COVID-19 in haematology patients: a multicentre West Midlands clinical outcomes analysis on behalf of the West Midlands Research Consortium

Since COVID-19 first appeared it has been clear that whilst many patients experience relatively minor symptoms, some develop a more serious disease.1,2 Studies have suggested that oncology patients, including those with haematological malignancies, have a greater 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 1st March and 31st May 2020. Demographic, clinical, laboratory, radiological and outcome data were collected using a standardised form. COVID-19 was diagnosed by reverse transcription-polymerase chain reaction. An ethical clearance waiver for the audit was received from the nine hospitals involved.

Patients were categorised based on their underlying haematological conditions. Those on active chemotherapy, having relapsed and/or with refractory disease, acute myeloid leukaemia with adverse cytogenetics, post- or auto-allogeneic transplant, extranodal T-cell lymphoma, multiple myeloma, post splenectomy and sickle cell disease, were classified high risk. Intermediate risks included Hodgkin and non-Hodgkin 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 >6 months ago, adapted from the 2012 categorisation by Armand.6 Severe COVID-19 infection was classified as 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 World Health Organization guidelines.7

Statistical analysis used IBM SPSS, version 26 (IBM, Armonk, NY, USA) and STATATA SE 16 (StataCorp LP; College Station, TX, USA). Kruskal–Wallis tests compared observations for the hazard event (i.e., survival and non-survival). For testing of the three groups, the ANOVA one-way test, and the Tukey post-test were utilised. The impact and the survival estimates of the various factors was studied using logistic regression and the Cox-proportional hazards model.
The median age of the patients (57.5% male, 41.5% female) was 70 years [IQR 61–78; range 18–95]. Regarding ethnicity, 76% were Caucasian. There were 82% of patients with a malignant haematological disorder, while 18% had non-malignant conditions. The most common co-morbidities in this study cohort were hypertension (41%), ischaemic heart disease (22%), diabetes mellitus (21%), chronic lung disease (20%) and obesity (10%); 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 19th June 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 rate was 55% (relative risk 1.8).

Chest X-ray findings ($P = 0.002$), pulmonary infiltrates on computerized 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, hypertension or ethnicity, were not associated with an adverse outcome in this cohort. Our study found 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 include breathlessness ($P = 0.011$), confirmatory CT of pulmonary infiltrates ($P = 0.27$) and patients showing abnormal findings on X-ray ($P = 0.003$). The details are provided in the supporting information. A multivariate analysis was used to examine the odds ratio of the various significant factors (Table I).

Our model included several interaction variables that significantly affected COVID-19 mortality. Among these, COVID-19 severity and the haematology disease-based risk profile had the 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 the greatest impact on mortality. While COVID-19 severity and older age increased the chance of death, by 24% and 15%,

### Table I. Predictive analysis on in-hospital mortality on a multivariate model.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathlessness</td>
<td>2.28</td>
<td>0.735 (0.100)</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.34</td>
<td>0.027 (0.058)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.01</td>
<td>0.002 (0.014)</td>
</tr>
<tr>
<td>SpO$_2$</td>
<td>1.01</td>
<td>0.002 (0.035)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>1.03</td>
<td>0.010 (0.002)</td>
</tr>
<tr>
<td>COVID-19 severity</td>
<td>1.95</td>
<td>0.493 (0.008)</td>
</tr>
<tr>
<td>Pulmonary infiltrates (CT)</td>
<td>1.68</td>
<td>0.397 (0.026)</td>
</tr>
<tr>
<td>Chest imaging positive$^3$</td>
<td>1.04</td>
<td>0.027 (0.078)</td>
</tr>
<tr>
<td>APTT</td>
<td>1.02</td>
<td>0.012 (0.016)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.12</td>
<td>0.076 (0.086)</td>
</tr>
<tr>
<td>Interaction variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19 severity and malignancy</td>
<td>1.58</td>
<td>0.414 (0.079)</td>
</tr>
<tr>
<td>COVID-19 severity and high risk group</td>
<td>2.14</td>
<td>0.697 (0.019)</td>
</tr>
<tr>
<td>COVID-19 severity and age</td>
<td>2.00</td>
<td>0.778 (0.075)</td>
</tr>
<tr>
<td>Age and high risk group</td>
<td>2.13</td>
<td>0.915 (0.080)</td>
</tr>
</tbody>
</table>

$^*$Indicates significant at 1% level.
$^†$Indicates significant at 5% level.
$^‡$Indicates significance at 10% level.
$^§$Positive, i.e., abnormal finding on X-ray.

P-values are provided in parenthesis.

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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 1 shows that the severity of COVID-19 significantly impacted patients with malignant haematological conditions (75% survival probability; the survival was 8 days for severe compared with 19 days for 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 with 11 days among the high risk groups) showing that haematology patients presenting as 'low risk' according to the criteria in use at the time of reporting, had worse prognosis.

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, such as diabetes or hypertension, did not confer adverse outcome.9 Overall mortality was 55%. This higher mortality could be due to the underlying conditions of 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 the developing coagulopathy.10 Limitations of this study result from the fact that at the height of the pandemic workload 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, being on systemic chemotherapy did not increase risk of mortality in this cohort. This suggests primary therapy for haematological conditions could be continued to avoid an adverse impact on the patients’ underlying haematological status.

Authors’ contributions

HM made substantial contributions to the research design, initial analysis and drafting the manuscript; PB made substantial contributions to research design, initial analysis and drafting the manuscript; AM made substantial contributions to the analysis and writing the results and the analysis of the statistical computations; AN undertook data description and initial analysis; SP made substantial contributions to research design, data collection coordination and revision of the final draft of the manuscript; SB made substantial contributions to the research design, data collection coordination and revision of the final draft of the manuscript; all other authors performed the research and contributed to clinical data collection. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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References

COVID-19 and myeloma clinical research – experience from the CARDAMON clinical trial

COVID-19 – caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – has spread to over 213 countries and territories, with 24,021,218 cases, including 821,462 deaths, reported to WHO by 28 August 2020.1 In the UK alone, there were 328,846 laboratory-confirmed cases and 41,465 COVID-19-associated deaths.2 Self-isolation and physical distancing measures were implemented in most jurisdictions to limit the spread of the virus. Changes to clinical practice saw the short-term reduction of routine and non-emergency care to liberate much-needed capacity in medical facilities, while minimising the risk to patients and healthcare workers by eliminating avoidable face-to-face interactions.

Haematology patients were shown to be particularly vulnerable to SARS-CoV-2 infection3 and in need of shielding; hence alternative management plans and new ways of delivering care were implemented wherever possible to reduce individual patient susceptibility.4 Various clinical guidelines were issued at unprecedented speed, including recommendations for multiple myeloma (MM) and patients needing stem cell transplantation (SCT).5–8 Conducting clinical trials in this environment poses unique challenges, having to strike a balance between patient safety, maintaining trial integrity, and ensuring adherence to good clinical practice (GCP) standards. The EMA, the EU Commission and the UK MHRA all published guidance to help stakeholders better manage clinical trials during the COVID-19 pandemic.9–11

We report the challenges and adaptations made to the CARDAMON trial during the peak of the COVID-19 pandemic.

Fig 1. This flow diagram illustrates the progress through the various phases of the CARDAMON phase II clinical trial, including the impact of COVID-19 on the 70 patients on maintenance K across the two treatment arms at the start of the lockdown period. The 15 patients who stopped K maintenance joined the 170 patients who were already on long-term follow-up on 24 March 2020, bringing the number up to a total of 185. SCT, stem cell transplantation; K, carfilzomib; C, cyclophosphamide; d, dexamethasone.