Impact of Tocilizumab on the mortality of patients with coronavirus disease 2019 reply

Malgie, J.; Schoones, J.W.; Pijls, B.G.

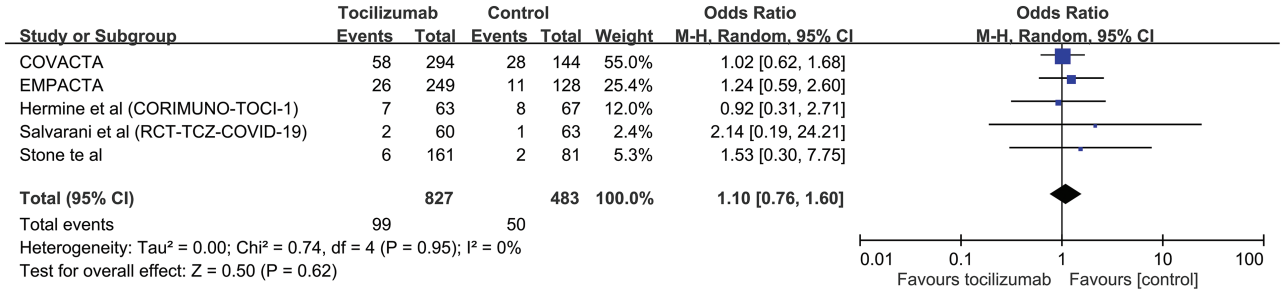

Figure 1. Forest plot of 28- or 30-day mortality rate between tocilizumab and comparators. Abbreviations: CI, confidence interval; COVACTA, EMPACTA, CORIMUNO-TOC1-1; RCT-TCZ-COVID-19.

References

1. Malgie J, Schoones JW, Pijls BG. Decreased mortality in COVID-19 patients treated with tocilizumab: a rapid systematic review and meta-analysis of observational studies. Clin Infect Dis **2020** Sep 23;ciaa1445. doi:10.1093/cid/ciaa1445
2. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med **2020** Oct 21. doi: 10.1056/NEJMoa2028836
3. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern Med **2020** Oct 20. doi: 10.1001/jamainternmed.2020.6820
4. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med **2020** Oct 20. doi:10.1001/jamainternmed.2020.6615
5. Parr JB. Time to reassess tocilizumab's role in COVID-19 pneumonia. JAMA Intern Med **2020** Oct 20. doi:10.1001/jamainternmed.2020.6557
6. F Hoffman-La Roche Ltd. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. Published 29 July **2020**. Accessed 22 October 2020. https://www.roche.com/investors/updates/inv-update-2020-07-29.htm
7. F Hoffman-La Roche Ltd. Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia. Published 18 September **2020**. Accessed 22 October 2020. https://www.roche.com/investors/updates/inv-update-2020-09-18.htm.
8. Lan SH, Lai CC, Huang HT, Chang SP, Lu LC, Hsueh PR. Tocilizumab for severe COVID-19: a systematic review and meta-analysis. Int J Antimicrob Agents **2020**; 56:106103.

Correspondence: Chih-Cheng Lai, No.427, Fuxing Rd., Yongkang Dist., Tainan City 710, Taiwan (dtmed141@gmail.com).

Clinical Infectious Diseases® 2021;72(12):e1156–7

DOI: 10.1093/cid/ciaa1738

Reply to Huang et al

To the Editor—We thank Huang and colleagues for their letter [1] on our article [2] and we appreciate the opportunity to respond.

Huang et al provide pooled analyses of 5 recently published randomized controlled trials (RCTs) that compare outcomes between patients treated with tocilizumab (TCZ) to patients not treated with TCZ [3–7]. They concluded that tocilizumab does not provide a beneficial effect on mortality and that there was no observed difference in serious adverse events [1]. Both findings provide valuable insights into the effect of TCZ in patients with coronavirus disease 2019 (COVID-19).

