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COVID-19 in Hematology patients: Real World Experience in Hospitals in the UK West Midlands

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Abstract

Objectives: This study aimed to understand the consequences of coronavirus disease 2019 (COVID-19) in patients diagnosed with haematological conditions, malignant and non-malignant.

Method: A detailed insight into the first 112 patients with comorbidity of haematological conditions and COVID-19, admitted into nine National Health Services Trusts in the West Midlands Area of the United Kingdom, between 1st of March 2020 and 31st May 2020.

Results: In the study cohort, 82% of patients had a malignant haematological disorder whilst 18% had a non-malignant haematological condition. Increasing age, breathlessness, reduction in oxygen saturation under 90% and abnormal chest x-ray were independently associated with higher mortality. Other long term co-morbidities did not present adverse impacts in this population. Survival analysis demonstrated that the COVID-19 severity score had a significant adverse correlation on patient outcome. COVID-19 patients who were classified as low risk, based on their primary haematological condition, showed significantly shorter survival time than those in the high risk category, which might be due to the shielding strategy for high infection risk patients.

Conclusion: The 55% overall mortality in this cohort suggests that patients with haematological conditions had a higher mortality rate than patients with other acute, chronic or long term conditions.

Significance: Previous studies have suggested poor outcomes for COVID 19 infection in patients with haematological cancers, with short term mortality rates ranging from 32% to 62%. We report here the outcome of COVID-19 infection in patients with haematological conditions with both malignant and non-malignant, admitted to secondary care in acute care hospitals of the UK West Midlands. This study also examined the impact of chemo immunotherapy on outcomes from COVID-19 infection. This will be useful information to guide decision making during this second UK national lockdown.

Keywords: Coronavirus pandemic • SARS-CoV-2 • COVID-19 • Haematological conditions • COVID-19 Severity and survival analysis

Introduction

Human infections with the new type of Coronavirus classified as 'severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were first reported in December 2019 [1]. The World Health Organisation (WHO) named the syndrome produced by the virus 'Covid-19.' As infections rapidly proliferated, it became apparent that there were several specific patterns of disease progression [2]. Respiratory involvement is common, but ranges from a dry cough to breathlessness, low oxygen saturations and lung field changes on X-ray [3]. The majority of those infected experience only mild to moderate symptoms; cough, sneezing, malaise and the initially unknown

but now well recognised loss of taste and smell, but around 5-10% of cases experience severe or critical illness including pneumonia and respiratory failure [4,5]. Although some cases of rapid progression have been reported, the pattern most commonly observed has been mild to moderate disease at presentation followed by a severe worsening of respiratory function 9-12 days post onset [2,5,6]. It has been further noted that worsening of respiratory function is associated with raised D-dimer levels, raised prothrombin time, low white cell count and X-ray opacities [5].

Faced with this new epidemic, with no established treatment strategies, hospitals around the world, despite massive workloads, began collecting prospective data to be later analysed to inform the future management of this condition. This data was collected at a time of great stress, and on a constantly moving stage, but has allowed important lessons to be learned. Publication of the findings from a number of hospitals in a range of countries provides the potential to combine these studies for meta-analysis, potentially providing stronger evidence to improve our management of this condition [7-9].

Prospective data collection and review has already produced clear benefits; the importance of lung function at presentation quickly emerged as an important prognostic factor [10]. Evaluation of COVID-19 therapy within the 'RECOVERY' trial, showing benefits of dexamethasone therapy in patients requiring respiratory support [11] has raised many questions, as steroids are an integral part of many chemotherapy regimens.

This study explored the trends that emerged from 112 patients with haematological conditions (malignant and non-malignant) reviewed at haematology services at the nine hospitals in the West Midlands region of the United Kingdom, from the start of the outbreak, in whom COVID-19 infection had been confirmed. The objectives of this study were three fold: First, examine the mortality of patients with haematological conditions with SARS-CoV-2 viral infection, second, investigate the possible factors that may significantly impact the outcome in haematology patients with COVID-19 and lastly, examine the likelihood of any adverse role of recent chemo-immunotherapy continuation or cessation.

