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Mortality and clinical outcomes following SARS-CoV-2 infection among individuals with haematological malignancies: A Danish population-based cohort study

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Abstract

Objectives: We aimed to quantify the risk of death following a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among individuals with haematological malignancies, stratified by virus variants and type of malignancy.

Methods: Using the Danish nationwide registries, we conducted a population-based cohort study among individuals who received a discharge diagnosis of haematological malignancies during the 5 years prior to testing positive for SARS-CoV-2 (February 2020–April 2023). All individuals were followed for 30 days after a positive test, and overall and time-stratified case fatality risks (CFR) were estimated.

Results: We identified 7154 individuals with a history of haematological malignancies who tested positive for SARS-CoV-2. Among these, we observed 223 deaths, yielding a CFR of 3.1%. The CFR was highest at the beginning of the pandemic (10%) and gradually declined to 1.9% during the period of Omicron BA1/BA2 predominance. The highest CFR was observed among individuals with acute leukaemia (CFR 6.2%, adjusted relative risk 1.95, 95% confidence interval 1.33–2.88) compared to individuals with lymphoma (CFR 3%).

Conclusions: We observed a reduction in the CFR over time, which may be attributed to new treatments, COVID-19 vaccination and the emergence of less aggressive variants.

KEYWORDS
COVID-19, hematologic neoplasms, mortality

1 | INTRODUCTION

Individuals with haematological malignancies are at an increased risk of adverse outcomes following SARS-CoV-2 infection, with reported case fatality risks (CFR) ranging between 14% and 70%.[1] A Danish study based on 108 individuals reported a 90-day mortality of up to 28%,[2] while an English study based on 128 patients reported sequentially falling 90-day mortality from 42% to 2% over the course of the pandemic.[3] Existing studies on the CFR of SARS-CoV-2 infection among individuals with haematological malignancies were often based in a hospital setting or conducted during the early phase of the pandemic but up-to-date, population-based studies are lacking. During the course of the pandemic, new treatments, COVID-19 vaccines[4] and virus variants have emerged which may have

impacted the CFR in this population.[5] Therefore, we aimed to quantify the risk of death following SARS-CoV-2 infection during different phases of the COVID-19 pandemic, among individuals with haematological malignancies.

2 | MATERIALS AND METHODS

For this, we identified all individuals who had a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 during the period 27 February 2020 to 01 April 2023, who were 18 years or older at the time of testing and had received a first diagnosis of a haematological malignancy up to 5 years prior to testing positive for SARS-CoV-2. We obtained data on vital status and demographics,[6] SARS-CoV-2 test results,[7] COVID-19 vaccination status,[8] hospital contacts and discharge diagnoses[9] and prescription drug use[10] from the Danish nationwide health registries.

All outcomes were assessed during the 30 days following a positive test for SARS-CoV-2. The main outcome was all-cause mortality. Secondary outcomes were hospitalization for COVID-19 and intensive care unit (ICU) admission. Individuals who were hospitalized or admitted to the intensive care unit during the 7 days prior to the positive SARS-CoV-2 test were excluded from respective analyses. Hospitalization was defined as any physical hospital contact with a duration of 12 hours or more. For a graphical representation of the study design, see Figure S1, for codes used to define outcomes and covariates, refer to Table S1.

We used descriptive statistics to characterize individuals at the time of the positive SARS-CoV-2 test, stratified by whether individuals survived for 30 days following the SARS-CoV-2 infection.

The main measure of interest was the CFR at different time points during the pandemic, that is, the probability of death during the 30 days following a positive test for SARS-CoV-2, among individuals with pre-existing haematological malignancies. We chose to evaluate mortality within 30 days, as we expected this to increase the specificity of the outcome, that is, the cause of death being COVID-19.

We investigated the relationship between the CFR and different time points during the pandemic in two ways: (1) we estimated the crude and adjusted probability of death using logistic regression with calendar time, modelled using restricted cubic splines, as the independent variable. In the adjusted model, we included information on age, sex, type of malignancy and other prognostic factors for moderate to severe COVID-19 (Table S1) as covariates. From this model, we obtained age and sex-standardized CFRs for the period March 2020 to April 2023. Information on the dominant variant of SARS-CoV-2 at the time of infection or vaccination status were not included in the model, due to potential collinearity with calendar time. (2) We estimated adjusted risk ratios for death, hospitalization and ICU admission using a semiparametric log-linear model comparing the SARS-CoV-2 wild-type to the Alpha, Delta and Omicron variants.[11] Using the same approach, we also estimated risk ratios for each outcome comparing the different types of haematological malignancies. We used the same covariates as in the logistic regression model, but also included information on vaccination status.

