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.

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Influence of IL-6 levels on patient survival in COVID-19

Editor

COVID-19 is characterized by a proinflammatory phenotype, with an underlying cytokine storm thought to be key in determining disease severity. Levels of the proinflammatory cytokine interleukin-6 (IL-6) discriminate between patients with mild and severe disease, [1] making IL-6 inhibition an attractive therapeutic strategy [2].

Despite a common underlying aetiology of COVID-19, outcomes from clinical trials are not consistent. Whilst some studies demonstrate an association between the use of Tocilizumab and reduction in mortality [3], others have been terminated early due to excess mortality associated with Tocilizumab [4]. It is difficult to reconcile such conflicting data. We therefore explored the association between patient demographics, respiratory failure severity, and IL-6 levels on mortality in a cohort of hospitalized COVID-19 patients who were naïve to immunotherapy. Differences in clinical outcome between clinical trials may relate to variable pre-treatment levels of IL-6.

We included patients aged ≥18 years admitted to University College London Hospitals with a positive real-time reverse transcription–polymerase chain reaction (rRT-PCR) test for SARS-CoV-2 RNA between 1 March and 30 June 2020, following local research ethics committee approval (REC reference 20/HRA/2505). Multiplex panels (MesoScale Discovery, Rockville, MD, USA) were used to analyse IL-6. For this analysis, blood was centrifuged within 4 h of collection, separated and sera frozen at −80 °C before batch analysis.

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). Cytokine values were analysed on a logarithmic scale. Categorical data were compared using the chi-square test. Area under the receiver operator curve (AUROC) was constructed to ascertain the predictive value of IL-6 for mortality. Graphs were constructed, and statistical analysis performed using Prism 9.0 (GraphPad Software, La Jolla, CA, USA) and SPSS version 24.0 (IBM Corp).

Eighty-six COVID-19 patients were included; 44 (51%) patients with mild disease, 22 (26%) with critical illness who survived, and 20 (23%) who died in hospital. Patients who died were older than those who survived critical illness or those with mild disease (both $p = 0{\cdot}002$). Compared to patients with mild disease, progression to critical illness and death was associated with severity of respiratory failure (lower SpO_2:FiO_2 ratio) ($p < 0.001$) and higher levels of CRP ($p < 0{\cdot}001$) on admission (Table 1).

IL-6 levels are significantly higher among patients who develop critical illness or who subsequently die compared to patients with mild illness ($p < 0.001$). Levels of IL-6 on admission correlated well with CRP ($r^2 = 0.398$; $P < 0.001$). On hospital admission, IL-6 discriminated between eventual survivors and non-survivors (AUROC 0·67, $p = 0.020$) (Fig. 1). Admission levels of IL-6 had better discriminatory value for development of critical illness or death compared to patients with mild illness (AUROC 0.78, $p < 0.001$).

We found a good correlation between serum IL-6 and CRP; IL-6 being a key regulator of C-reactive protein (CRP) production. However, co-interventions, particularly the use of corticosteroids, affect CRP levels. This may explain the lack of association between the treatment effect of Tocilizumab with baseline CRP in clinical trials [5]. Furthermore, a significant proportion of our patients had IL-6 levels that were only marginally elevated, consistent with other studies. [6] No clinical

Table 1
Baseline demographics, seroconversion rates and treatments used for patients subdivided by World Health Organisation (WHO) COVID-19 ordinal severity scale. WHO 4–5 (hospitalized with or without supplemental oxygen via nasal prongs or face mask), WHO 6–9 (hospitalized requiring non-invasive or invasive respiratory support), and WHO 10 (died following hospital admission). Ct value (cycle threshold) represents viral load, with higher values representing a lower viral load.

