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SHORT REPORT

Mortality and burden of post-COVID-19 syndrome have reduced with time across SARS-CoV-2 variants in haematology patients

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Summary

Haematology patients contracting SARS-CoV-2 were identified at the start of the pandemic to be at higher risk of death or of persistent symptoms (post-COVID-19 syndrome). As variants with altered pathogenicity have emerged, uncertainty remains around how that risk has changed. We prospectively set up a dedicated post-COVID-19 clinic to monitor haematology patients infected with COVID-19 from the start of the pandemic. In total, 128 patients were identified and telephone interviews were conducted with 94 of 95 survivors. Ninety-day mortality attributed to COVID-19 has fallen sequentially from 42% for the Original and Alpha strains to 9% and to 2% for the Delta and Omicron variants respectively. Furthermore, the risk of post-COVID-19 syndrome in survivors has fallen from 46% for the Original or Alpha strains to 35% for Delta and 14% for the Omicron strain. Since vaccine uptake has been nearly universal in haematology patients, it is not possible to determine whether improved outcomes reflect the reduced pathogenicity of the virus, or widespread vaccine deployment. Whilst mortality and morbidity remain higher in haematology patients than in the general population, our data suggest that the absolute risks are now significantly lower. Given this trend, we believe clinicians should initiate conversations about risk with their patients on whether to maintain any self-imposed social isolation.

KEYWORDS
COVID-19, haematological malignancy, long COVID, Omicron, post-COVID-19 syndrome

INTRODUCTION

It was recognised during the SARS-CoV-2 (COVID-19) pandemic that patients with haematological disorders were among those at the highest risk of death.[1] Furthermore, a high proportion of patients surviving initial infection displayed ongoing symptoms beyond 12 weeks (post-COVID-19 syndrome).[2] As such, haematology patients were encouraged during the early waves to reduce the risk of contracting the virus by shielding, and later were prioritised for vaccination. As successive COVID-19 variants have arisen to become dominant, with altered pathogenicity, it is important to understand how post-infection outcomes have changed in haematology patients in order to guide public health practices.

The most recent strain, known as Omicron, carries a lower risk of hospitalisation, mortality[3] and post-COVID-19 syndrome[4] in the general population. Recent work suggests that Omicron infection has a lower risk of death in patients with chronic lymphocytic leukaemia,[5] whilst other studies caution that there is still considerable mortality in haematological malignancies.[6,7] There remains a lack of prospective data comparing post-infection outcomes following different COVID-19 variants in haematology patients and, in particular, the persistence of post-COVID-19 symptoms following Omicron infection is poorly understood.

From the start of the pandemic, we set up a dedicated single-centre, post-COVID-19 clinic, in which we sought to understand the clinical course following COVID-19 infection in haematology patients. All patients surviving 12 weeks after infection were interviewed by a consultant haematologist, to identify the extent to which they had recovered from their infection. This report charts the evolving natural history of COVID-19 infection among haematology patients in a single-centre.

METHODS

We prospectively identified all patients in a single-centre haematology service who contracted COVID-19 infection from the start of the pandemic. First, we cross-referenced National Health Service numbers with COVID-19 polymerase chain reaction (PCR) tests performed by our regional testing centre. Second, we set up a prospective local alert system for patients to self-report infection, to detect cases with positive lateral flow testing in the community. We included all patients with a haematological malignancy (irrespective of treatment) or immunohaematological disorder (with current or previous treatment). We excluded patients who contracted infection after 10 March 2022, were less than 18 years of age and those with monoclonal gammopathy of uncertain significance.

Whilst some patients had PCR sequencing to determine their COVID-19 variant, the majority did not. Comparing the date that patients with an unknown variant tested positive with the results of UK-wide viral genome testing at the time,[8] patients were allocated a probability of each possible variant. Using a similar approach to other studies,[3] we assigned patients to a likely variant where there was a greater than 90% probability and excluded the remainder from analysis. Patients contracting the Original and Alpha variants were grouped together for analysis, due to the paucity of genome sequencing at the time, the relatively slow transition between these strains and similar mortality rates.[9] For the majority of the pandemic, there were single dominant variants present in the UK population at frequencies close to 100%.

