DR. JEFF K DAVIES (Orcid ID : 0000-0002-3192-6995)
PROF. JOHN G GRIBBEN (Orcid ID : 0000-0002-8505-7430)
DR. JOHN CHARLES RICHES (Orcid ID : 0000-0002-3425-7686)

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Corresponding author mail id:- j.riches@qmul.ac.uk

Title: Clinical Outcome of Coronavirus Disease 2019 in Haemato-oncology Patients

To the Editor:

Since being identified in China in December 2019, coronavirus disease 2019 (Covid-19) has rapidly evolved into a global pandemic with over 4 million cases and more than 270,000 deaths.(1) Following the first reported cases in the United Kingdom (UK) in late January 2020, numbers have continued to rise with 223,060 cases and 32,065 deaths reported as of 11th May 2020.(2) Initial reports from China have indicated that Covid-19 has an overall mortality rate of 1.4%. However, the prognosis varies widely between groups, with age over 60 years and underlying conditions including hypertension, diabetes, cardiovascular disease and cancer identified as risk factors for severe disease and death.(3) The initial reports from China show that patients with cancer are over-represented among individuals who develop severe Covid-19 after contracting the virus.(4) Patients with haematological malignancies are expected to be at increased risk of adverse outcomes from this viral infection, due being immunosuppressed as a consequence of the underlying cancer, and from the effects of therapy. This has led to a variety of recommendations to reduce the risk from Covid-19, including “shielding” by self-isolating at home for prolonged periods, and alterations to therapy such as delaying or even omitting chemotherapy, radiotherapy or transplantation.(5-8) However, at the time of writing there is virtually no published data on the impact of Covid-19 in patients with haematological malignancies.

We identified 35 adult patients with a known diagnosis of a haematological malignancy under the care of Barts Cancer Centre who developed a laboratory-confirmed Covid-19 infection between 11th March and 11th May, 2020. A confirmed case of Covid-19 was defined by a positive result on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab. Only laboratory-confirmed cases were included and each

patient had at least 14 days of follow-up. The demographic and clinical characteristics of the patients are shown in Table 1. The median age of the patients was 69 years; 66% were men. 12 patients had multiple myeloma, 5 patients had chronic lymphocytic leukaemia, 4 patients respectively had diffuse large B cell lymphoma and acute lymphoblastic leukaemia, 3 patients had follicular lymphoma, 2 patients had acute myeloid leukaemia, along with 1 patient with each of aplastic leukaemia, myelofibrosis, monoclonal gammopathy of undetermined significance, mantle cell lymphoma and myelodysplastic syndrome. 54% of patients were known to have pre-existing hypogammaglobulinaemia at baseline. 24 (69%) patients were on active treatment at the time of Covid-19 diagnosis; the treatment history for each case is given in the data supplement. Many patients had co-existing chronic medical conditions, most frequently hypertension (29%), chronic kidney disease (14%) and diabetes mellitus (15%). The most common symptoms were fever (77%), cough (60%) and shortness of breath (54%).

Table 2 shows correlation of clinical and laboratory findings with outcome. As of 11th May, 14 (40%) patients had died and 21 (60%) patients had recovered. Age was most significantly associated with outcome in our series with all but one of the patients who died being 70 years or older at the time of Covid-19 diagnosis. The number of co-existing comorbidities such as hypertension, chronic kidney disease or diabetes was also predictive of outcome with patients who died having significantly more concurrent diagnoses than patients who recovered. This reflects the observations seen in initial studies where the elderly and those with underlying conditions were at a significantly higher risk for severe disease and death.(3) Importantly we did not see a correlation between active treatment and outcome in our series. Furthermore, we document 15 patients who have recovered from Covid-19 despite being on treatment at the time of diagnosis of their infection, including patients on highly immunosuppressive regimens such as R-CHOP for lymphoma, induction regimens for acute leukaemia and triplet combinations for myeloma. In terms of laboratory parameters hypoxia on admission and a highly elevated C-reactive protein level were predictive of a poor outcome. In contrast, there was no association between admission haemoglobin concentration, platelet count or neutrophil:lymphocyte ratio and outcome. Perhaps unexpectedly, patients who recovered had a lower neutrophil and lymphocyte count on admission than the patients who died. This probably reflects inclusion of younger fitter patients receiving more myelosuppressive and lymphodepleting therapy, who nevertheless went on to recover from their infection. However, this highlights that the impact of Covid-19 on haematological parameters such as a lymphopenia, or the prognostic utility of neutrophil:lymphocyte ratio may be confounded by other factors in haemato-oncology patients.(9, 10)