Method and Data Description

This was a multicentre retrospective study, carried out in nine hospitals in the West Midlands under the West Midlands Research Consortium (WMRC). All adult patients with underlying haematological disorder (both malignant and non-malignant) and confirmed COVID-19 diagnosed between 1st March 2020 and 31st May 2020 were included in the study. A standardised data collection form was used across all nine hospitals for collecting demographic, clinical, laboratory, radiological and outcome data. SARS-CoV-2 was diagnosed by real time polymerase chain reaction (RT-PCR). The study received ethical clearance waiver for the audit of the medical records from the research and development committees of all

participating hospitals.

Patients were categorized based on their underlying haematological conditions to have high, intermediate, or low risk disease status. All patients on active chemotherapy, having relapsed and or refractory disease, acute myeloid leukaemia with adverse cytogenetics, post auto or allogeneic transplant, extranodal T-cell lymphoma, multiple myeloma, post splenectomy and sickle cell disease were categorized as high risk. Intermediate risk included Hodgkin's and non-Hodgkin's lymphoma patients not on any treatment, myeloproliferative neoplasms and myelodysplastic syndrome. The low risk cohort were patients with non-malignant haematological conditions and patients in complete remission who had completed treatment more than six months ago which was adapted from the 2012 published categorisation for people diagnosed with haematological conditions [12]. Patients were identified as having severe COVID-19 infection on the presence of any one of the following: oxygen saturation ≤90% on room air, respiratory rate higher than or equal to ≥ breaths per minute; bilateral infiltrates on lung imaging as defined in WHO guidelines [13].

Statistical analysis was carried out using IBM SPSS® software version 26 and STATA SE®16. Kruskal–Wallis tests were used for comparing observations for the hazard event, i.e. survival and non-survival. For testing of three groups, the ANOVA one way test, coupled with the Tukey post-test was utilized. Using logistic regression and the Cox-proportional hazards model, the impact, and the survival estimates of these various factors was studied.

Results

Preliminary findings were presented in a letter earlier to attract specialist's attention to our findings for this unique population of patients diagnosed with haematological disorders [14]. Comparing outcomes (alive or dead) for patients from black, Asian and minority ethnic groups (BAME) and white ethnic background, there was no significant difference identified in this study, with 56% from each category (BAME or White) died. However, 84% of this study cohort was white Caucasian.

Table 1 summarizes the general characteristics of the patients: the median age of the study cohort was 70 years (IQR 61,78; range 18,95). Men (57.5%) were the majority compared to women (41.5%). Regarding ethnicity, 76% of patients were Caucasian. There were 82% of patients who had a malignant haematological disorder whereas 18% had non-malignant haematological conditions. The most common haematological condition in our cohort was multiple myeloma (16.8%) followed by 13.2% of acute myeloid leukaemia (AML) and 13.2% of diffuse large B-cell lymphoma (DLBCL). Most of the patients (60%) fell into the high infection risk category due to their primary haematological disease. The commonest co-morbidities in this study cohort were hypertension (41%), ischaemic heart disease (22%), diabetes mellitus (21%), chronic lung disease (20%) and obesity (10%).

Population	Observation	Proportion out of patients with available data	Total Number with available data	Number of patients Survived with available data	Number of patients Died with available data
Sex	Male	57.50%	112	31	34
	Female	41.50%		18	29
	Not recorded	1%		1	
Ethnicity	White	76%	102	36	40
	Black	4%		2	3
	Asian	10%		5	6
	Not recorded	10%		7	4
Haematological Condition	Malignant	82%	112	42	51
	Non-Malignant	18%		8	12

Non-Haem co-morbidities	Diabetes	21%	112	9	15
	Ischaemic Heart Disease (IHD)	22%	112	10	15
	Hypertension	41%	112	18	28
	Chronic lung disease	20%	112	7	16
	Obesity	10%	100	7	4
	Smoker	12%	100	6	8
Hospital admission	Admitted	96%	112		
	Not admitted (died or short stay)	4%			
Respiratory Support	Intubated-ventilated	11%	12	2	6
	Respiratory support not-intubated	6%	7	5	9
Time from onset of symptoms to outcome in days	Time to recovery (median–SD) and range	14(9.14) 1-34	94		
	Time to death (median–SD) and range	13(12.83) 1-65			

Table 1. Baseline Population Characteristics Table 1. Baseline Population Characteristics