In supplementary analyses, we restricted the study population to individuals who received their first diagnosis of a haematological malignancy during the year prior to testing positive for SARS-CoV-2. To increase comparability with previous findings, we also calculated risks of 90-day mortality. Finally, we evaluated the impact of testing activity on the CFR, by determining the monthly number of tests performed during the study period.

3 | RESULTS

We identified 7154 individuals with haematological malignancies who tested positive for SARS-CoV-2, of whom 3140 (44%) were female and the median age was 69 years (Table S2). The majority ($N = 4718$, 66%) of patients tested positive between 15 December 2021 and 1 June 2022, when the Omicron BA1 and BA2 variants were dominant and test activity was high (Figure S2). Likewise, 6395 cases (89%) had received one vaccine dose or more at the time of infection. The most frequently administered vaccine was BNT162b2 (90%, 5778/6395 first vaccinations). Of all SARS-CoV-2 positive patients, 223 (CFR 3.1%) died within 30 days of testing positive. Most deaths ($N = 92$) occurred during the period of Omicron BA1/BA2 dominance (15 December 2021 to 01 June 2022). The observed CFR was highest during the period of wild-type dominance (10%), while the lowest CFR was observed for the Omicron BA1/BA2 variant (1.9%, adjusted RR versus wild-type 0.33, 95% confidence interval [CI] 0.15–0.73; Table 1). When modelling the CFR over time, the largest reduction of the CFR was seen between March and December 2020 (Figure 1).

When stratifying by type of malignancy, patients with acute leukaemia were at the highest risk of death (51 deaths/824 infected, CFR 6.2%, adjusted RR versus lymphoma 1.95, 95% CI 1.33–2.88), while 30-day mortality for the other malignancies ranged between 1.6% and 3.8%.

When considering the secondary outcomes, 1555 individuals were hospitalized for COVID-19 and 96 received intensive care. The risk of hospitalization was highest among patients with multiple myeloma (37%, RR 2.35, 95% CI 2.08–2.66) or acute leukaemia (33%, RR 1.99, 95% CI 1.74–2.26), compared to a lower risk among patients with lymphoma (22%, RR 1.0 [reference]), CLL (21%, RR 1.24, 95% CI 1.07–1.43) and MPN and other malignancies (8%, RR 0.54, 95% CI 0.45–0.66). Among known prognostic factors for COVID-19-related death, we found a high CFR among patients treated with anti-CD20 monoclonal antibodies (53 events/909 infected, 6%) (Table S2).

When restricting the analyses to individuals with an incident diagnosis of a haematological malignancy during the year prior to a positive test for SARS-CoV-2, we consistently found elevated CFRs compared to the main analysis with 5 years of lookback (Table S3). When assessing mortality at 90 days after a positive test, the overall CFR was slightly higher (390 deaths, 5.5%) compared to the main analysis. Finally, testing activity increased steeply during the fall and winter of 2020 and returned to early pandemic levels during spring 2022 (Figure S2).

TABLE 1 Number of events, observed risks and adjusted risk ratios for the primary and secondary outcomes.

