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.

Journal of Critical Care 70 (2022) 154053

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

The utility of CRP with the use of dexamethasone and Tocilizumab in critically ill patients with COVID-19

Harry Zacharias [a], Ritwik Mungara [a], Andrew Peter Wilson [b], Mervyn Singer [a], Nishkantha Arulkumaran [a,*]

[a] Bloomsbury Institute for Intensive Care Medicine, University College London, London, United Kingdom
[b] Department of Clinical Microbiology, University College London NHS Foundation Trust, London, United Kingdom

Editor,

C-reactive protein (CRP) levels have been shown to predict survival among patients hospitalised with COVID-19 [1]. The early use of dexamethasone and Tocilizumab in patients hospitalised with COVID-19 has become commonplace following the publication of large RCTs [2,3]. However, both dexamethasone and tocilizumab are known to suppress the pro-inflammatory response including CRP and temperature. The effect of dexamethasone and Tocilizumab on the trajectory of CRP in relation to survival in COVID-19 is less well understood. Furthermore, secondary infections associated with COVID-19 are of concern and the use of CRP and temperature to help identify the presence of a bacterial infection may be compromised by the use of dexamethasone and Tocilizumab.

We sought to evaluate the effect of dexamethasone and Tocilizumab on the trajectory of CRP and temperature among critically ill patients with COVID-19. Where trajectory of CRP was no longer able to distinguish between eventual survivors and non- survivors, we sought to evaluate if the trajectory of other routinely collected biochemical or haematological parameters predicted survival. Our secondary objective was to ascertain the association between the change in CRP and temperature around the time of diagnosis of bacteraemia.

We included patients aged ≥18 years admitted to University College London Hospital intensive care unit with a positive real-time reverse transcription–polymerase chain reaction (rRT-PCR) test for SARS-CoV-2 RNA between March 2020 and March 2021. All patients who had received dexamethasone and/or Tocilizumab were included. We included patients if at least 50% of CRP values were available in the ten days.

Continuous and categorical variables are reported as median (interquartile range) and n (%), respectively. Comparison of non-parametric continuous data between groups was performed using the Kruskal Wallis test (for comparison between >2 groups). Categorical data were compared using the chi-square test. Two- way ANOVA was used to assess the change in biomarkers over time among eventual survivors and non- survivors. Graphs were constructed, and statistical analysis performed using Prism 9.0 (GraphPad Software, La Jolla, CA, USA) and SPSS version 24.0 (IBM Corp).

A total of 215 patients received dexamethasone alone and a further 45 patients received Tocilizumab in addition to dexamethasone. There were no significant differences in age ($p = 0.120$), sex ($p = 0.233$), or APACHE II score ($p = 0.253$) between patients receiving dexamethasone alone or Tocilizumab in addition to dexamethasone (Supplementary Table 1). Of the 215 who reveived dexamethasone alone, 105 patients (49%) died. Of the 45 patients who received Tocilizumab in addition to dexamethasone 22 (49%) died ($p = 0.999$).

Sequential CRP data were available in 174 (81%) patients receiving dexamethasone and in 40 (89%) patients receiving Tocilizumab. Among patients who received dexamethasone, CRP was higher among non- survivors ($p = 0.0003$). A reduction in CRP was seen in the first three days of treatment among survivors and non- survivors ($p < 0.0001$), with no difference in the change in CRP over time ($p = 0.120$). Over the subsequent week, CRP levels increased among non-survivors but not survivors ($p < 0.001$) (Fig. 1).

Among patients who received Tocilizumab, a reduction in CRP was seen in the first three days of treatment among survivors and non-survivors ($p < 0.0001$), and CRP was higher among non- survivors ($p = 0.023$). Over the subsequent week, CRP levels continued to fall among survivors and non-survivors, with no difference between groups ($p = 0.295$) (Fig. 1).

As CRP was no longer able to differentiate between eventual survivors and non- survivors among patients receiving Tocilizumab, we evaluated other routinely collected clinical biomarkers associated with systemic inflammation. Levels of ferritin, D-dimer, BNP, lymphocytes, and neutrophils in eventual survivors and non- survivors who received Tocilizumab were assessed over a 10-day period (Fig. 2). There were no differences in the change of ferritin ($p = 0.361$), D-dimer ($p = 0.310$), BNP ($p = 0.970$), lymphocytes ($p = 0.493$) or neutrophils ($p = 0.629$) over time between eventual survivors and non- survivors who received Tocilizumab.

Nine patients of 45 (20%) who received Tocilizumab developed a positive blood culture. The time to positive blood culture was 19 (17–27) days from receiving Tocilizumab. Levels of inflammatory markers two- days prior to and three days after a positive blood culture showed a significant change in CRP ($p = 0.002$) but not neutrophils ($p = 0.903$), lymphocytes ($p = 0.997$), or temperature ($p = 0.064$) (Supplementary Fig. 1).

