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RESEARCH LETTER

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Adjuvant corticosteroid therapy for critically ill patients with COVID-19



Xiaofan Lu^{1†}, Taige Chen^{2†}, Yang Wang^{3†}, Jun Wang^{4†} and Fangrong Yan^{1*}

Dear Editor,

A substantial portion of patients with coronavirus disease (COVID-19) developed rapidly progressive pneumonia leading to acute respiratory distress syndrome (ARDS) and multiple organ dysfunctions, conditions associated with high mortality [1]. Adjuvant corticosteroid therapy of such patients is common in clinical practice, but evidence is scarce regarding the efficacy of adjuvant corticosteroids in patients who are critically ill with COVID-19.

We retrospectively reviewed medical records of adult patients with COVID-19 who were admitted to Tongji Hospital (Wuhan, China) from January 25 to February 25, 2020. Two hundred forty-four eligible patients who had complete records and were critically ill and treated with antiviral agents were enrolled. Critically ill patients were defined as those with ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg; when PaO_2 is not available, $\text{SpO}_2/\text{FiO}_2 \leq 315$ suggests ARDS) or sepsis with acute organ dysfunction [2]. We converted all preparations to hydrocortisone-equivalent doses (methylprednisolone 1:5, dexamethasone 1:25) [3]. The clinical outcome was 28-day mortality after admission.

We adjusted for differences in baseline characteristics by propensity score, using multivariate logistic regression without regard to outcomes [4]. Potential confounders considered in propensity score matching (PSM) were variables included in the final model by step-wise backward elimination with $P < 0.20$ [5]. Corticosteroid treatment effect on outcome was analyzed by multivariate logistic regression with

adjustment for major variables (age, $\text{SpO}_2/\text{FiO}_2$, and lymphocytes) associated with mortality; individual propensity score was incorporated as a covariable to calculate the propensity-adjusted odds ratio (OR) [5]. PSM generated propensity score-matched pairs without replacement, and survival probability was compared by the Kaplan-Meier curve and analyzed with the log-rank test. Cox regression was used to estimate hazard ratio (HR) with 95% CI. For unadjusted comparisons, a two-sided $P < 0.05$ was considered statistically significant.

Of the 244 critically ill patients with COVID-19, the median age was 62 (50–71) years, and 52% were male. All patients were given antiviral therapy (e.g., oseltamivir, arbidol, lopinavir/ritonavir, ganciclovir, interferon- α), and 151 (62%) were given adjuvant corticosteroid treatment (median hydrocortisone-equivalent dosage 200 [range 100–800] mg/day). Five (5.4%) and 79 (52.3%) patients died in non-steroid and steroid groups, respectively. The median (IQR) administration duration of corticosteroid treatment was 8 (4–12) days. Multiple organ dysfunctions were more common in the steroid group than in the non-steroid group. Multivariate analysis that adjusted for major mortality-associated variables and propensity score indicated that corticosteroid treatment was independent from overall mortality (adjusted OR 1.05; 95% CI 0.15–7.46). One hundred forty-seven (60%) had dyspnea and 87 (36%) had ARDS, and subgroup analyses revealed corticosteroid treatment was not associated with 28-day mortality (both, $P > 0.3$). Sixty-two patients in 31 pairs were matched (Table 1), and 28-day mortality rate was 39% in case subjects and 16% in control subjects ($P = 0.09$). Likewise, addition of adjuvant corticosteroid therapy to standard antiviral treatment was not associated with 28-day mortality ($P = 0.17$; Fig. 1). However,

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Table 1 Baseline characteristics for steroid treatment and non-steroid treatment groups comprising critically ill patients with COVID-19 before and after propensity score matching