	WHO 4–5	WHO 6–9	WHO 10	*p*-value
Number of patients	44 (51%)	22 (26%)	20 (23%)	–
Male sex	24 (56%)	16 (73%)	15 (75%)	0.219
Age (years)	59 (46–69)	59 (47–68)	73 (65–83)	0.002
Days from symptom onset to hospital admission	10 (5–14)	7 (4–10)	5 (2–7)	0.034
SpO_2:FiO_2 ratio (mmHg)	448 (424–462)	402 (260–448)	395 (107–457)	<0.001
C-reactive protein (mg/L)	78 (32−121)	214 (94–288)	166 (75–342)	<0.001
Lymphocyte count (10^9/L)	1.1 (0.7–1.6)	0.7 (0.6–1.0)	0.8 (0.5–1.4)	0.047
C_t value*	38 (35–43)	33 (29–41)	36 (36–43)	0.018
Co-morbid illness				
- Diabetes mellitus	9 (21%)	3 (14%)	6 (30%)	0.426
- Hypertension	15 (34%)	5 (23%)	11 (55%)	0.087
- Cardiovascular disease	4 (9%)	0 (0%)	3 (15%)	0.196
- Smoker	5 (11%)	2 (9%)	0 (0%)	0.300
Seroconversion (anti-SARS-CoV-2 antibody positive)	32 (73%)	15 (71%)	9 (45%)	0.079
Neutralising antibody titre (log_{10})	2.9 (2.2–2.3)	3.2 (3.0–3.8)	3.0 (2.7–3.7)	0.149
IL-6 levels (pg/ml)	8 (3–18)	26 (13–83)	22 (14–44)	<0.001
Treatments				
Steroid	2 (5%)	3 (14%)	6 (30%)	0.019
Antiviral	0 (0%)	1 (5%)	1 (5%)	0.329
Continuous positive airways pressure	–	21 (95%)	13 (65%)	–
Mechanical ventilation	–	7 (32%)	7 (35%)	–
Vasopressors	–	7 (32%)	7 (35%)	–
Renal replacement therapy	–	0 (0%)	3 (15%)	–

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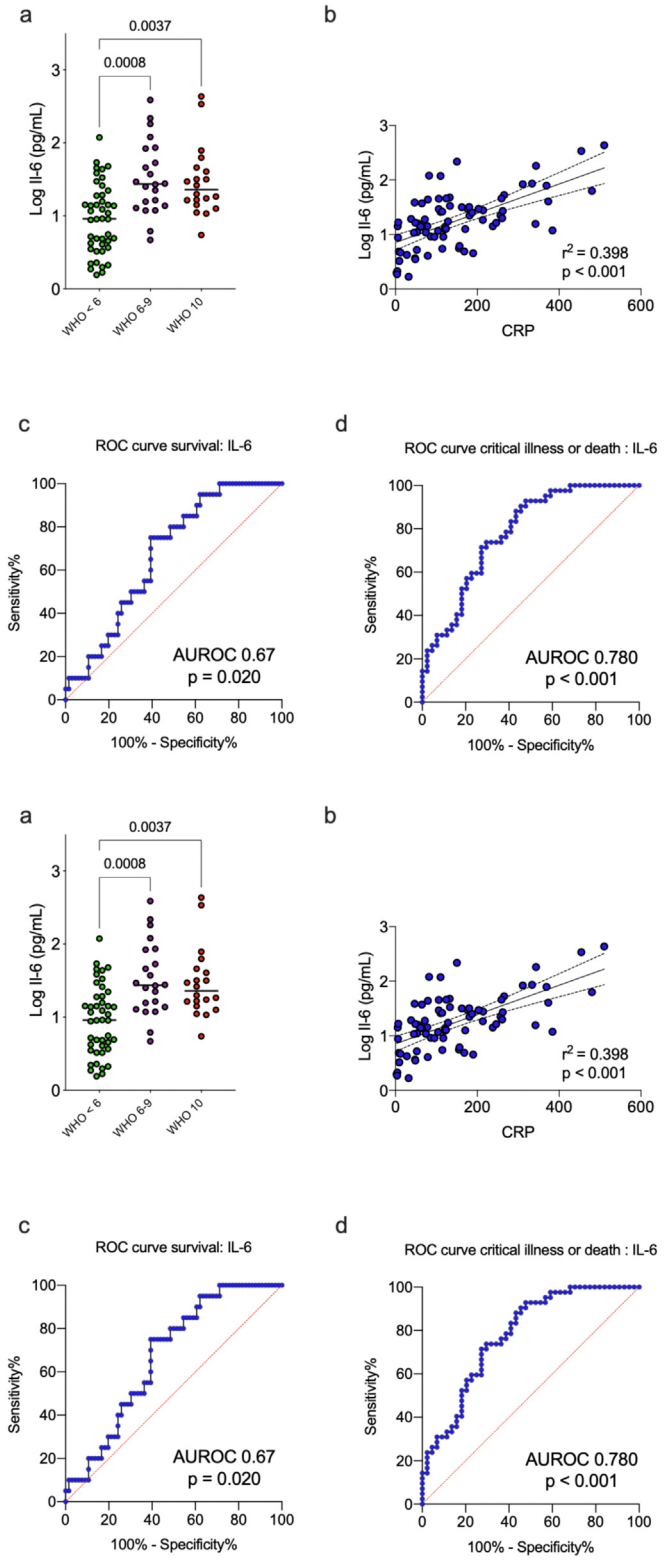

