COVID-19 in haematology patients

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COVID-19 in Haematology patients: A Multi-centre West Midlands Clinical Outcomes Analysis on Behalf of West Midlands Research Consortium

Running title: COVID-19 in Haematology patients

Since first encountered, it has been clear that whilst many patients with COVID-19 experience relatively minor symptoms, some develop more serious disease.[1-2] Studies have suggested that oncology patients, including haematological malignancies, have increased risk of severe COVID-19 disease with increased morbidity and mortality.[3-5]

This retrospective study, conducted by clinicians and researchers from nine West Midlands hospitals, included all adult patients with both an underlying haematological disorder and confirmed COVID-19, diagnosed between 01/03/2020 and 31/05/2020. A standardised data collection form collected demographic, clinical, laboratory, radiological and outcome data. SARS-Cov-2 was diagnosed by RT-PCR. Ethical clearance waiver for the audit was received from all hospitals.

Patients were categorized based upon their underlying haematological conditions; those 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 classified 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 having completed treatment >6months ago, adapted from the 2012 categorisation by Armand.[6] Severe COVID-19 infection was classified on the presence of any one of: oxygen saturation ≤90% on room air, respiratory rate ≥24 breaths per minute; and/or bilateral infiltrates on lung imaging as defined in WHO guidelines.[7]

Statistical analysis used IBM SPSS® version 26 and STATA SE®16. Kruskal–Wallis tests compared 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.

The median age 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 with a malignant haematological disorder whilst 18% had non-malignant conditions. 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%), and 30% had no documented co-morbidity. The most common symptoms experienced on admission were shortness of breath (58%), cough (43%) and fever (33%). Only 4.4% of patients were asymptomatic and 63% of patients had severe COVID-19 symptoms at presentation. The UK government COVID-19 data (coronavirus.data.gov.uk) on 19/6/2020 reported 300,469 confirmed COVID-19 cases and 42,285 deaths, indicating 14% mortality for all infections and 30% for hospitalised patients. Our mortality was 55% (RR 1.8).

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. Our study finds that low oxygen saturation (p =0 015), increased respiratory rate (p=0.001) and high C-reactive protein (p=0.073) were statistically significant predictors of mortality. Other

factors that were statistically significant includes breathlessness (p=0.011), confirmatory CT of pulmonary infiltrates (p=0.27) and patients showing abnormal finding on x-ray (p=0.003). The details are provided in the supplement. A multivariate analysis examined the odds ratio of the various significant factors (Table I).