Patients, who died, had a greater proportion of symptoms. Of all patients, 30% had no documented co-morbidity. The symptoms experienced on admission are detailed in. The most common were shortness of breath (58%), cough (43%) and fever (33%). Only 4.4% of patients were completely asymptomatic and 63% of patients had severe COVID-19 symptoms at presentation. There were 4% of patients were either seen as outpatients or died before admission, the remaining 96% of patients were admitted to hospital. The median time from symptom onset to hospital admission was two days (range 0-35 days), 17% of patients required admission to a high dependency or intensive care unit, with 11% requiring invasive ventilation. The median number of days of intensive therapy unit (ITU) stay was seven days. The median age of patients admitted to ITU was 61.5 years. Based on the UK government COVID-19 statistical data (coronavirus.data.gov.uk) on the 19/6/2020, there were 300,469 confirmed COVID-19 cases and 42,285 deaths, indicating mortality rate of 14% of all infections and 30% for hospital patients. In this study population of haematological patients', the mortality was 55% (RR 1.8). From patients deemed as high risk for poor prognosis (n=68), 59% died. Under the system in use in local National Health Service (NHS) Trusts at the time, 91 patients were categorised as severe and 59% of those died. The study sample had a small number of patients with non-malignant conditions (n=20). Of those with malignancy, 53% died compared to 60% of those with non-malignant conditions. This preliminary finding may suggest that pre-existing haematological conditions influence prognosis and survival outcomes (Table 2).

Symptoms	Proportion out of patients with available data	Number of patients with available data
Fever	33%	100
Cough	43%	100
Myalgia	76%	100
Gastrointestinal	18%	92
Breathlessness	58%	111
Positive finding of respiratory imaging	20%	108
Heart rate equal and above 120 bpm	5%	92
Respiratory rate equal and above 24 rpm	23%	92
Oxygen saturation (SpO2) equal and under 90%	16%	92

Table 2. COVID-19 Symptoms on Presentation

The study cohort chest x-ray findings (p=0.002), pulmonary infiltrates on computerised tomography (CT) scan (p=0.023), age (p=0.032) and obesity (odd's ratio: 2.34) were independent variables and significant predictors of mortality. Risk factors identified in other series such as diabetes or hypertension or ethnicity, were not associated with an adverse outcome in this cohort of patients diagnosed with haematological conditions pre-COVID19. Table 3 reports on the significance value of the various observations categorized in two groups, (survival and death). It shows low oxygen saturation, increased respiratory rate and high C-reactive protein (CRP) were statistically significant predictors of outcome. The prothrombin time (PT) was slightly lower, the activated partial thromboplastin time (APTT) was slightly higher, and the Fibrin Degradation Fragment (D-dimer) was slightly higher in those died suggesting greater susceptibility to thromboembolism. Additionally, the results showed increased risk of clotting in both dead and surviving patients. While inflammation can increase ferritin levels, in our sample ferritin elevation was an expected finding, considering the population type and the haematological conditions present. In this study lymphocytes showed slight elevation in those died but neutrophils remained within range. Lastly the elevation in lactate dehydrogenase (LDH) may indicate tissue damage.

Continuous Variables			Categorical Variables		
Observations	test-statistic	p-value	Observations	Chi-square	p-value
Heart Rate	1.35	0.181	Breathlessness	6.416**	.011
SpO2	-2.52**	0.015	Confirmatory CT of Pulmonary infiltrates	4.921**	.027
Respiratory Rate	3.44***	0.001	Chest x-ray positive findingsa	8.750***	.003
Lymphocyte	1.13	0.263			

Neutrophil	0.70	0.488			
LDH	1.08	0.29			
CRP	1.81*	0.073			
Ferritin	-0.54	0.592			
PT	-0.40	0.688			
APTT	1.64	0.107			
Fibrinogen	-1.70	0.096			
D Dimers	1.08	0.296			

Note: *** indicates significant at 1 percent level, ** indicates significant at 5 percent level and * indicates significance at 10 percent level. The p-values are provided in parenthesis. a Positive i.e. abnormal finding on x-ray