| | Cohort study | | | Case-control study (PSM) | | |
|---|----------------|------------------|----------|--------------------------|------------------|----------|
| | Steroid (151) | Non-steroid (93) | <i>P</i> | Steroid (31) | Non-steroid (31) | <i>P</i> |
| Age, years | 64 (53–71) | 59 (47–69) | .09 | 57 (51–69) | 58 (50–67) | .98 |
| Gender, male | 83 (55) | 45 (48) | .39 | 16 (52) | 16 (52) | 1 |
| Signs and symptoms | | | | | | |
| Fever | 136 (90) | 81 (87) | .61 | 30 (97) | 26 (84) | .2 |
| Dry cough | 112 (74) | 57 (61) | .05 | 21 (68) | 21 (68) | 1 |
| Dyspnea | 94 (62) | 53 (57) | .5 | 20 (65) | 19 (61) | 1 |
| Fatigue | 70 (46) | 48 (52) | .51 | 12 (39) | 13 (42) | 1 |
| Expectoration | 69 (46) | 30 (32) | .05 | 12 (39) | 12 (39) | 1 |
| Diarrhea | 45 (30) | 22 (24) | .37 | 10 (32) | 7 (23) | .57 |
| Anorexia | 42 (28) | 25 (27) | .99 | 5 (16) | 8 (26) | .53 |
| Original comorbidities | | | | | | |
| Hypertension | 61 (40) | 34 (37) | .64 | 16 (52) | 12 (39) | .44 |
| Diabetes | 34 (23) | 10 (11) | .03 | 4 (13) | 7 (23) | .51 |
| CVD | 15 (10) | 13 (14) | .45 | 2 (7) | 2 (7) | 1 |
| COPD | 9 (6) | 3 (3) | .51 | 0 | 1 (3) | 1 |
| Vital signs | | | | | | |
| T, °C | 37.0 (36.2–38) | 36.7 (36.4–37.3) | .02 | 37 (36.5–37.6) | 37 (36.5–37.3) | .93 |
| Breathing, rpm | 22 (20–25) | 20 (20–22) | <.01 | 21 (20–24) | 20 (20–22) | .08 |
| Pulse, bpm | 92 (82–105) | 88 (78–98) | .03 | 95 (78–106) | 93 (82–100) | .51 |
| SpO ₂ /FiO ₂ | 259 (121–303) | 297 (279–388) | <.01 | 291 (212–452) | 294 (246–396) | .57 |
| Laboratory findings (WBCs, lymphocytes, neutrophils, platelets, × 10 ⁹ /L) | | | | | | |
| WBCs | 6.7 (4.9–8.9) | 5.0 (4.0–6.5) | <.01 | 6.6 (4.0–8.6) | 5.1 (3.5–6.8) | .12 |
| Lymphocytes | 0.7 (0.5–1.0) | 1.2 (0.9–1.6) | <.01 | 0.9 (0.5–1.3) | 1.1 (0.6–1.2) | .64 |
| Neutrophils | 5.4 (3.6–7.6) | 3.2 (2.4–4.2) | <.01 | 5.2 (2.6–7.4) | 3.5 (2.3–4.7) | .09 |
| Platelets | 181 (138–248) | 224 (170–298) | <.01 | 168 (138–214) | 206 (155–230) | .23 |
| HGB, g/L | 130 (117–141) | 127 (117–139) | .42 | 128 (118–138) | 125 (117–133) | .56 |
| Organ function damage | | | | | | |
| ARDS | 81 (54) | 6 (7) | <.01 | 12 (39) | 6 (19) | .16 |
| Septic shock | 69 (46) | 2 (2) | <.01 | 8 (26) | 2 (7) | .08 |
| Myocardial infarction | 64 (42) | 3 (3) | <.01 | 10 (32) | 3 (10) | .06 |
| AKI | 46 (31) | 5 (5) | <.01 | 8 (26) | 3 (10) | .18 |
| DIC | 39 (26) | 2 (2) | <.01 | 6 (19) | 2 (7) | .26 |
| Liver injury | 28 (19) | 6 (7) | <.01 | 7 (23) | 3 (10) | .3 |
| Treatment | | | | | | |
| Anti-bacteria | 142 (94) | 42 (45) | <.01 | 25 (81) | 26 (84) | 1 |
| Gamma globulin | 84 (56) | 8 (9) | <.01 | 11 (36) | 8 (26) | .58 |
| MV | 78 (52) | 4 (4) | <.01 | 11 (36) | 4 (13) | .08 |
| Muscle relaxant | 25 (17) | 0 | <.01 | 4 (13) | 0 | .12 |
| HFNC | 21 (14) | 1 (1) | <.01 | 6 (19) | 1 (3) | .11 |

Abbreviations: CVD cardiovascular disease, COPD chronic obstructive pulmonary disease, WBCs white blood cells, ARDS acute respiratory distress syndrome, AKI acute kidney injury, DIC disseminated intravascular coagulation, MV mechanical ventilation, HFNC high flow nasal cannula. Continuous variables were described as the median (IQR) while categorical variables were expressed as frequencies (%). Hypothesis testing using Fisher's exact test for categorical data and Mann-Whitney test for continuous data