	Death			COVID-19 hospitalization			ICU admission		
Stratum	**Events**	**CFR (95% CI)**	**RR (95% CI)**	**Events**	**CFR (95% CI)**	**RR (95% CI)**	**Events**	**CFR (95% CI)**	**RR (95% CI)**
Type of malignancy									
Lymphoma ($N = 3105$)	93	3.0 (2.5–3.7)	1.00 (ref.)	658	22 (20–23)	1.00 (ref.)	41	1.3 (1.0–1.8)	1.00 (ref.)
Acute leukaemia ($N = 824$)	51	6.2 (4.7–8.1)	1.95 (1.33–2.88)	257	33 (30–37)	1.99 (1.74–2.26)	11	1.3 (0.7–2.4)	0.91 (0.43–1.94)
Multiple myeloma ($N = 1019$)	39	3.8 (2.8–5.2)	1.30 (0.86–1.96)	359	37 (34–40)	2.35 (2.08–2.66)	19	1.9 (1.2–2.9)	1.34 (0.71–2.55)
CLL ($N = 861$)	18	2.1 (1.3–3.3)	0.78 (0.47–1.30)	176	21 (18–24)	1.24 (1.07–1.43)	15	1.7 (1.1–2.9)	1.85 (0.98–3.48)
MPN/Others ($N = 1345$)	22	1.6 (1.1–2.5)	0.80 (0.49–1.29)	105	8.0 (6.6–9.6)	0.54 (0.45–0.66)	10	0.7 (0.4–1.4)	0.97 (0.47–1.99)
Variant of concern									
Wild-type ($N = 506$)	51	10 (7.7–13)	1.00 (ref.)	188	40 (36–45)	1.00 (ref.)	40	7.9 (5.9–11)	1.00 (ref.)
Alpha ($N = 121$)	7	5.8 (2.8–12)	0.52 (0.21–1.27)	159[a]	32 (28–36)[a]	0.85 (0.63–1.13)	12[a]	2.3 (1.3–4.0)[a]	0.70 (0.25–1.98)
Delta ($N = 404$)	20	5.0 (3.2–7.5)	0.47 (0.21–1.09)			1.01 (0.78–1.30)			0.44 (0.14–1.41)
Omicron [BA1/BA2] ($N = 4718$)	92	1.9 (1.6–2.4)	0.33 (0.15–0.73)	860	19 (18–20)	0.71 (0.55–0.90)	31	0.7 (0.5–0.9)	0.19 (0.06–0.65)
Omicron [BA4/BA5] ($N = 1405$)	53	3.8 (2.9–4.9)	0.49 (0.22–1.10)	348	26 (24–29)	0.86 (0.67–1.10)	13	0.9 (0.5–1.6)	0.23 (0.06–0.91)
Sex									
Female ($N = 3140$)	83	2.6 (2.1–3.3)	1.00 (ref.)	611	20 (19–22)	1.00 (ref.)	27	0.9 (0.6–1.3)	1.00 (ref.)
Male ($N = 4014$)	140	3.5 (3.0–4.1)	1.22 (0.93–1.59)	944	24 (23–26)	1.09 (1.00–1.18)	69	1.7 (1.4–2.2)	1.67 (1.07–2.60)

Note: Information on virus variants was derived from periods of pre-dominance for each variant. Infections prior to 1 February 2021 were assumed to represent the wild-type, infections between 1 February 2021 and 14 July 2021 were assumed to represent the Alpha variant, infections between 15 July 2021 and 14 December 2021 were assumed to represent the Delta variant and infections between 15 December 2021 and 31 May 2021 were assumed to represent the Omicron BA1 and BA2 variants, and finally infections detected on or after 1 June 2022 were assumed to represent Omicron BA4 or BA5 variants.

Abbreviations: CFR, case fatality risk; CI, confidence interval; CLL, chronic lymphocytic leukaemia; MPN, myeloproliferative neoplasm; RR, risk ratio.

[a]Number of events and crude risks are reported combined for the Alpha and Delta variants to comply with data privacy regulations.