We report a significant reduction in CRP three days following the administration of dexamethasone, which subsequently increased in

* Corresponding author at: Bloomsbury Institute of Intensive Care Medicine, Division of Medicine University College London, Cruciform Building, Gower St, London WC1E 6BT, United Kingdom.
E-mail address: nisharulkumaran@doctors.org.uk (N. Arulkumaran).

https://doi.org/10.1016/j.jcrc.2022.154053
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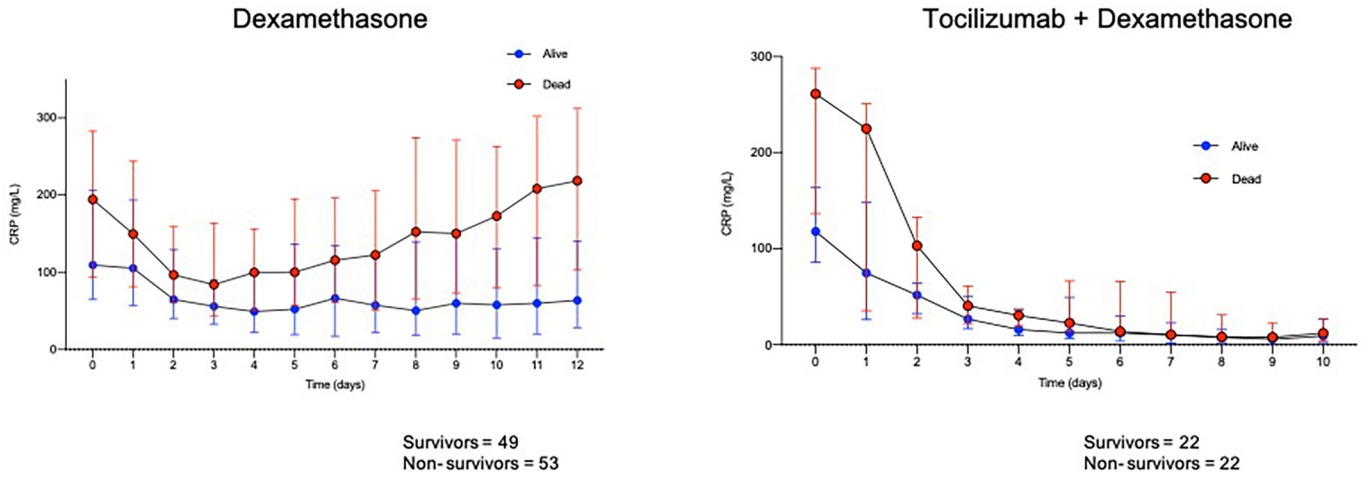

Fig. 1. CRP trajectory of patients receiving dexamethasone alone or dexamethasone with Tocilizumab.

non-survivors, but remained low in survivors. In contrast, CRP levels fell and remained low in survivors and non-survivors who received tocilizumab. The suppression of CRP for more than a week in patients with COVID-19 receiving Tocilizumab has been described by others [4]. We therefore sought to investigate the effect of Tocilizumab on CRP and other biomarkers which have been associated with poor outcome among patients with COVID-19, including ferritin, D-dimer, and neutrophil: lymphocyte ratio [5]. None of the biomarkers distinguished between survivors and non-survivors who received tocilizumab.

The concurrent use of dexamethasone and Tocilizumab have been associated with a reduction in mortality among patients with COVID-19 [6]. However, the risk of secondary infections remains a significant concern [7]. Among patients receiving tocilizumab, the time to develop a bloodstream infection (BSI) was between 2 and 3 weeks; as reported by others [4,8]. The investigation and diagnosis of a BSI was triggered by an increase in CRP levels and temperature. We cannot exclude the possibility of occult BSI which was undiagnosed closer to the time of dexamethasone and Tocilizumab administration, as clinical features associated with BSI, including a rising temperature and CRP may have been attenuated [4].

As with all retrospective analyses, we cannot correct for residual confounding, data are associative. Additionally, our sample size was limited. We did not have report data on procalcitonin as this was not collected on a daily basis. There are a number of other biomarkers of

