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Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy

Dear Editor,

Infection with the novel coronavirus SARS-CoV-2, resulting in an acute respiratory disease (COVID-19), is the cause of the current pneumonia pandemic, with a rapid rise in cases being reported in the European Union and UK.[1,2] The UK index case was identified on January 31, 2020 and, given the rapid spread and high mortality rate of COVID-19, it is imperative to define the impact on patients with co-existing medical conditions.[3]

Multiple myeloma (MM), the second-most common haematological malignancy, is a cancer of the mature B-cell lineage, and is associated with both cellular and humoral immune dysfunction that renders patients susceptible to infections, especially of the respiratory tract.[4-7] This, coupled with a median age at presentation of 70 years in a population with frequent co-existing medical conditions, means the outcomes of MM patients infected with COVID-19 warrants particular attention. We conducted a fully-anonymised prospective clinical audit where only MM patients with documented symptomatic COVID-19, whether managed in the inpatient or outpatient setting, were reported. All patients were tested within the secondary care setting and were receiving systemic anti-cancer therapy (SACT).

At the time of analysis (May 18, 2020), 75 completed proformas from MM patients who tested swab-positive for COVID-19 had been received (Table I). The median age of COVID-19-positive MM patients was 73 years (range, 47–88), with 27·5% of patients >80 years of age. Where ethnicity details were available (n = 51), most (82%) were Caucasian, with 16% being Afro-Caribbean. 41% of patients were newly-diagnosed MM receiving frontline therapy (NDMM); 24% had relapsed from their frontline therapy and were now receiving second-line therapy (1st REL); and 35% had relapsed and/or refractory disease (RRMM). The median absolute lymphocyte count at presentation with COVID-19 symptoms was 600 cells/μl (range, 0–2500), with 90% of patients demonstrating hypo-gammaglobulinaemia affecting at least 1 sub-class (IgG> IgM>IgA). The male/female ratio was 1·5, but varied with age (<75 years ratio 2·33 vs. >75 years ratio 0·94) as a consequence of significant age difference between the groups (P = 0·049).

The median time from the UK Index case to COVID-19 symptoms was 54 days (range, 23–88). 20·5% of patients did not have a temperature on presentation but did have a cough, and 16% reported GI symptoms, with 20·5% of patients acquiring COVID-19 whilst an inpatient for other reasons. 75% had evidence of pulmonary infiltrates primarily detected by chest radiograph. All but three patients were admitted for clinical care. Systemic anticancer therapy (SACT) was stopped a median of 0·5 days (range, 5–23) after the onset of COVID-19 symptoms. Only nine of 70 patients received critical care support, with five patients requiring non-invasive ventilation, two of whom escalated to invasive ventilation and four patients going straight to invasive ventilation, with all nine patients dying. Six patients had clinical/laboratory features of cytokine release syndrome.[8,9] One patient was treated with ruxolitinib, but did not survive; one patient received tocilizumab (recovered); and four patients received supportive care only, none of whom survived. Only one patient received treatment with hydroxychloroquine.

Table I. Patient characteristics

Median age, months (range)	73 (47–71·2)
Sex	
Male	45
Female	30
Ethnicity (*n*)	
Caucasian	41
Afro-Caribbean	8
Asian	2
Other	0
Disease Stage (*n*)	
NDMM	31
1st Rel	18
RRMM	26
Median time from diagnosis, months (range)	28·3 (0–195)
ISS at diagnosis (*n*)	
I	12
II	28
III	27
Not known	7
High risk (*n*)	
Number	19
Del17p	6
t(4:14)	3
1q+/1q−	5
Other	5
Creatinine Clearance (mls/min) at diagnosis (range)	55 (15–157)
Prior Lines of Therapy (*n*)	
Median (range)	1 (0–5)
Prior ASCT	23
PI-based	27
IMID-based	39
Daratumumab exposed	16
Current SACT (*n*)	
ASCT	2
PI-based	16
IMiD-based	15
PI/IMiD-based	16
Daratumumab-based	16
Other	4
Receiving prophylactic antibiotics at COVID-19 positivity (*n*)	
Yes	44
No	28
N/K	3

N/K, not known; PI, proteasome inhibitor (bortezomib, ixazomib, carfilzomib); IMiD, Immunomodulatory drug (thalidomide, lenalidomide, pomalidomide; NDMM, newly diagnosed MM; 1st Rel, first relapse MM; RRMM, relapsed &/or refractory MM.