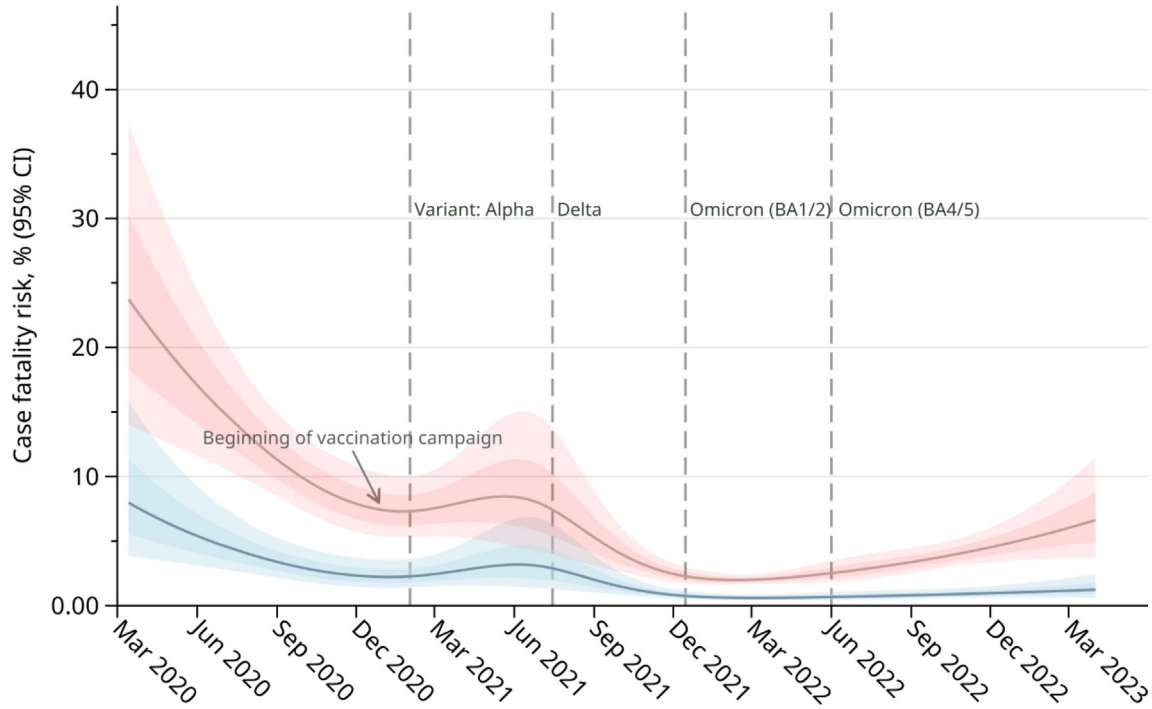

FIGURE 1 Observed and standardized case fatality risks for SARS-CoV-2 infection in patients with haematological malignancies between 27 February 2020 and 01 April 2023 modelled using restricted cubic splines. Dashed lines indicate the respective periods of dominance for different virus variants. The solid red line represents the predicted CFR from the simple model only including calendar time as independent variables. The darker red area indicates the CFR ± 1 standard error, and the light red area indicates the 95% confidence interval. The solid blue line represents the standardized CFR from the adjusted model for a woman who is 65 years old, with no other prognostic factors of moderate to severe COVID-19. The darker blue area indicates the CFR ± 1 standard deviation, and the light blue area indicates the 95% confidence interval. CI, confidence interval.

4 | DISCUSSION

Overall, the CFR among patients with haematological malignancies was 3.1% between February 2020 and April 2023. The CFR was highest during the first months of the pandemic, prior to the arrival of the Alpha variant, and fell gradually throughout 2020 and 2021. The CFR for the latest Omicron variants (BA4/BA5 and subtypes) was 3.8%. In analyses adjusted for vaccination status, we found a reduced CFR for the Omicron BA1 and BA2 variants.

The major strength of our study is the use of population-based data, compared to previous studies that mainly included hospitalized patients, making our study generalizable to the entire target population. The major limitation of our study is that multiple important factors (vaccination status, virus variants, test rates) changed rapidly over time, that is, these were not observed simultaneously, making the comparisons susceptible to calendar time-related biases.

We found a lower CFR compared to other studies,[1,2] especially when considering the later stages of the pandemic, albeit newer studies also found a decreased CFR for the Delta and Omicron variants.[3] Possible explanations for these differences are the inclusion of non-hospitalized individuals in our study, shorter duration of follow-up, and the inclusion of data from 2021 and onwards, when most individuals already had received a COVID-19 vaccine. The observed reduction in the CFR over time may be attributed to several factors: An increasing availability of testing for SARS-CoV-2 between fall 2020 and spring 2022, possibly increasing the number of mild cases that were detected, and multiple treatments for COVID-19 having been introduced during Summer 2020.[5] In addition, a reduction in the CFR during the spring of 2021 may be attributable to vaccine uptake. Finally, the intrinsic virulence of the Omicron variant appears to be lower than the earliest, leading to a low CFR from winter 2021 and onwards. From the available data, it was not possible to reliably quantify the effect of each of these changes separately. Whether a further reduction of the CFR could be achieved through routine administration of monoclonal antibodies against the SARS-CoV-2 spike protein remains to be elucidated.[12,13]

5 | CONCLUSION

We found an overall CFR of 3.1%, with the lowest variant specific being Omicron BA1/BA2 with a CFR of 1.9%. The observed reduction in the CFR may be attributed to an increased availability of tests for SARS-CoV-2, new treatments and the arrival of COVID-19 vaccines.

AUTHOR CONTRIBUTIONS

Lars Christian Lund, Jesper Hallas and Henrik Frederiksen conceived the study. All authors provided important input to the methodology

and design of the study. Lars Christian Lund performed data management and statistical analyses. Lars Christian Lund and Martin Torp Rahbek wrote the original draft. All authors provided important feedback on the original draft, and reviewed and accepted the final manuscript.

CONFLICT OF INTEREST STATEMENT

Lars Christian Lund reports participation in research projects funded by Menarini Pharmaceuticals and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the current proposal. Lars Christian Lund has personally received fees for teaching epidemiological methods related to COVID-19 research from Atrium, the Danish association of the pharmaceutical industry. Henrik Frederiksen reports research funding from Sanofi, Novartis, Gilead and Alexion without relation to the current project. Peter Brown has personally received fees from Gilead, Incyte and Novartis for participation on a data safety monitoring or advisory board. Jesper Hallas, Martin Torp Rahbek and Niels Obel report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to Danish privacy regulations. Danish data are available to authorized researchers after application to the Danish health data authority (https://sundhedsdatastyrelsen.dk).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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