a
0.0037
0.0008
Log Il-6 (pg/mL)
WHO < 6
WHO 6-9
WHO 10
b
Log Il-6 (pg/mL)
r² = 0.398
p < 0.001
CRP
c
ROC curve survival: IL-6
Sensitivity%
AUROC 0.67
p = 0.020
100% - Specificity%
d
ROC curve critical illness or death : IL-6
Sensitivity%
AUROC 0.780
p < 0.001
100% - Specificity%

Fig. 1. Interleukin-6 levels in hospitalized patients with COVID-19. Patients subdivided by World Health Organisation (WHO) COVID-19 ordinal severity scale. WHO 4–5 (hospitalized with or without supplemental oxygen via nasal prongs or face mask (mild disease)), WHO 6–9 (hospitalized requiring non-invasive or invasive respiratory support (critical illness)), and WHO 10 (died following hospital admission). (a) IL-6 levels are significantly higher among patients who develop critical illness or who subsequently die compared to patients with mild illness ($p < 0.001$). (b). Levels of IL-6 on admission correlate well with CRP ($r^2 = 0.398$; $P < 0.001$). (c–d) Admission levels of IL-6 had discriminatory value for development of critical illness or death compared to patients with mild illness (AUROC 0.78, $p < 0.001$). In comparison, the ability of IL-6 to discriminate between survivors and non- survivors was less effective (AUROC 0.67, $p = 0.020$).
Comparison of continuous data between groups was performed using the Kruskal Wallis. Pearsons correlation is used to assess correlation between IL-6 and CRP levels. Area under the receiver operator curve (AUROC) was constructed to ascertain the predictive value of cytokines for mortality.

trial investigating the use of IL-6 receptor antagonists have stratified patients based on circulating levels of IL-6 levels [5].

Personalized medicine has struggled to find a foothold in critical care trials. Patient stratification by theragnostic biomarker levels will allow clinicians to identify those who may specifically benefit from treatment, and avoid possible harm in patients where treatment is likely to be futile.

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Declarations

This database has been used for previous publications, although addressing different hypotheses with different analyses, figures and tables:

- Sex differences in immunological responses to COVID-19: A cross-sectional analysis of a single centre cohort. Brit J Anaes. *In press*.
- Therapeutic targets in COVID-19: A cross-sectional analysis of a single centre cohort. Crit Care Explorations. *Accepted for publication*

Author data access

All authors had access to data.

Author contributions

NA, TACS, EN, and MS designed the study.

TACS, AK, DB, HR, CRS, MoS, JH, EG, CH, BW, ML, PC, GK, LEM, and EN acquired study data.

NA and TACS analysed the data.

NA and TACS wrote the manuscript.

MeS critically reviewed the manuscript.

NA, TACS, and MeS have accessed, and verified, the data in this article.

All authors approved the final version.

Declaration of Competing Interest

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References

[1] McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, et al. Characterization of the inflammatory response to severe COVID-19 illness. Am J Respir Crit Care Med. 2020;202(6):812–21. https://doi.org/10.1164/rccm.202005-1583OC.

[2] Snow TAC, Singer M, Arulkumaran N. Immunomodulators in COVID-19: two sides to every coin. Am J Respir Crit Care Med. 2020;202(10):1460–2. https://doi.org/10.1164/rccm.202008-3148LE.
[3] Group, Recovery Collaborative. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45. https://doi.org/10.1016/S0140-6736(21)00676-0.
[4] Veiga VC, Prats Jagg, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021:372 p. n84 https://doi.org/10.1136/bmj.n84.
[5] Snow TAC, Saleem N, Ambler G, Nastouli E, Singer M, Arulkumaran N. Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials. Intensive Care Med. 2021;47(6):641–52. https://doi.org/10.1007/s00134-021-06416-z.
[6] Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med. 2020;8(12):1233–44. https://doi.org/10.1016/S2213-2600(20)30404-5.

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