Given the focus on hospital-based testing for suspected Covid-19 in the UK, a crude case fatality rate in a comparable group of hospital-assessed patients of 14.4% can be calculated from current UK government statistics.(2) In contrast we observed a

case fatality rate of 40% in haemato-oncology patients, which is comparable to the proportion of patients with cancer who reached a composite endpoint of requiring admission to intensive care, invasive ventilation or death in a previous report.(4) Therefore our patients who developed Covid-19 have an approximately 3-fold increased risk of death compared to the general population. Due to the current lack of widespread community testing for Covid-19 in the UK, the case fatality rate reported here is likely to be an overestimate within this patient group. While only patients with laboratory-confirmed Covid-19 were included in our series, we were aware of other haemato-oncology patients who had mild symptoms and were advised to self-isolate at home rather than attend hospital for assessment, and were therefore not tested for SARS-CoV-2. Furthermore, it is likely other patients with no/mild symptoms have not presented to our network.

Our study does have several limitations, including the relatively small sample size and lack of data on patients who developed Covid-19 in the community and were not tested. Ultimately, some of these questions will be addressed by larger multi-national and registry studies. However, given the rapidly evolving nature of the global Covid-19 pandemic there is a place for case series in guiding haematological practice during these challenging times. Our data demonstrate that while patients with haematological cancers have worse outcomes after Covid-19 than the background population, the majority still survive.

Conflict of Interest: The authors declare no potential conflicts of interest.

Author contributions: JA and JCR devised and directed the research project, analysed data and wrote the paper. JKD, JGG, JDC, and RLA provided clinical data, contributed to the interpretation of results and wrote the paper. SLH, SM, SA, HO, BS, MS, JO, BW, VF, SA, RLD, KZ, ET, and TE worked on patient enrolment and provided clinical data. All authors provided critical feedback and approved the final version of the manuscript.

Authors:
James A. Aries[1,2]
Jeffrey K. Davies[1,2]
Rebecca L. Auer[1]
Simon L. Hallam[1]
Silvia Montoto[1]
Matthew Smith[1]
Belen Sevillano[1]
Vanessa Foggo[1]
Bela Wrench[1,2]
Krzysztof Zegocki[3]
Samir Agrawal[1]
Rifca Le Dieu[1,2]

Edward Truelove[1,2]
Thomas Erblich[1,2]
Shamzah Araf[1,2]
Jessica Okosun[1,2]
Heather Oakervee[1]
Jamie D. Cavenagh[1]
John G. Gribben[1,2]
John C. Riches[1,2,4]

[1]Department of Haemato-oncology, Barts Health NHS Trust, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE
[2]Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom
[3]Department of Haematology, Barts Health NHS Trust, Whipps Cross University Hospital, Whipps Cross Road, Leytonstone, London E11 1NR
[4]The Francis Crick Institute, 1 Midland Road, London, NW1 1AT, United Kingdom

References

1. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/.
2. https://coronavirus.data.gov.uk/.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020.
4. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
5. Gavillet M, Carr Klappert J, Spertini O, Blum S. Acute leukemia in the time of COVID-19. Leuk Res. 2020;92:106353.
6. Spicer J, Chamberlain C, Papa S. Provision of cancer care during the COVID-19 pandemic. Nat Rev Clin Oncol. 2020.
7. Willan J, King AJ, Hayes S, Collins GP, Peniket A. Care of haematology patients in a COVID-19 epidemic. Br J Haematol. 2020;189(2):241-3.
8. Yahalom J, Dabaja BS, Ricardi U, Ng A, Mikhaeel NG, Vogelius IR, et al. ILROG Emergency Guidelines for Radiation Therapy of Hematological Malignancies During the COVID-19 Pandemic. Blood. 2020.
9. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020.
10. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020.