All patients who survived more than 12 weeks after infection were invited to a 30-min appointment in a dedicated post-COVID-19 clinic. The same haematology consultant assessed each patient to exclude interobserver variability. A series of pre-defined questions was used to assess the severity of primary infection as well as ongoing symptoms following infection. The judgement of the consultant and patient were considered in determining whether ongoing symptoms were likely to be related to the previous COVID-19 infection or to the underlying haematological disease or its treatment. In patients who did not survive to follow-up, hospital admission notes and death certificates were reviewed to establish whether COVID-19 infection contributed to their death. For all patients, data were collected on COVID-19 vaccinations that had been administered at least 2 weeks prior to infection.

RESULTS AND DISCUSSION

Patient characteristics

In total, 128 patients with an underlying haematological disorder who contracted the COVID-19 virus were identified, with a greater than 90% probability of an assigned variant (Table 1). The mean age was 69.9 years and 57% were male. The majority (97%) of patients had diagnoses of a malignant haematological disorder, including lymphoid (61%), myeloid (26%) and myeloma (10%). There were 64 patients (50%) in the group who contracted either the Original or Alpha variants, 22 patients (17%) with Delta and 42 (33%) with Omicron.

Risk of mortality

Of 128 patients, 33 died within 90 days of their positive test (26% all-cause mortality), of which COVID-19 contributed to deaths in 30 cases overall (23% COVID-related mortality). Patients surviving infection were on average 13.1 years younger than those who died (66.5 vs 79.6 years, $p < 0.0001$, Mann–Whitney test).

Mortality varied by variant *log-rank test*: $p < 0.0001$ (Figure 1A). Ninety-day mortality following either the Original or Alpha variants was 42% (27/64 patients), compared with 9% (2/22 patients) for the Delta variant. In all these cases, COVID-19 contributed to the death. In comparison, 90-day mortality with the Omicron variant was 10% (4/42 patients), consistent with 9%–16% mortality reported in other, similar cohorts;[6,10,11] however, COVID-19 did not contribute to death in three of these cases; therefore, the 90-day COVID-19-related mortality linked to Omicron infection was 2% (1/42 patients).

The absolute mortality rate for haematology patients remains elevated above that of the general population,[3] but risk is greatly reduced compared with previous variants. This is likely due to the decreased pathogenicity of the Omicron strain and the rollout of vaccinations,[6] although, as both factors overlapped temporally, it has not been possible to determine their relative contributions.

Risk of post-COVID-19 syndrome

Telephone follow-up consultations were conducted for 94 of the 95 patients who survived COVID-19 infection, the remaining patient declined follow-up. Forty-six per cent of patients (17/37) with either Original or Alpha variants met criteria for post-COVID-19 syndrome, compared with 35% (7/20) with Delta and 14% (5/37) with the Omicron variant. The most common persistent symptoms were fatigue, shortness of breath, cough, and mood disturbance, all of which were less prevalent in the Omicron group, when compared with previous strains (Figure 1B).

We analysed factors from initial COVID-19 infection that affected the risk of post-COVID-19 syndrome (Figure 1C). There was an increased risk in those who, at initial infection, had shortness of breath [odds ratio (OR): 11.5 (95% confidence interval (CI): 3.8–34.9)], required hospitalisation [OR: 8.4 (95% CI: 3.1–22.9)], or had an oxygen requirement [OR: 23.6 (95% CI: 6.7–83.5)], suggesting that more severe infection was associated with greater persistence of symptoms beyond 12 weeks. Infection in patients with Omicron (compared to

TABLE 1 Patient and disease demographics, stratified by their likely COVID-19 variant.