Table 3. Univariate Analysis of continuous and categorical observations

To gain deeper insights on the survival rates and the marginal effects of each of the parameters, we examined the impact of age, COVID-19 severity (based on the WHO classification) and malignant or non-malignant haematological condition on mortality. Using logistic regression and the Cox-proportional hazards model, the impact, and the survival estimates of these various factors were examined. We demonstrate that the mean survival time for the disease based risk category are 11 days, 13 days and 7 days for categories, High, Intermediate and Low, respectively. The mean survival time for the COVID-19 severity category is 11 days for both severe and non-severe classification. The mean survival times for the malignancy classification are 11 days and 10 days for malignant and non-malignant categories, respectively [13] (Figure 1).
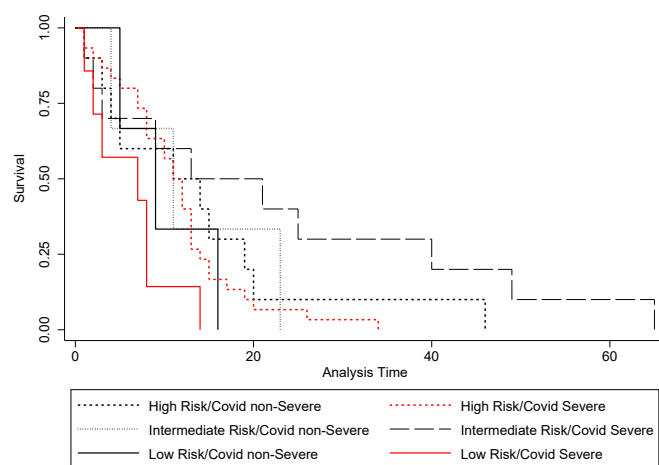

Figure 1. Kaplan-Meier survival estimates of COVID-19 mortality

Figure 1 shows the graph of the survival functions. The mean survival time for the disease-based risk category are 11 days, 13 days and 7 days for categories, High, Intermediate and Low, respectively. The mean survival time for the COVID-19 severity category is 11 days for both severe and non-severe classification. The mean survival times for the malignancy classification are 11 days and 10 days for malignant and non-malignant categories, respectively. The X-axis represents the Analysis Time, which is the duration in days between the dates of onset of COVID-19 symptoms and death.

Using logistic regression and a predictive marginal model, key factors affecting mortality were examined. Table 4 reports on the odds ratios and the marginal effects of our estimates model. An odds ratio of greater than one indicates that the variable has a positive impact on death. COVID-19 severity has the highest impact on mortality in our cohort. The marginal effect shows that, while severity of COVID-19 and age increases the chances of their death, by 24% and 15%, respectively, non-malignancy

reduces the mortality. The Wald Chi-square statistic suggests a significant relationship between the independent variables and mortality.

Factors	Odds Ratio (OR)	Std. Err. of OR	Marginal Effect (dy/dx) (ME)	Std. Err. of ME
COVID-Severity	2.963	1.251*** (0.010)	0.240	0.083*** (0.004)
Age	1.972	0.811* (0.098)	0.150	0.087* (0.084)
Non-Malig-nancy	0.467	0.177** (0.045)	-0.168	0.078** (0.031)
Wald chi2(3)	11.45***			
p-value	0.0095			

Note: The table presents the robust logistic regression model results along with the marginal effects. An odds ratio of greater than one suggests that the variable has a positive impact on the event and a value of less than one state otherwise. The Wald Chi-square statistic suggests that lays significant relationship between the independent variables and the event. *** indicates significant at 1 percent level, ** indicates significant at 5 percent level and * indicates significance at 10 percent level. The p-values are provided in parenthesis.