Table 1. Clinical characteristics of the Patients

Clinical Characteristics of the Patients	Patients
Enrolment Site – no. (%)	N = 35
Barts Health NHS Trust	25 (71%)
Homerton University Hospital NHS Foundation Trust	4 (11%)
The London Clinic	3 (9%)
Southend University Hospital NHS Foundation Trust	1 (3%)
Barking, Havering and Redbridge University Hospitals NHS Trust	1 (3%)
Basildon and Thurrock University Hospitals NHS Foundation Trust	1 (3%)
Median age (range) - years	69 (31 – 87)
Sex – no. (%)	N = 35
Male	23 (66%)
Female	12 (34%)
Haemato-oncological diagnosis – no. (%)	N = 35
Multiple myeloma	12 (34%)
Chronic lymphocytic leukaemia/Small lymphocytic lymphoma	5 (14%)
Diffuse large B cell lymphoma	4 (11%)
Acute lymphoblastic leukaemia	4 (11%)
Follicular lymphoma	3 (9%)
Acute myeloid leukaemia	2 (6%)
Mantle cell lymphoma	1 (3%)
Aplastic anaemia	1 (3%)
Myelofibrosis	1 (3%)
Myelodysplastic syndrome	1 (3%)
Monoclonal gammopathy of undetermined significance	1 (3%)
Pre-existing hypogammaglobulinaemia	N = 24
Yes	13 (54%)
No	11 (46%)
Number of lines of treatment – no. (%)	N = 35
Untreated	3 (9%)
1st line treatment	19 (54%)
2nd line treatment	8 (23%)
≥ 3rd line treatment	5 (14%)
Patients on active treatment at time of Covid-19 diagnosis	N = 35
Yes	24 (69%)
No	11 (31%)
Co-existing disorders – no. (%)	N = 35
Hypertension	10 (29%)
Renal failure	5 (14%)
Diabetes	5 (14%)
Previous cancer	4 (11%)
Previous Venous thromboembolism	3 (9%)
Atrial fibrillation	3 (9%)
Ischaemic heart disease	2 (6%)
Asthma	2 (6%)
Valvular Heart Disease	2 (6%)
Chronic lung disease/COPD	2 (6%)
Co-existing non-haematological cancer	1 (3%)
Hyper-obstructive cardiomyopathy	1 (3%)
Liver fibrosis	1 (3%)
Symptoms – no. (%)	N = 35
Fever	27 (77%)
Cough	21 (60%)
Shortness of Breath	19 (54%)
Weakness	5 (14%)
Myalgia	4 (11%)
Diarrhoea	3 (6%)
Coryza	2 (6%)
Chest pain	2 (6%)
Headache	1 (3%)

Vasovagal episode	1 (3%)
Anosmia	1 (3%)

Table 2. Correlation of clinical and laboratory findings with outcome

Clinical/laboratory parameter	Patients	*P* value
Median age (range) - years		
Deceased patients (N = 14)	78 (33 – 87)	<0.0001
Recovered patients (N = 21)	59 (31 – 81)	
Patients on treatment at Covid-19 diagnosis – no. (%)		
Deceased patients (N = 14)	9 (64%)	0.72
Recovered patients (N = 21)	15 (71%)	
Patients on $\geq 3^{rd}$ line treatment – no. (%)		
Deceased patients (N = 14)	3 (21%)	0.37
Recovered patients (N = 21)	2 (10%)	
Median number of major comorbidities		
Deceased patients (N = 14)	2.5 (1 – 4)	<0.0001
Recovered patients (N = 21)	1 (0 – 2)	
Median admission oxygen saturations (%)		
Deceased patients (N = 13)	88 (60 – 100)	0.0038
Recovered patients (N = 17)	96 (88 – 100)	
Median admission haemoglobin (g/dL)		
Deceased patients (N = 12)	108 (53 – 123)	0.46
Recovered patients (N = 17)	103 (78 – 146)	
Median admission neutrophil count (x 10^9/L)		
Deceased patients (N = 12)	5.0 (1.6 – 14.2)	0.0020
Recovered patients (N = 17)	2.1 (0.1 – 10.1)	
Median admission lymphocyte count (x 10^9/L)		
Deceased patients (N = 12)	1.2 (0.3 – 306)	0.048*
Recovered patients (N = 17)	0.5 (0.1 – 1.5)	
Median admission platelet count (x 10^9/L)		
Deceased patients (N = 12)	130 (21 – 244)	0.80
Recovered patients (N = 17)	144 (36 – 280)	
Median admission neutrophil:lymphocyte ratio		
Deceased patients (N = 12)	6.1 (0.0 – 20.7)	0.49*
Recovered patients (N = 17)	3.7 (0.3 – 14.4)	
Median maximum c-reactive protein (mg/L)		
Deceased patients (N = 13)	279 (88 – 367)	0.0006
Recovered patients (N = 17)	102 (3 – 400)	

*A patient with a lymphocytosis due to CLL was excluded for these calculations.