	Original and alpha		Delta		Omicron		All variants		
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Total
Demographics	37	27	20	2	38	4	95	33	128
Average age	66.4	80.3	66.6	70.6	66.6	79.3	66.5	79.6	69.9
Male (%)	57	74	50	100	53	75	54	76	59
Average number of COVID vaccinations	0.07	0.04	1.95	2.00	3.00	2.75	2.11	0.50	1.62
3+ vaccines (%)	0	0	15	0	84	75	37	9	30
Diagnosis	37	27	20	2	38	4	95	33	128
Lymphoid	19	16	13	2	25	3	57	21	78
CLL/SLL	12	8	4	0	5	1	21	9	30
FL	3	0	6	1	6	0	15	1	16
DLBCL	2	0	2	0	7	1	11	1	12
HCL	0	1	0	0	0	0	0	1	1
T-cell lymphoma	0	0	0	0	0	1	0	1	1
Hodgkin lymphoma (not NLPHL)	1	2	0	0	2	0	3	2	5
MALT/LPL/other low-grade NHL	1	4	0	0	4	0	5	4	9
Mantle cell lymphoma	0	1	1	1	0	0	1	2	3
ALL	0	0	0	0	1	0	1	0	1
Myeloid	13	6	5	0	8	1	26	7	33
MDS/CMML	4	3	1	0	0	0	5	3	8
AML	1	0	1	0	3	1	5	1	6
MPN	7	3	3	0	5	0	15	3	18
AA with allogeneic transplant	1	0	0	0	0	0	1	0	1
Myeloma	1	5	2	0	5	0	8	5	13
Non-malignant	4	0	0	0	0	0	4	0	4
ITP	3	0	0	0	0	0	3	0	3
CHAD	1	0	0	0	0	0	1	0	1
Disease status									
Immunosuppressive treatment at time of infection	11	10	7	1	16	3	34	14	48
Anti-CD20 treatment at any stage	12	3	10	1	13	1	35	5	40
Comorbidities									
Hypertension	6	10	8	1	11	3	25	14	29
Diabetes mellitus	8	7	1	0	4	3	13	10	23
Ischaemic heart disease	9	5	1	0	4	1	14	6	20
Congestive cardiac Faflure	2	6	0	0	0	2	2	8	10
Atrial aibrillation	3	3	3	0	5	3	11	6	17
Asthma	4	3	3	1	4	0	11	4	15
COPD	4	4	2	0	4	1	10	5	15
Cerebrovascular disease	3	3	0	0	3	0	6	3	9
Chronic kidney Ddsease	1	3	2	0	3	0	6	3	9

Note: Alive or dead status was evaluated at 90-days following a positive test result, due to all-cause mortality. Co-morbidities are listed if present in at least 5% of the total patient population.

Abbreviations: AA, aplastic anaemia; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CHAD, cold haemagglutinin disease; CLL, chronic lymphocytic leukaemia; CMML, chronic myelomonocytic leukaemia; COPD, chronic obstructive pulmonary disease; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukaemia; ITP, immune thrombocytopenic purpura; LPL, lymphoplasmacytic lymphoma; MALT, mucosal-associated lymphoid tissue lymphoma; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic leukaemia.

