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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.

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Dear Editor,

Infection with the novel coronavirus SARS-CoV-2 virus resulting in an acute respiratory disease (COVID-19 disease) 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 the 31st of January, 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 anonymized 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 receiving systemic anti-cancer therapy (SACT).

At the time of analysis (18th of May 2020), 75 completed proformas from MM patients who tested swab-positive for COVID-19 had been received (Table 1). 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 now receiving second line therapy (1st REL), and 35% had relapsed &/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 3 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 9 of 70 patients received critical care support, with 5 patients requiring non-invasive ventilation, 2 of whom escalated to invasive ventilation and 4 patients going straight to invasive ventilation with all 9 patients dieing. 6 patients had clinical/laboratory features of cytokine release syndrome (8, 9). One patient was treated with ruxolitinib but did not survive, one patient received tocilizimab (recovered) and 4 patients received supportive care only, none of whom survived. Only 1 patient received treatment with hydroxychloroquine. 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=0.017, Figure 1A). Seventeen out of 24 (71%) patients >80 years having 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 comorbidity 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 (Figure 1B). A disproportionate level of COVID-19 related mortality is noted in patients of Afro-Caribbean origin in our cohort (Figure 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.

Word Count: 1000

Table 1. 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**	**1 (0-5)**
(range)		**23**

		Prior ASCT	**27**
		PI-based	**39**
		IMID-based	**16**
		Daratumumab exposed	
Current ASCT	**SACT**	**(n)**	**2**
			16
		PI-based	**15**
		IMiD-based	**16**
		PI/IMiD-based	**16**
		Daratumumab-based	**4**
		Other	
Receiving prophylactic antibiotics at COVID-19 positivity (n)			
		Yes	**44**
		No	**28**
		N/K	**3**

Key: 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**;**

Figure 1. (A) Violin-plots demonstrating the distribution of age amongst MM patients, as a complete cohort (All) and by outcome. (B) Number of comorbities (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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Figure 1A

