n (%)	9 (0.1%)	1 (0.1%)	10 (0.1%)
Dialysis, n (%)	185 (1.4%)	10 (1.1%)	195 (1.4%)
Remdesivir, n (%)	8724 (65.3%)	547 (57.7%)	9271 (64.8%)
Anakinra, n (%)	417 (3.1%)	416 (43.9%)	833 (5.8%)
Selected laboratory values on day 1 of hospital admission[a]			
C-reactive protein, n	12305	902	13207
Median (IQR), mg/L	125.6 (68.0,188.0)	142.3 (75.4, 221.5)	126.3 (68.6,190.0)
D-Dimer, n	11643	881	12524
Median (IQR), mcg FEU/mL	1.0 (0.6, 1.7)	1.1 (0.7, 2.1)	1.0 (0.6, 1.7)

[a]Based on highest value within 24 hours of admission

Abbreviations: DEXA=dexamethasone or equivalent corticosteroid dosing; mg=milligram; SD=standard deviation; y=years; IQR=interquartile range; N/C=nasal cannula; l/min=liters per minute; FiO2=fraction of inspired oxygen; NIV=non-invasive ventilation; mcg=microgram; FEU/mL=fibrinogen equivalent units per milliliter

Table 2. Corticosteroid Dose on Day 1 of Admission and Primary and Secondary Outcomes

	6-10mg DEXA	
N	13,366	
Mortality, n (%)	1974 (14.8)	
Unadjusted, OR (95% CI)	Reference	
Propensity score adjustment (IPTW) with robust standard errors, OR (95% CI)[a]	Reference	
Hospital length of stay, mean (SD), days	9.8 (10.5)	
Unadjusted mean difference (95% CI)	Reference	
Propensity score adjustment (IPTW) with robust standard errors, mean difference (95% CI)[a]	Reference	
Ventilator days, mean (SD)	2.4 (7.9)	
Unadjusted mean difference (95% CI)	Reference	

Propensity score adjustment (IPTW) with robust standard errors, mean difference (95% CI)[a]	Reference	
Hospital acquired infection (%)	9.5	
Unadjusted, OR (95% CI)	Reference	
Propensity score adjustment (IPTW) with robust standard errors, OR (95% CI)[a]	Reference	
Bloodstream infection (%)	7.2	
Unadjusted, OR (95% CI)	Reference	
Propensity score adjustment (IPTW) with robust standard errors, OR (95% CI)[a]	Reference	
Pulmonary infection (%)	2.9	
Unadjusted, OR (95% CI)	Reference	
Propensity score adjustment (IPTW) with robust standard errors, OR (95% CI)[a]	Reference	
Urinary tract infection (%)	1.7	
Unadjusted, OR (95% CI)	Reference	
Propensity score adjustment (IPTW) with robust standard errors, OR (95% CI)[a]	Reference	

[a]The propensity score model for all outcomes included age, gender, race and ethnicity, smoking, body mass index, Elixhauser comorb severity of respiratory impairment and dialysis on day 1 of admission; remdesivir, convalescent plasma, or anakinra use on day 1 of a outpatient and urgent care utilizations in the 12 months prior to admission.

Abbreviations: DEXA= dexamethasone or equivalent corticosteroid dosing; mg=milligram; OR=odds ratio; CI=confidence interval; IPTW treatment weights; SD=standard deviation

Table 3. Severity of Respiratory Impairment on Day 1 of Admission, Corticosteroid Dose, Mortality and Hospital Acquired Infections

	6-10mg DEXA	>10-20mg DEXA
Mild, n	7749	447
Mortality, n (%)	381 (4.9%)	22 (4.9%)
Hospital acquired infection (%)	5.7	4.9
Moderate, n	1429	118
Mortality, n (%)	200 (14.0)	17 (14.4)
Hospital acquired infection (%)	7.7	7.6
Severe, n	3745	294
Mortality, n (%)	1146 (30.6)	95 (32.3)
Hospital acquired infection (%)	15.8	22.8
Invasive Mechanical Ventilation, n	443	89
Mortality, n (%)	247 (55.8)	44 (49.4)
Hospital acquired infection (%)	28.2	30.3

Abbreviations: DEXA=dexamethasone or equivalent corticosteroid dosing