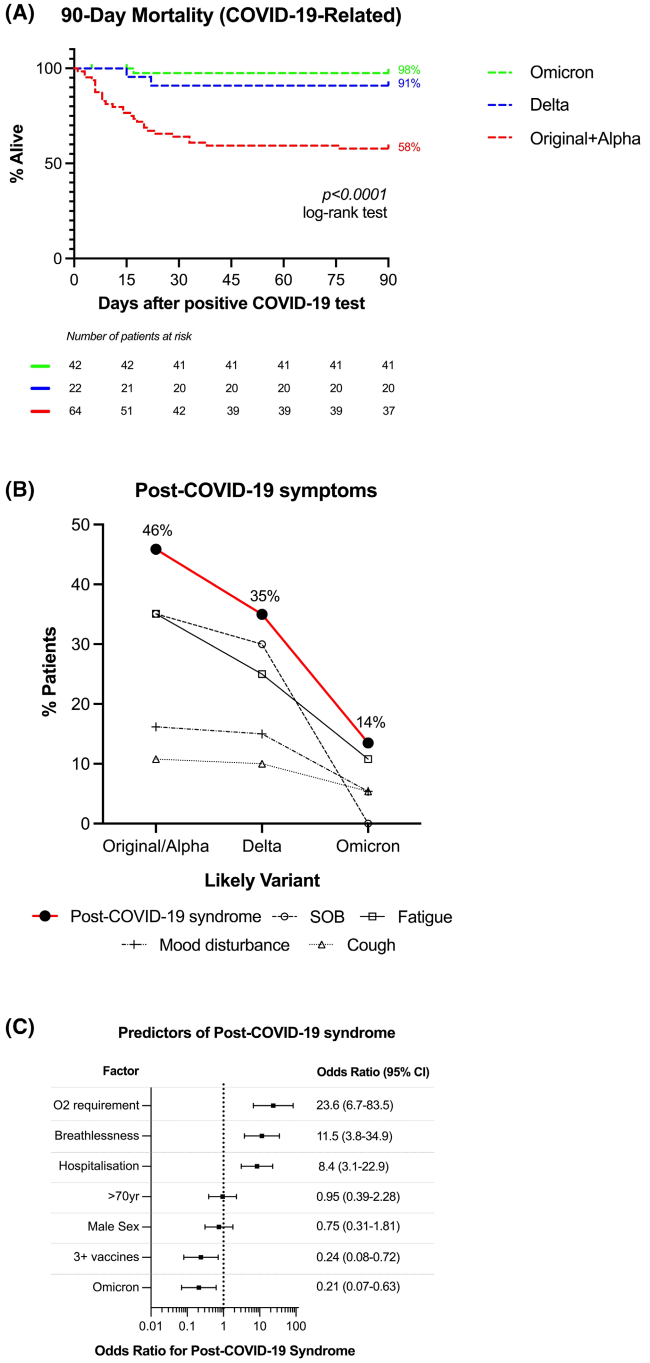

FIGURE 1 Decreased mortality and post-COVID morbidity following Omicron infection in patients with haematological disorders. (A) Kaplan–Meier survival graphs for COVID-19-related 90-day mortality following date of positive COVID-19 test for patients infected during dominant variants. *Log-rank test*: $p < 0.0001$. (B) Prevalence of post-COVID-19 syndrome symptoms by likely variant (%). (C) Predictors of post-COVID-19 syndrome. Odds ratios are displayed for factors present at time of initial infection.

Original, Alpha or Delta) variants had a lower risk of post-COVID-19 syndrome [OR: 0.21 (95% CI: 0.07–0.63)].

Our data show reduced persistence of post-COVID-19 syndrome following Omicron compared to previous variants in haematological patients. Nevertheless, with high rates of COVID-19 infection in the community, the possibility of post-COVID-19 symptoms should be considered by clinicians as a possible alternative explanation to disease progression or toxicity of chemotherapy in symptomatic patients. Detecting post-COVID-19 syndrome may guide specialist referrals to aid recovery.

CONCLUSIONS

Our data support reduced mortality and post-COVID-19 sequelae with time, suggesting Omicron infection is a self-limiting illness for the majority of haematology patients. Nevertheless, many patients continue to exercise a great deal of caution due to the perceived threat from the virus. Such prolonged, self-imposed social isolation may have negative effects on psychological and physical health as well as restricting occupational activities. As clinicians, we have a duty to communicate risk and to help our patients to make informed choices about whether to ease their self-isolation.

AUTHOR CONTRIBUTIONS

John Willan initiated the project and performed all patient interviews. John Willan and Gaurav Agarwal analysed the data, and wrote the initial drafts of the manuscript. Nicola Bienz provided senior support for the project. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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