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Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King's College Hospital experience

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged at the end of 2019 and caused an infection named coronavirus disease 19 (COVID-19).[1] Patients with compromised immune systems are at increased risk of complications of COVID-19 but this risk is not precisely defined.[2] Although age, gender, comorbidities and ethnicity are risk factors for adverse outcomes,[3] various pre-existing conditions, including haematological cancers, have also been reported to correlate with poor outcomes.[4–8]

Our aim was to compare the first 80 patients with a haematological malignancy with all other patients admitted to our hospital with COVID-19 in the same time frame, to precisely define their relative risk and identify factors that increase mortality within this subgroup.

The mean age of our cohort was 69·4 years (range 30–95 years); 52 (65%) males; 76% had at least one comorbidity. Overall, 62 (77%) patients had lymphoid malignancies/plasma cell dyscrasias and 18 (23%) had myeloid neoplasms. Nine patients had previously undergone allogeneic (n = 6) and autologous (n = 3) haematopoietic stem cell transplantation. One patient had received chimeric antigen receptor T-cell (CAR-T) therapy. Treatment type included intensive therapy (n = 16; 20%,), non-intensive therapy (n = 35; 44%) and 'watch and wait' (n = 29, 36%), with 31 (40%) on active treatment (Tables SI and SII).

The most common symptoms on admission were fever (60%), cough (58%), dyspnoea (54%) and gastrointestinal symptoms (13%) (Table SI). Both the baseline pre-COVID-19 (median $1{\cdot}25 \times 10^9$/l) and the nadir (median $0{\cdot}6 \times 10^9$/l) lymphocyte count were lower than the normal range (1·3–4).

Overall, 23 (29%) patients had a mild symptoms, 22 (27%) had moderate symptoms needing ward-based care and oxygen and 35 (44%) had severe symptoms. On the date of censoring, 28 patients had died due to COVID-19, with a crude case fatality rate of 39%.

The haemato-oncology patients who died or were transferred to the intensive care unit were older (73 vs. 66 years; P = 0·065); but male gender (61% vs. 67%, P = 0·76) was not associated with poorer outcome. Differences in ethnicity were noted, with a higher black population among those who died (45% vs. 17%, P = 0·02). Higher total white cell count (15·8 vs. $4{\cdot}9 \times 10^9$/l, P = 0·015), neutrophil count (5·7 vs. $3{\cdot}8 \times 10^9$/l, P = 0·04) and C-reactive protein (CRP) (200 vs. 82, $P < 0{\cdot}001$) were associated with poorer outcome (Table SI). A lower baseline pre-COVID-19 lymphocyte

Table I. Comparison of baseline characteristics of patients with COVID-19 without underlying haematological malignancies (general cohort,) and haemato-oncology patients with COVID-19 (haematology cohort).

Characteristic	Total n = 1,183	General cohort n = 1,115	Haematology cohort n = 68	P-value
Age, median [IQR]	71 [57–82]	70 [56–82]	73 [62–82]	0·16
Male	682 (57·7)	636 (57·0)	46 (67·6)	0·086
Grouped ethnicity				
White or White British	543 (45·9)	502 (45·0)	41 (60·3)	0·011
Black or Black British	334 (28·2)	315 (28·3)	19(27·9)	
Asian or Asian British	58 (4·9)	54 (4·8)	4 (5·9)	
Unclassified	248 (21·0)	244 (21·9)	4 (5·9)	
Social deprivation*	439 (39·7)	430 (40·3)	9(22·0)	0·018
O_2 required	534 (45·1)	496 (44·5)	38 (55·9)	0·067
O_2 saturation	96 [95–98]	96 [95–98]	96 [94–98]	0·69
Respiratory rate (per minute)	20 [18–22]	20 [18–22]	20 [18–24]	0·27
Radiological score†	2 [1–4]	2 [1–4]	3 [2–6]	0·005
Lymphocytes (median [IQR]) × 10^9/l	1·0 [0·7–·4]	1·0 [0·7–1·4]	0·6 [0·4–1·1]	<0·001
Neutrophils (median [IQR]) × 10^9/l	5·5 [3·8–7·8]	5·7 [3·9–7·9]	3·8 [2·3–6·1]	<0·001
CRP (median [IQR]), mg/l	80·3 [37·0–149·0]	80·0 [36·0–146·8]	99·5 [47·6–198·0]	0·099
Albumin (median [IQR]), g/l	37 [34–40]	37 [34–40]	35 [31–39]	0·002
Creatinine (median [IQR]), umol/l	94 [72–134]	93 [71–131]	121 [82–210]	<0·001
DM	408(35·3)	399 (35·8)	9 (21·4)	0·055
HTN	611 (52·9)	590 (53·0)	21 (50·0)	0·71
IHD	152 (13·2)	147 (13·2)	5 (11·9)	0·81
COPD	106 (9·2)	103 (9·2)	3 (7·1)	0·64
Other lung disease	139 (12·0)	134 (12·0)	5 (11·9)	0·98

CRP, C reactive protein; COPD, chronic obstructive pulmonary disease (other lung disease, includes asthma; interstitial lung disease); DM, Diabetes mellitus; HTN, hypertension; IHD, ischaemic heart disease.