The absence of an effect on mortality in these RCTs seems to contradict the decreased mortality observed in our meta-analysis on observational studies [2]. If this is true, this finding suggests that the difference in effect on mortality between the pooled estimates of observational studies and RCTs is due to bias and confounding in the observational studies, provided that the RCTs are perfect and free of such bias and confounding. However, reality may be more complex. Although randomization may achieve balanced groups at baseline, it is not guaranteed that no differences could occur after randomization. Differences in co-medication use are of interest in the postrandomization period as they could potentially confound the observed effect of TCZ on mortality [2]. In particular, the administration of systemic corticosteroids is associated with a lower all-cause mortality [8]. In 3 of 5 RCTs, the patients in the control group received more corticosteroids than the patients in the TCZ group [4, 6, 7]; in the study by Hermine et al [4], 55% of patients in the control group received corticosteroids compared with 30% of patients in the TCZ group, and 28% of the patients in the control group received dexamethasone compared with 14% of patients in the TCZ group. In the study by Salama et al [7], 88% of patients in the control group received corticosteroids compared with 80% of patients in the TCZ group, and 67% of patients in the control group received dexamethasone compared with 55% of patients in the TCZ group. In the study by Rosas et al [6], 55% of patients in the control group received corticosteroids compared with 36% of patients in the TCZ group. In the study by Salvarani et al [5], the patients in the control group had a lower mean C-reactive protein, lower mean interleukin 6, lower mean ferritin, and lower mean D-dimer and received more antivirals compared with patients in the TCZ group. In the same study, TCZ rescue medication was given in 14 of 66 patients in the control group before the 30-day follow-up. The use of TCZ in the control group could therefore confound the effect of TCZ on 30-day mortality rates. In addition, the overall mortality rate in the control groups was approximately 11% for the RCTs [1] compared with 31% for the observational studies [2], suggesting that the patients in the RCTs are very different from those in the observational studies.

We therefore agree with Huang et al that more evidence from ongoing RCTs is needed.

Notes

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Jishnu Malgie,[1] Jan W. Schoones,[2] and Bart G. Pijls[1]

[1]Department of Orthopedics, Leiden University Medical Center, Leiden, The Netherlands, and [2]Directorate of Research Policy (formerly Walaeus Library), Leiden University Medical Center, Leiden, The Netherlands

References

1. Huang YT, Chao CM, Lai CC. The impact of tocilizumab on the mortality of patients with COVID-19. Clin Infect Dis **2021**; 72(12):e1156–7.
2. Malgie J, Schoones JW, Pijls BG. Decreased mortality in COVID-19 patients treated with tocilizumab: a rapid systematic review and meta-analysis of observational studies [manuscript published online ahead of print 23 September 2020]. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa1445.
3. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19 [manuscript published online ahead of print 21 October 2020]. N Engl J Med **2020**. doi:10.1056/NEJMoa2028836.
4. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial [manuscript published online ahead of print 20 October 2020]. JAMA Intern Med **2020**. doi:10.1001/jamainternmed.2020.6820.
5. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial [manuscript published online ahead of print 20 October 2020]. JAMA Intern Med **2020**. doi:10.1001/jamainternmed.2020.6615.
6. Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv [Preprint]. Posted 12 September **2020**. doi:10.1101/2020.08.27.20183442.
7. Salama C, Han J, Yau L, et al. Tocilizumab in non-ventilated patients hospitalized with Covid-19 pneumonia. medRxiv [Preprint]. Posted online 23 October **2020**. doi:10.1101/2020.10.21.20210203.
8. World Health Organization Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA **2020**; 324:1330–41.

Correspondence: B. G. Pijls, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, The Netherlands (b.g.c.w.pijls@lumc.nl).