Caution should be raised over the use of anecdotal experience to influence clinical practice, and even in these difficult times, we need to generate evidence from well-designed clinical trials.

Currently, the UK mortality rate for COVID-19 is 14·5%, with an all-cancer mortality rate of 5·6% (https://coronavirus.data.gov.uk/). The impact of COVID-19 on specific cancers, especially blood cancers, is not known. In our cohort to date, 41 patients (54·6%) have died. The median time from symptom onset to death was 8·5 days (range, 0–23), and for those who have died, the median length of stay (LoS) was 7 days (range, 0–57), compared to those who survived COVID-19 infection who had a median time from symptom onset to discharge of 7 days (range 0–42) and a median LoS of 6·5 days (range, 0–21). The median age of patients who have died was significantly higher than those who survived [78 years (range, 51–88) compared to 66 (47–88); $P = 0{\cdot}017$; Fig 1A]. 17 out of 24 (71%) patients >80 years died, compared to 24 out of 51 (47%) patients <80 years. This reflects the national mortality age impact. It is important to note a greater representation of females with MM who have died, which is at odds with the national picture.

Co-existing medical conditions have been linked to outcomes from COVID-19.[3] There was a median of 1 (range, 0–4) comorbidities in the group, and 0/1 comorbidities reported in 60% of the >80 year old cohort. Hypertension was the commonest comorbidity (41·3% of patients), and a greater level of comorbidity was seen in those who have succumbed to COVID-19 (Fig 1B). A disproportionate level of COVID-19-related mortality is noted in patients of Afro-Caribbean origin in our cohort (Fig 1C) compared to Caucasian patients, but extreme caution is advised in relation to over-interpreting this data, given the actual low numbers of patients of non-Caucasian origin ($n = 10$) reported in this audit despite the prevalence of MM.[10]

RRMM may be at greatest risk of an adverse outcome from COVID-19.[11] The median time from diagnosis to COVID-19 infection was 28·3 months (range, 1–195), with no significant difference between those who survived and those who did not. However, 54·8% of symptomatic COVID-19 patients with NDMM did not survive, compared to 50% of RRMM. This may reflect a greater impact of tumour-induced immune suppression and infective risk associated with NDMM.[12-14]

This early review of emerging, real-world data highlights the impact of COVID-19 in patients with MM in the UK. There is a higher-than-expected mortality from concomitant viral infection, though this may represent the more vulnerable and symptomatic of MM patients presenting to secondary care and over-estimate the true mortality, given the absence of primary care data. There is currently insufficient data to extrapolate whether the type of SACT being received has any impact on the severity of infection, which may be important in determining longer-term management of MM patients during the COVID-19 pandemic.

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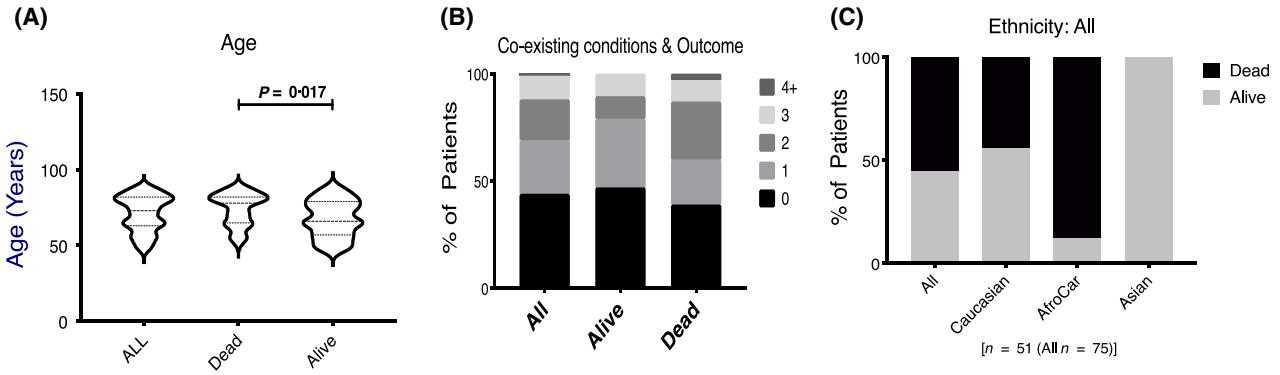

Fig 1. (A) Violin-plots demonstrating the distribution of age amongst MM patients as a complete cohort (All) and by outcome. (B) Number of comorbidities (diabetes, cardiovascular disease, hypertension, chronic lung disease, obesity and smoking) in MM patients within the overall cohort (All) and by outcome. (C) The ethnicity of the complete cohort (All) and by outcome.