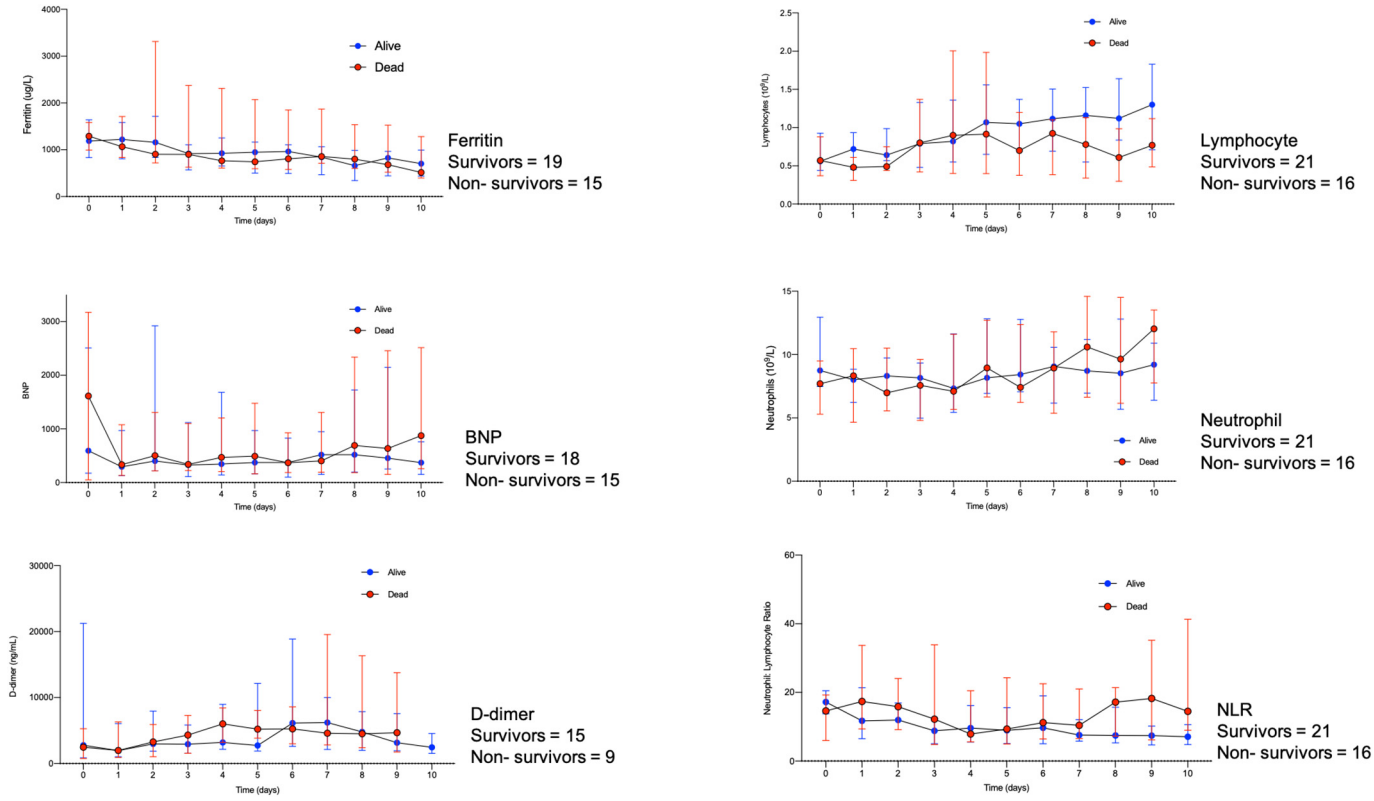

Fig. 2. Trajectory of ferritin, B-type natriuretic peptide (BNP), D-dimer, neutrophils, lymphocytes, and neutrophil: lymphocyte ratio (NLR) among patients receiving dexamethasone with Tocilizumab.

interest including lactate and IL-6 levels which may have prognostic value, which we have not reported. We have chosen to focus on the few inflammatory markers that are routinely available and have been shown to be associated with mortality in COVID-19. While multiple reports describe the trajectory of physiological parameters and laboratory biomarkers among survivors and non-survivors with COVID-19 [5,9], few have described the utility of these biomarkers in response to therapy and the therapeutic and prognostic implications.

The trajectory of CRP distinguished between survivors and non-survivors among patients who received dexamethasone, but not among those who receive tocilizumab in conjunction with dexamethasone. The trajectory of alternative biomarkers including ferritin, D-dimer, BNP, neutrophils and lymphocytes do not distinguish between survivors and non-survivors who receive tocilizumab. However, at the time of a bloodstream infection, occurring on average 18 days following tocilizumab, CRP levels increase. Further research is required to ascertain the optimal biomarker to detect secondary infections closer to the time of tocilizumab administration.

Funding

NA receives salary support from UCLH BRC (University College London Biomedical Research Council).

Ethical approval

Ethical approval was granted by the London-Westminster Research Ethics Committee, the Health Research Authority and Health and Care Research Wales (HCRW) on 2nd July 2020 (REC reference 20/HRA/2505, IRAS ID 284088).

Author contributions

HZ and RM curated data.
APRW curated data and reviewed the manuscript.
MS reviewed the manuscript.
NA designed the study, performed statistics, wrote the manuscript.

Declaration of Competing Interest

The authors have no competing interest to declare.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154053.

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