Data are presented as n (%) or median [IQR] (excluding Radiological score: score [range]).

*Social deprivation was calculated using the index of multiple deprivation (IMD), with lowest three deciles of deprivation according to the IMD.

†Radiological score: chest radiographs were assessed using an adapted radiographic assessment of lung oedema (RALE) score for COVID-19.[12] The severity score attributes a number between 0 and 4 to each lung, depending on the extent of consolidation or ground glass opacities (0 = no involvement, 1 = <25%, 2 = 25–49%, 3 = 50–75%, 4 = >75% involvement).

count (1·1 vs. 1·5 × 10^9/l, P = 0·02) was associated with better outcome, even when chronic lymphocytic leukaemia (CLL) cases were removed from the analysis. Figure S1 shows the fall in lymphocyte count from before COVID-19 infection to its nadir during COVID-19 infection.

We compared baseline characteristics and outcome of COVID-19 in hospitalised patients with no underlying haematological malignancy (n = 1115) with our haemato-oncology cohort (n = 68) (Table I), admitted within the same time frame where identical follow-up was available. No difference was observed in age, gender or comorbidities between the two groups. There was a higher proportion (60·3% vs. 45%, P = 0·011) of white British and lower incidence of social deprivation (22% vs. 40·3%, P = 0·018) in the haemato-oncology cohort. The median lymphocyte and neutrophil count were lower (0·6 vs. 1·0 × 10^9/l, P < 0·001 and 3·8 vs. 5·7 × 10^9/l, P < 0·001 respectively) in the haemato-oncology group.

The crude mortality rate at day 28 from admission was significantly worse for the haemato- oncology cohort 39% (95% CI: 27–52) *versus* 20% (95% CI: 18–23) in the medical cohort (hazard ratio (HR) 2·06; 95% CI: 1·36–3·14; P = 0·001] and was retained on adjusting for age and gender (HR 1·74; 95% CI: 1·12–2·71; P = 0·014) (Table SIII and Fig 1A,B). Although the type of underlying malignancy (lymphoid vs. myeloid), did not influence the outcome (Table SIII and Fig 1C), the intensity of treatment had a strongly negative impact on mortality. Patients on both intensive (HR 4·66; 95% CI: 2·29–9·47; P = 0·001) and non-intensive (HR 1·90; 95% CI: 1·05–3·48; P = 0·035) treatments, did worse compared with the age- and gender-matched general cohort (Table SIII and Figure S2D).

SARS-CoV-2 ribonucleic acid (RNA) was detected in nasopharyngeal swabs/bronchoalveolar lavage in all 80 patients. We evaluated the persistence of viral RNA in 22 patients who had a repeat positive test beyond 7 days. The median duration of virus detection in the respiratory samples was 29 days (Figure S2A). Of the 22 patients, nine became negative at a median of 13 days (range 7–60) and 13 patients had ongoing RNA persistence (Figures S2 and S3). We noted several cases of clinical deterioration beyond the 10–14 day window.

In conclusion, we report on outcomes and predictive factors for the largest series to date of patients with COVID-19