Table I: Predictive Analysis on in-hospital mortality on multivariate model

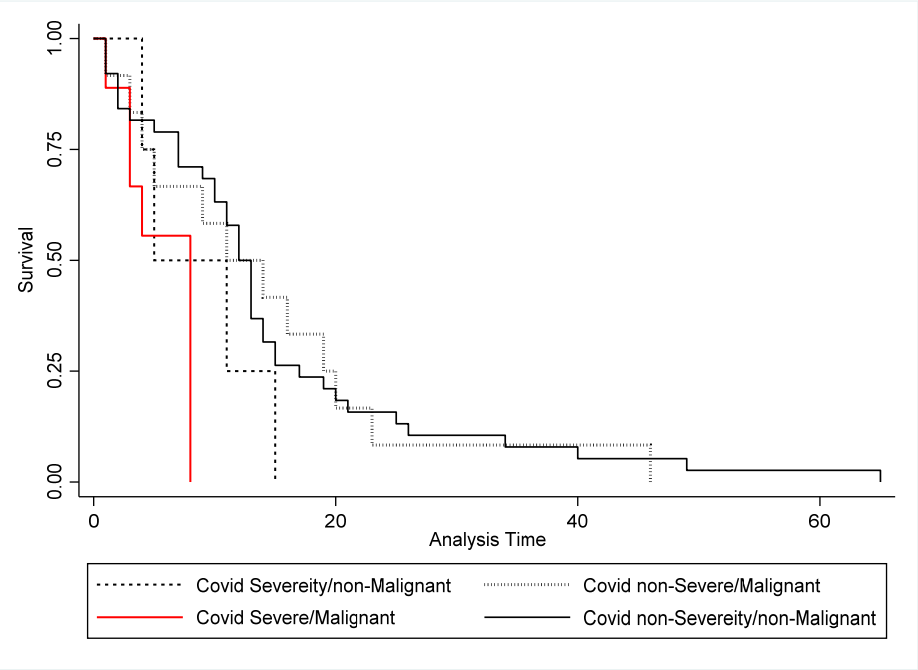
Variables	Odds Ratio	Std. Err.
Breathlessness	2.28	0.735** (0.010)
Obesity	2.34	0.027* (0.058)
Heart Rate	1.01	0.002** (0.014)
SpO_2	1.01	0.002** (0.035)
Respiratory Rate	1.03	0.010*** (0.002)
COVID-19 Severity	1.95	0.493*** (0.008)
Pulmonary Infiltrates (CT)	1.68	0.397** (0.026)
Chest imaging positive[a]	1.04	0.027* (0.078)
APTT	1.02	0.012** (0.016)
Fibrinogen	1.12	0.076* (0.086)
Interaction Variables:		
COVID-19 Severity and Malignancy	1.58	0.414* (0.079)
COVID-19 Severity and High Risk Group	2.14	0.697** (0.019)
COVID-19 Severity and Age	2.00	0.778* (0.075)
Age and High Risk Group	2.13	0.915* (0.080)

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

Our model included several interaction variables that significantly affected COVID-19 mortality. Amongst the variables concerned, COVID-19 severity and haematology disease-based risk profile had greatest impact. Using logistic regression and a predictive marginal model, factors affecting mortality were examined. An odds ratio >1 indicated that the variable had a positive impact on death. COVID-19 severity had greatest impact on mortality. While COVID-19 severity and increase age increased the chance of death, by 24% and 15%, respectively, non-malignancy reduced the mortality. Of interest, obesity negatively impacted survival.

Using logistic regression and the Cox-proportional hazards model, the impact and survival estimates were examined. Figure I show that the severity of COVID-19 significantly impacted patients with malignant haematological conditions (75 % survival probability, the survival was 8 days as compared to 19 between severe & non-severe patients). Additionally, haematological disease-based risk status was significant for COVID-19 mortality (mean survival 7 days in the low risk group compared to 11 days among the high-risk group).

Figure I: COVID-19 Severity and Malignancy



Note: Figure 1 shows the graph of the survival functions. The X-axis represents the Analysis Time, which is the duration in days between the dates of onset of COVID-19 symptoms and death.

This is the largest series of patients yet reported with haematological conditions infected by SARS-Cov-2. These patients may present with COVID-19 differently. Fever was observed in 33% of our patient cohort as compared to 71% in the Clinical Characterisation Protocol UK (CCP-UK) study.[8]As in previous reports in the general population and specific blood cancers, older age was associated with higher mortality in this cohort. However other co-morbidities like diabetes or hypertension did not confer adverse outcome.[9] Overall mortality was 55%. This higher mortality could be due to this cohort, or that the West Midlands was the second most-affected region in the country. Atypical presentation, particularly the lower proportion with fever (33%) as highlighted in our series may have caused delay in patients seeking medical attention. This underlines the importance of close attention to inflammatory markers and identifying signs of developing coagulopathy.[10] Limitations result from collection at the height of the pandemic workload, where not all data parameters were collected for every patient. Additionally, only hospital managed patients' outcomes are reported.

The presence of lung infiltrates and other underlying lung pathology denotes a particularly high-risk group. Contrary to expectations, this cohort highlights that being on systemic chemotherapy did not increase risk of mortality. This suggests primary therapy for the haematological condition could be continued to avoid adverse impact on their underlying haematological condition.

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coordination and revision of the final draft of the manuscript, sixth author: Data description and initial analysis, all other authors performed the research and contributed to clinical data collection.

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