Response to 'Impact of immunosuppression on mortality in critically ill COVID-19 patients'

Fox TA [1,2], Troy-Barnes E [1], Kirkwood AA [3], Chan WY [1,9], Day JW [1,2,7], Chavda SJ [1,9], Kumar EA [1,4], David K [5], Tomkins O [1], Sanchez E [5], Scully M [1,7], Khwaja A [1,9], Lambert J [1, 7], Singer M [7,8], Roddie C [1,7], Morris EC [1,2,6,7], Yong KL [1,7,9], Thomson KJ [1,7], Ardeshna KM [1,7]

1. Department of Haematology, University College London NHS Foundation Trust, London, UK.
2. UCL Institute of Immunity and Transplantation, UCL, London, United Kingdom
3. CR UK & UCL Cancer Trials Centre, UCL Cancer Institute, UCL, London, UK.
4. Centre for Cancer Genomics and Computational Biology, Barts Cancer Institute, Queen Mary University of London, UK.
5. Department of Clinical Virology, University College London NHS Foundation Trust, London, UK.
6. Department Immunology, Royal Free London Hospitals NHS Foundation Trust, London, UK.
7. UCLH NIHR Biomedical Research Centre, London, UK.
8. Bloomsbury Institute of Intensive Care Medicine, UCL, London, UK.
9. Department of Haematology, UCL Cancer Institute, London, UK.

Sir, we thank Mirouse and colleagues for their correspondence in response to our recently published article (Fox*, et al* 2020). The authors describe the outcomes of their prospective single-centre cohort of 100 critically ill COVID-19 patients of whom 26 had a degree of "immunocompromise", as defined by the presence of haematological malignancy, solid tumours or solid-organ transplant (SOT) (Mirouse 2020). Whilst the authors report a higher rate of 28-day mortality amongst the immunocompromised patients, after matching these patients to non-immunocompromised patients (by clinical variables including age and comorbidity), immunocompromised status was no longer associated with day 28 mortality. The authors subsequently conclude that critical care should be offered to immunocompromised patients with COVID-19.

Whilst these observations are of interest, we do note that the cohort described by Mirouse and colleagues is of limited comparability with our own. In contrast with our study, only 12/26 (46%) immunocompromised patients described have a haematological malignancy, with detail on diagnosis and systemic anti-cancer therapy (SACT) unavailable, while all are defined as "critically ill". Only 25/55 patients in our cohort had severe disease (WHO ordinal score $\geq$5). Mirouse and colleagues include 10 SOT recipients and report high rates of chronic kidney disease in the immunocompromised group (62%), with kidney disease known to be associated with a higher risk of mortality from COVID-19 (Cheng*, et al* 2020).

The authors state that we could not compare immunosuppressed and non-immunosuppressed patients. Although it may be true that all haematology patients have some degree of immunosuppression, we did try and identify whether systemic immunosuppression confers inferior outcomes in haematology patients with COVID-19 in our study. We analysed outcomes for patients on systemic immunosuppression (corticosteroids, ciclosporin or mycophenolate mofetil) against those that were not. Patients in our cohort who had received systemic immunosuppression within 14 days of COVID-19 diagnosis had numerically increased risk of both severe disease and death, but this was not statistically significant (Odds ratio (OR) for death 1.79 (95% confidence interval (CI) 0.56-5.66) p = 0.32) (Fox*, et al* 2020). Thus, although the immunosuppressed patients in our two studies likely differ substantially in the degree of immunosuppression, the findings are broadly in agreement (although given both sample sizes are small this requires validation in a larger cohort).

SACT leads to a further and variable degree of immunosuppression. Although mortality from COVID-19 is higher in patients with cancer compared to the general population, patients on SACT do not appear to be at greater risk of mortality than those not on active treatment (Kuderer*, et al* 2020, Lee*, et al* 2020). Our results and those of larger recent studies corroborate these findings in patients with haematological malignancies (Fox*, et al* 2020, Passamonti*, et al* 2020). Similar to the findings of Mirouse and colleagues in immunocompromised patients, the excess mortality from COVID-19 in cancer patients appears to be driven by other risk factors such as age, gender, ethnicity and comorbidities (Kuderer*, et al* 2020, Lee*, et al* 2020).

Modification or delay of SACT may be sensible in patients with COVID-19 where such changes are unlikely to result in inferior outcomes from the haematological malignancy. However, where treatment is urgently indicated we would reiterate that the priority should

be to treat the underlying malignancy and such patients should be referred urgently to specialist centres for prompt initiation of potentially lifesaving SACT.

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