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Managing sickle cell patients with COVID-19 infection: the need to pool our collective experience

Coronavirus disease 19 (COVID-19) has posed unparalleled challenges for healthcare communities, the general population and, in particular, for patients suffering from various comorbidities. Patients with haematological disorders, both benign and malignant, need special attention during this crisis, to ensure uninterrupted delivery of optimal care.[1]

Sickle cell disease (SCD) is the most common inherited anaemia in the USA and the UK with an approximately 80 000–100 000 and 12 500–15 000 individuals living with the disease in the USA and UK respectively.[2,3] Patients with SCD are prone to an increased risk of infections that can trigger acute chest syndrome (ACS) and related pulmonary complications. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the agent responsible for the current COVID-19 pandemic, has been found to be a trigger for the development of ACS and veno-occlusive crisis (VOC) in patients with SCD.[4–8] We hereby discuss the recently reported literature on patients with SCD who developed COVID-19.

Our literature review showed 19 SCD patients with COVID-19 were reported from December 2019 till 17 May 2020,[2,5,6,9-11] (Table 1). The largest case series by McCloskey *et al*. included 10 patients, six with confirmed COVID-19 (laboratory-confirmed COVID-19, reverse transcription polymerase chain reaction (RT-PCR)-positive) and four with suspected COVID-19 (clinical COVID-19 based on laboratory/imaging findings).[7] Similarly, in Nur *et al*.'s two patient series, one patient with SCD required repeat RT-PCR swab testing to confirm COVID-19.[8] Patients received a varied combination of supportive care for SCD-VOC/ACS with hydration, analgesics, empirical broad-spectrum antibiotics, red blood cell exchange, and simple blood transfusions. With regard to COVID-19 pneumonia, most of the patients (15/19) required oxygen support ranging from low flow (2 l/min) to high flow, non-invasive and mechanical ventilation in critically ill patients. Only one patient from Hussain *et al*.'s series required mechanical ventilation. The patient improved and was discharged home after 13 days of hospital stay.[6] Tocilizumab (IL-6 inhibitor, an investigational drug for COVID-19) and hydroxychloroquine were used in two and three patients respectively.[4–6,12] A single dose of tocilizumab was used (8 mg/kg) in both the patients with a good response.[6,11]

Except for one death reported by McCloskey *et al*. (a 57-year-old person with a history of stroke, bedbound with a neurological compromise), the rest of the 18 patients had a complete recovery from COVID-19.[7] Barring one improved patient, reported by Nur *et al*., who was still hospitalized at the time of reporting of the case, the remaining 17 patients were successfully discharged home with a median hospital stay of 7·2 days.[8]

ACS is considered one of the leading causes of death in patients with SCD. Thromboembolism, pulmonary infection, rib infarction and fat embolism are common causes of ACS. Experience from the 2009 H1N1 influenza pandemic has shown the H1N1 influenza virus to be a trigger for ACS with a significant proportion of SCD patients requiring intensive care support.[9] In most of the COVID-19 patients, the disease presents in the milder form. Only in a small percentage of patients is COVID-19 pneumonia likely to cause hypoxia and ventilation-perfusion mismatch. SCD has a complex pathogenesis leading to vaso-occlusion and hypercoagulability, which can result in serious complications and multiple organ dysfunction (Fig 1). Based on this vicious cycle, it is likely that COVID-19 patients with SCD will have a poorer outcome than patients without COVID-19, but more evidence is required to confirm this.

From lessons learned from previous viral outbreaks and currently available literature on the COVID-19 pandemic, SARS-CoV-2 viral infection should be considered as one of the important triggering factors for sickle-cell crisis. Any patient with SCD presenting with ACS/VOC symptomatology should be evaluated for COVID-19 with a SARS-CoV-2 PCR testing.[8]

SCD is the most common genetic disease in the world, and we believe that SCD patients suffering from COVID-19 are underreported. Patients with SCD have various reasons (functional hyposplenism, vasculopathy and recurrent VOCs) for an impaired immune system, which puts them in the 'high-risk category' of acquiring SARS-CoV-2, like patients with other blood disorders.[13,14]