Table 4. Odds ratios and the marginal effects of the key factors

When a multivariate analysis was performed to examine the odds ratio of the various significant factors, we found that increase in respiratory rate (p=0.010) and COVID-19 severity (p=0.008) were significant at 1% level. Breathlessness (p=0.002), heart rate (p=0.002), oxygen saturation (SpO2, p=0.035), pulmonary infiltrates (CT) (p=0.026), APTT (p=0.016) high risk group (p=0.019) indicated significant at 5% level. Obesity (p=0.058), chest imaging positive (p=0.012), age and high risk group (p=0.080), Fibrinogen (p=0.086) indicates significance at 10% level (13). Of interest is that obesity negatively impacted on survival? In our model, we also included several interaction variables that significantly affected COVID-19 mortality. Amongst the variables concerned, COVID-19 severity along with disease bask risk profile had the most significant impact (Figure 2).
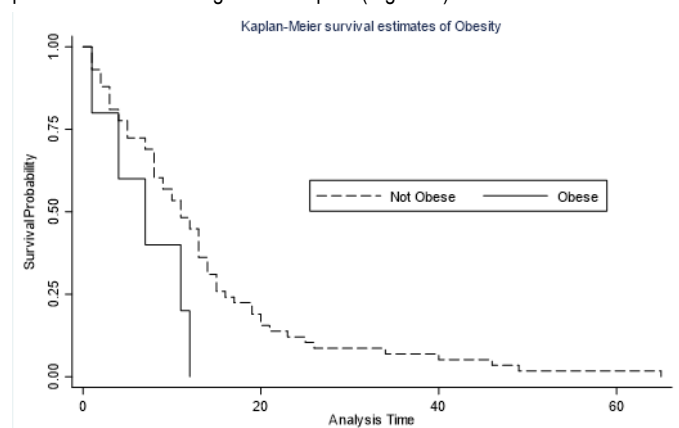

Figure 2. Kaplan-Meier survival estimates of obesity

The X-axis represents the Analysis Time, which is the duration in days between the dates of onset of COVID-19 symptoms and death'.

Discussion

This is the largest series of patients with both malignant and non-malignant haematological conditions infected by SARS-CoV-2. This study highlights patients with haematological conditions may present with COVID-19 differently to the general population. Fever was observed in 33% of our patient cohort as compared to 71% in the Clinical Characterisation Protocol UK (CCP-UK) study [15]. Similar to previous reports in the general

population and specific blood cancers, older age was associated with higher mortality in our cohort as well. However other co-morbidities like diabetes or hypertension did not confer adverse outcome [16]. Interestingly there was no suggestion of poor outcomes in BAME patients; this probably reflects the small sample size of this patient group in our cohort.

Overall mortality in our cohort was 55%. This higher mortality could be due to this cohort being retrospectively reported during the early peak of COVID-19 pandemic in our region. Also, West Midlands was the second most affected region in the country. Another factor is that polymerase chain reaction (PCR) testing to detect COVID-19 infection early in the peak was reserved for unwell patients attending hospital, and this study is likely to significantly under report outpatient and less symptomatic cases. Only a small proportion of this study cohort had their oxygen support data was collected and only small proportion of those received ITU support, as 10.7% compared 18% UK wide [15]. Similar higher mortality among patients with haematological malignances was recently reported by the Italian group [17]. Initial results of the RECOVERY trial [11] have shown survival benefit from the use of dexamethasone in the general population and the WMRC is eagerly waiting to see if this result is also applicable for patients with haematological conditions.

Atypical presentation, noticeably lower proportion with fever (33%) with of COVID-19 as highlighted in our series may have led to delay in patients seeking medical attention. Also, strict instructions to shield may have led to delayed presentation. Mortality observed in disease specific cohorts like chronic lymphocytic leukaemia (CLL) is around 35% which is lower than our cohort (55%). This may be due to the possible protective effect of Bruton's tyrosine kinase (BTK) inhibitor therapy in CLL patients [16,18]. This study results underlines the importance of paying close attention to inflammatory markers and identifying signs of developing coagulopathy [19].

Conclusion

As the pandemic has developed many lessons have been learned and guidelines have evolved. The outcomes identified are still cause for concern and reflection. In this series the presence of lung infiltrates and other underlying lung pathology denotes a particularly high risk group. Contrary to expectations, the study cohort highlights that being on systemic chemotherapy did not confer excess risk of mortality. This suggests primary therapy for the haematological condition could be possibly continued to avoid adverse impact on their underlying haematological condition.

Study limitation

This study was carried out rapidly at the height of the pandemic, where the uncertainty and the workload were immense. As a result, not all data parameters were available for every patient. This report also reflects the outcome of hospital managed patients. This may not mirror the outcome for haematological patients in the community. Despite these limitations, to the best of our knowledge this is one of the largest reports describing the outcome in COVID-19 in malignant and non-malignant haematology patients from UK.

Acknowledgement

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