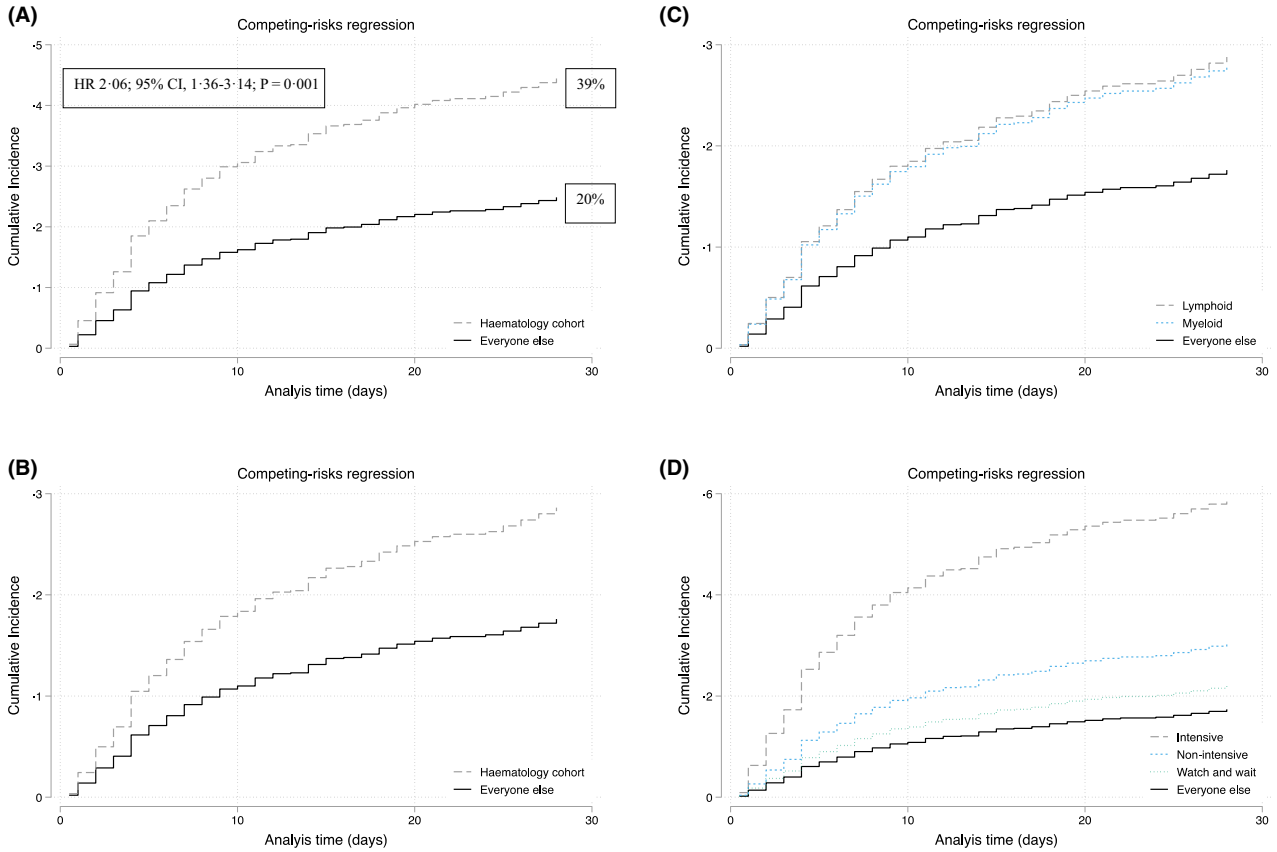

Fig 1. Competing risk regression model evaluating mortality rate at day 28. Crude mortality rate (A), age/gender adjusted mortality rate (B), mortality rate by diagnostic category (C, lymphoid vs. myeloid), mortality rate by treatment intensity (D, intensive vs. non-intensive vs. 'watch and wait') in patients with underlying haematological malignancies compared with general cohort without haematological malignancies.

and underlying haematological malignancies ($n = 80$) and compare outcomes to general medical patients admitted with COVID-19 during the same time. We found no correlation between age or male gender between survivors and non-survivors with COVID-19 and haematological cancer, compared to a general, non-haematology cohort, and contrary to previous publications.[1] However, haemato-oncology patients with COVID-19 had a twofold increased risk of death, with a 28-day mortality rate of 39%, which was fourfold higher in those undergoing intensive treatment. Our data suggests that the current caution around delivery of intensive treatments during the COVID-19 outbreak is justified and that continuation of shielding in this subgroup should be considered.

Lymphopenia during COVID-19 is present in high proportion (40–83%) of cases and is also associated with a worse prognosis in the general population.[1,3,9,10] Our data show a lower lymphocyte and neutrophil count in the haematology cohort. Furthermore, both worsening of lymphopenia during and the depth of lymphopenia prior to infection had a beneficial impact on survival. This is in line with several recent studies suggesting that overactivation of the adaptive immune system can be responsible for the high mortality associated with COVID-19. This is, however, speculative and further study of both innate and adaptive immunity within the haematology cohort may be useful.

Prolonged detection of viral RNA, for up to 2 months in a subset of patients, has not been reported in the immunocompromised setting.[11] Prolonged persistence in haemato-oncology patients has significant implications for scheduling subsequent chemotherapy, shielding and self-isolation.

Despite limitations and caveats, our data, with the added benefit of a large cohort of non-haematology COVID-19 patients, show a doubling of mortality in haemato-oncology patients with COVID-19 and a prolonged persistence of viral RNA.

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Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

VS, TKK, MZ and AGK designed the concept, collected and analysed data, and wrote the manuscript. SN and JG collected data for the medical cohort and did statistical analysis. JV, SS, VM, SG, AK, DY, DA, RS, CR, AS, JM, HDL, PK, RB, PP, VP, MMC, GJM, AP and AGK enrolled patients and provided clinical data. All authors reviewed and approved the final version.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Paired boxplot of lymphocyte count $\times 10^9$ of patients with haematological malignancy prior to COVID-19 and their nadir lymphocyte count in cohort of patients without CLL (a) and CLL patients (b).

Fig S2. 1A Duration of swab positivity in two groups – remained positive at last testing (red) and negative swab at the last testing (green).

Fig S3. Dynamics of viral load, as assessed by semi-quantitative RT-PCR, represented as change from baseline and duration of swab positivity.

Table SI. Treatment intensity groups (intensive vs. non-intensive vs. surveillance).

Table SII. Baseline demographics and COVID-19-related features ($n = 80$) and comparison of patients with known outcomes who died or went to ITU compared to those who recovered ($n = 75$).

Table SIII. Hazards Table (compared to non-haematology COVID-19 cohort, group 2).

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