Clinical Infectious Diseases® 2021;72(12):e1157–8

DOI: 10.1093/cid/ciaa1739

Comparison Between Hospitalized Patients Affected or Not Affected by Coronavirus Disease 2019

To the Editor—In the recent report of Munblit and coworkers [1], authors observed that the combination of clinical features was sufficient to diagnose coronavirus disease 2019 (COVID-19), indicating that laboratory testing is not critical in real-life clinical practice. To date, all patients admitted to the emergency department with acute respiratory failure and/or fever should be suspected to have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [2, 3], and early recognition of etiology and prompt therapeutic management are crucial to improve survival [4, 5].

From March to July 2020, we performed a prospective, multicenter study (RESILIENCY study). During the study period, all patients hospitalized for suspected or confirmed COVID-19 were prospectively recruited in 3 large hospitals in Rome, Italy. All patients with suspected SARS-CoV-2 infection, admitted to the hospital in case of fever and/or hypoxemic respiratory failure (partial pressure of oxygen [PaO_2] <60 mm Hg at rest in ambient air) or of exacerbation of underlying diseases or severe symptoms not manageable outside the hospital, were evaluated according to a predefined protocol (Figure 1).

Overall, 653 patients were included in the study: 309 (47.3%) patients with confirmed COVID-19 and 344 (52.7%) without COVID-19, hospitalized for other causes. Baseline characteristics and outcomes of the study population showed that the main causes of hospitalization among patients without COVID-19 were acute heart failure (47%), bacterial pneumonia (38.5%), and pulmonary embolism (9.2%). Overall, 67 (21.7%) patients from the COVID-19 group and 45 (13.1%) hospitalized for other causes were admitted to the intensive care unit (ICU); 30-day mortality was observed in 59 (19%) patients of the COVID-19 group and 62 (18%) of the non–COVID-19 group.

Multivariate analysis of risk factors for COVID-19 etiology at the time of hospitalization showed that dry cough (odds ratio [OR], 3.76 [95% confidence interval {CI}, 1.98–7.92]; $P < .001$), duration of fever >3 days (OR, 5.21 [95% CI, 2.34–9.21]; $P < .001$), lymphocytopenia (OR, 1.98 [95% CI, 1.27–4.22]; $P = .002$), and PaO_2/fraction of inspired oxygen (FiO_2) ratio <250 (OR, 4.98 [95% CI, 2.22–9.71]; $P < .001$) were independently associated with COVID-19 etiology, whereas procalcitonin value >1 ng/mL (OR, 0.21 [95% CI, .08–.82]; $P < .001$) and lactate >2 mmol/L (OR, 0.41 [95% CI, .15–.77]; $P < .001$) were associated with non–COVID-19 etiology.

Finally, analysis about predictors of 30-day mortality showed that age (per-year increase: OR, 1.33 [95% CI, 1.11–2.10]; $P < .001$), cardiovascular disease (OR, 4.58 [95% CI, 2.07–8.25]; $P < .001$), and ICU admission (OR, 2.1 [95% CI, 1.48–4.4]; $P < .001$) were independently associated with all-cause 30-day mortality, while the use of low-molecular-weight heparin (OR, 0.22 [95% CI, .03–.45]; $P = .002$) was associated with survival.

The findings of the present study can be summarized as follows: (1) Prompt identification of specific clinical characteristics (eg, dry cough or duration of fever >3 days) and laboratory findings (eg, lymphocytopenia, PaO_2/FiO_2 ratio <250, procalcitonin value >1 ng/ mL, and lactate >2 mmol/L) can help physicians to distinguish rapidly between COVID-19 or other etiologies [6]; (2) the application of a standard approach to management of patients with acute respiratory failure and/or fever associated with the knowledge of clinical and laboratory characteristics of COVID-19 can drive physicians to early therapeutic choices; and (3) age, cardiovascular disease, and ICU admission showed an independent association with all-cause 30-day mortality [7], whereas the use of low-molecular-weight heparin was associated with survival [8].

In conclusion, COVID-19 is characterized by a heterogeneous clinical, laboratory, and radiological presentation,