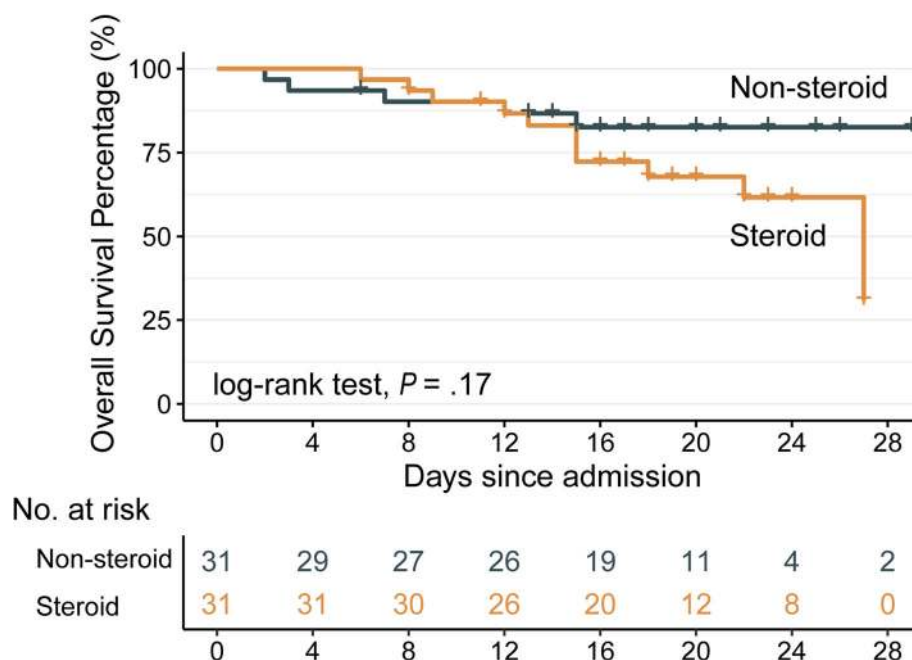


Fig. 1 Survival curves stratified by adjuvant corticosteroid treatment. Thirty-one critically ill patients with COVID-19 who received corticosteroid treatment (yellow line) are compared with 31 matched control subjects (green line) who did not receive corticosteroid treatment

increased corticosteroid dosage was significantly associated with elevated mortality risk after adjustment for administration duration ($P = 0.003$); every 10-mg increase in dosage was associated with additional 4% mortality risk (adjusted HR 1.04, 95% CI 1.01–1.07).

We acknowledged limitations. First, we did not distinguish patients who received corticosteroids for underlying disease (e.g., COPD), the number of which was however small. Second, PSM is limited by adjusting for observed covariables only; randomized placebo-controlled trials are therefore warranted. Altogether, our investigation indicated limited effect of corticosteroid therapy could pose to overall survival of critically ill patients with COVID-19. Given the adverse effects, corticosteroid therapy must be commenced with caution, and prudent dosage should be promoted under certain circumstances.

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Authors' contributions

Conceptualization: X. Lu, T. Chen. Acquisition, analysis, or interpretation of the data: J. Wang, Y. Wang, X. Lu, T. Chen. Statistical analysis: X. Lu, F. Yan. Investigation: X. Lu, T. Chen, Y. Wang. Drafting of the manuscript and editing: X. Lu, T. Chen, Y. Wang. Funding acquisition: J. Wang, Y. Wang, F. Yan. Supervision: J. Wang, F. Yan. The author(s) read and approved the final manuscript.

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Availability of data and materials

Dr. J. Wang had full access to all of the data in the study. After publication, the data will be made available to others on reasonable requests after approval from the corresponding author (J.W, dr_wangjun@suda.edu.cn) and Wuhan Tongji Hospital.

Ethics approval and consent to participate

Ethical approval was waived by the Ethics Committee of Tongji Hospital (Wuhan, China) in view of the retrospective and observational nature of the study and all the procedures being performed were part of the routine care.

Consent for publication

The informed consents of patients were waived by the Ethics Commission of Tongji Hospital (Wuhan, China) for the rapid emergence of this epidemic.

Competing interests

The authors declared no conflict of interest.

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