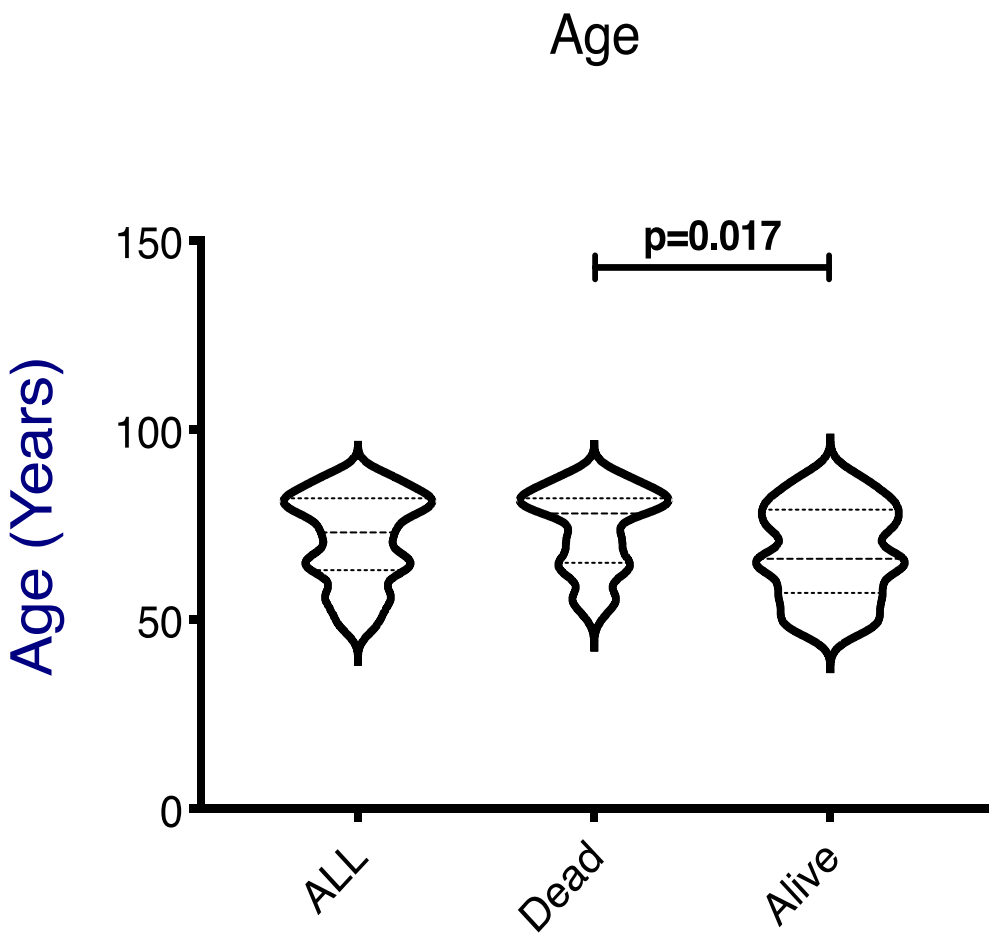


Figure 1B

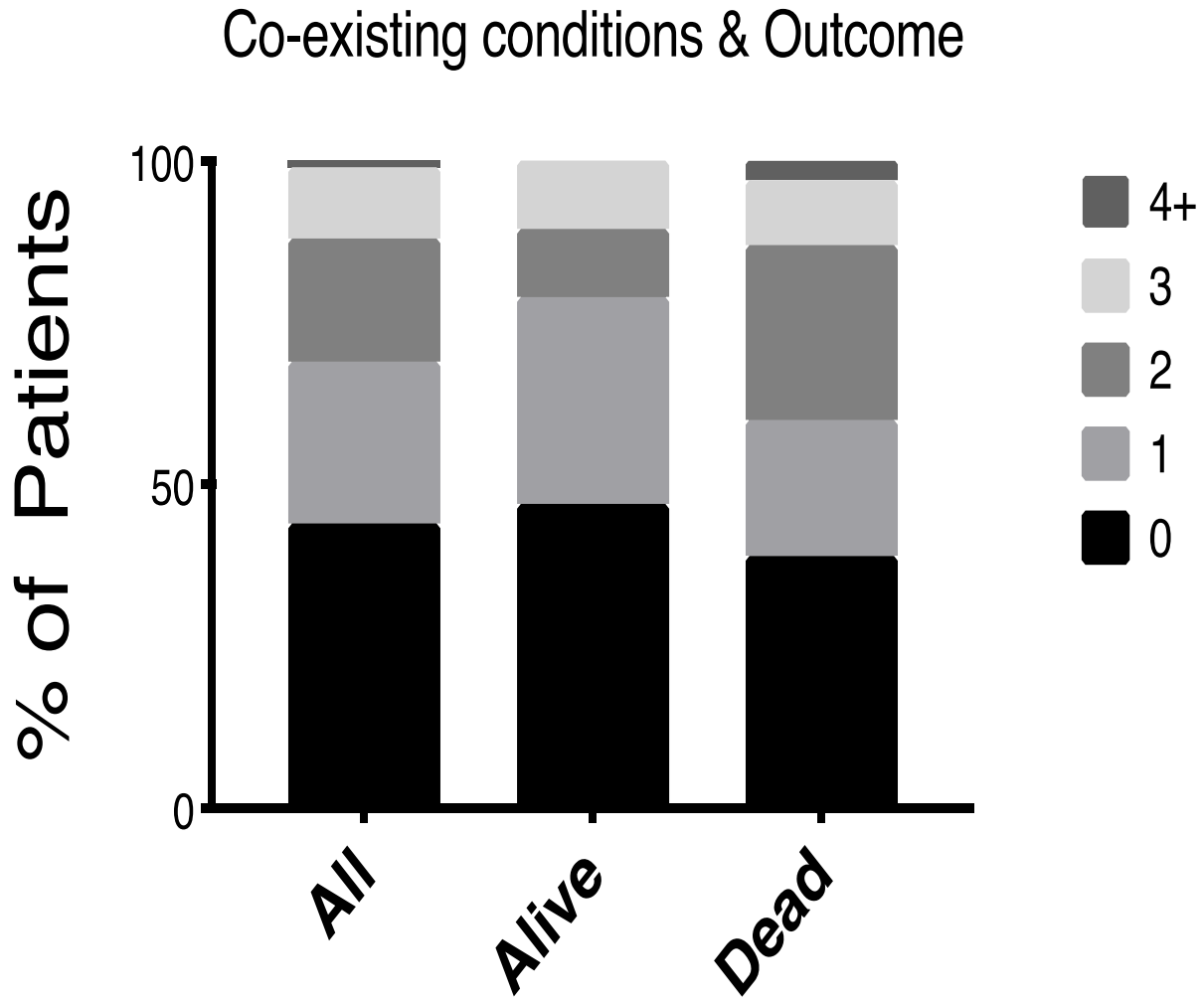
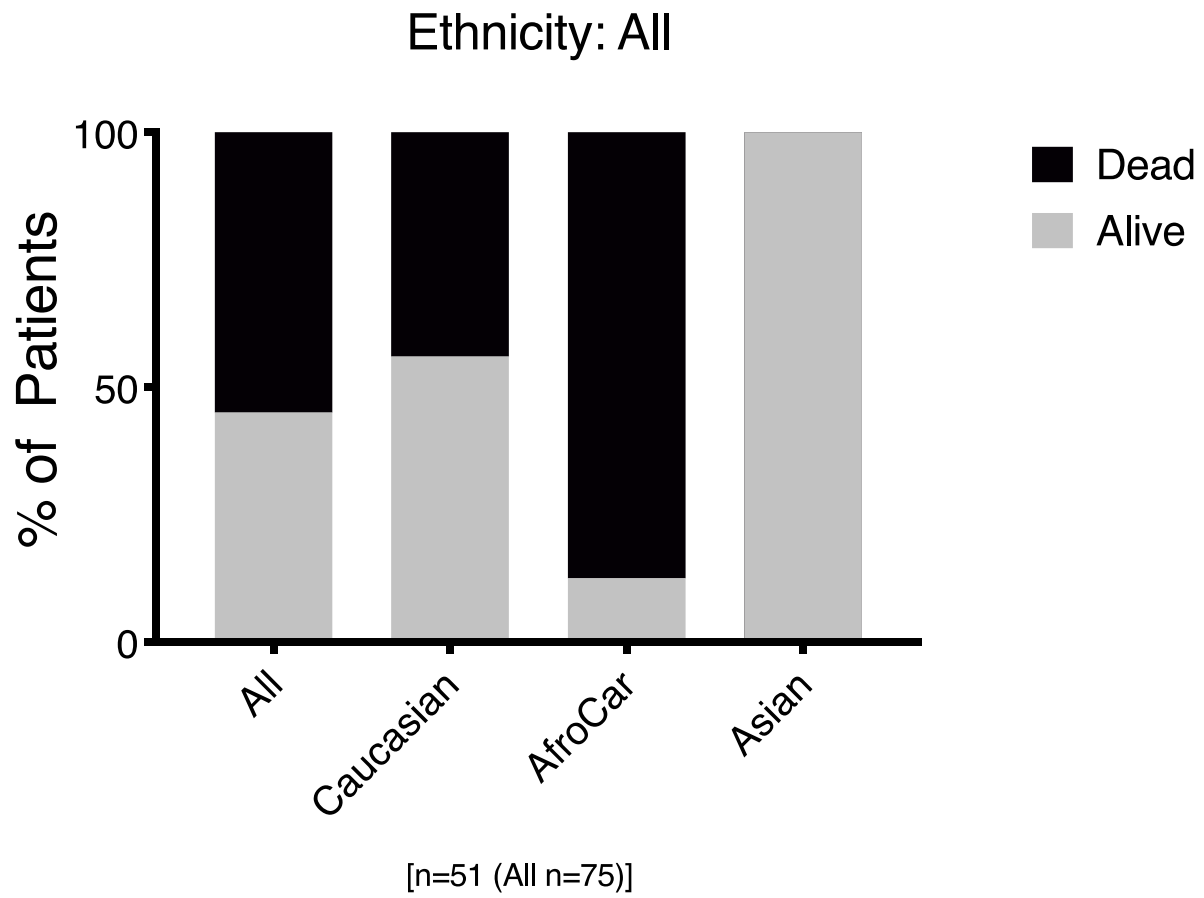

Co-existing conditions & Outcome
% of Patients
100
50
0
All
Alive
Dead
4+
3
2
1
0

Figure 1C


Ethnicity: All
100
50
0
% of Patients
All
Caucasian
AfroCar
Asian
Dead
Alive
[n=51 (All n=75)]