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LETTER

Mortality in patients with lymphoid malignancies and multiple myeloma was stable upon and during the COVID-19 pandemic: A population-based, nation-wide study

Tereza Faitová[1] | Christian Brieghel[1] | Frank Eriksson[2] | Carsten U. Niemann[1,3]

Correspondence: Carsten U. Niemann (carsten.utoft.niemann@regionh.dk)

Patients with B-cell-derived malignancies are at increased risk of severe coronavirus disease 2019 (COVID-19) due to the inherent immune dysfunction and/or treatment. To protect patients in general and patients with B-cell-derived malignancies in particular from COVID-19, management of these patients was changed toward virtual consultations during the pandemic. Whether the COVID-19 pandemic itself and/or changes in management have led to excess mortality among hematological patients during the COVID-19 pandemic in Denmark has not yet been investigated.

During the COVID-19 pandemic, a series of lockdowns were implemented in Denmark from March 2020 onwards to mitigate transmission.[1,2] Patients with B-cell-derived cancers have an increased susceptibility to severe COVID-19 due to immune dysfunction related to the disease itself and/or treatment. In particular, the use of anti-CD20 antibodies is associated with a high risk of severe and prolonged COVID-19, as well as low rates of seroconversion after vaccination.[3,4] Further, the COVID-19 pandemic presented enormous challenges for the clinical management of patients with lymphoid cancer and multiple myeloma (MM)[5] as nearly all Danish in-hospital visits were converted to telephone consultations, except for patients receiving active treatment. Thus, diagnostics might have been delayed and relapse/progression may have been missed due to lack of routine clinical controls during the telemedicine era of the COVID-19 pandemic. Here we assess the cancer incidence and mortality rate in patients with B-cell-derived malignancies before and during the COVID-19 pandemic to evaluate whether the COVID-19 pandemic or the management of it caused excess mortality in this patient population.

We identified all patients registered with a diagnosis of chronic lymphocytic leukemia (CLL) since 2008 and MM, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) or classical Hodgkin lymphoma (cHL) since 2005 from nationwide Danish Health Registers.[6–8] All study participants were followed from the time of diagnosis or April 1, 2018, whichever occurred last, until death, or last follow-up, whichever occurred first. The date of last follow-up was April 1, 2022 for all patients to mitigate potential seasonal bias (2 full years of follow-up prior to and during the pandemic). Throughout the pandemic, in-person hospital visits were arranged only for assessments such as biopsies, scans, and blood samples, while virtual consultations with the physician occurred if no physical exams or treatment were required. For each disease entity (CLL, MM, DLBCL, FL, MCL, cHL), we defined the population at risk on the first of each month (patients alive with the diagnosis in question) and monitored monthly mortality rates. We calculated monthly mortality rates from April 1, 2018 until the date of last follow-up as the fraction of number of deaths divided by the number of patients at risk at the beginning of the month in question.

We defined two time periods: (1) from April 1, 2018 to March 31, 2020 (prepandemic) and (2) from April 1, 2020 to March 31, 2022 (pandemic). Next, Cox's proportional hazards regression analyses using time since diagnosis as time scale and following patients for death from any cause from April 1, 2018 were applied. Patients diagnosed in 2008–March 2018 (CLL) or 2005–March 2018 (MM, DLBCL, FL, MCL, cHL), and still alive at the start of the follow-up period, enter with delayed entry. Cox's proportional hazards model was adjusted for age at diagnosis and sex, and designed with COVID-19 pandemic as a time-varying covariate.

We identified a total of 20,316 patients including 1900, 5413, 5233, 3070, 787, and 3913 patients with cHL, CLL, DLBCL, FL, MCL, and MM, respectively. For all disease entities, the prevalence steadily increased during the study period (Figure S1), and the number of newly diagnosed patients in each year did not show any clear trends between 2018 and 2021 (Figure 1, right). In the entire cohort, the median monthly mortality rate was stable prepandemic and during the pandemic: overall 0.54% (interquartile range [IQR]: 0.32–0.77) versus 0.53% (IQR: 0.33–0.77), respectively (Poisson regression: $p = 0.67$). Moreover, the monthly mortality rates for individual disease entities were similar prepandemic and during the pandemic (median, IQR): cHL: 0.19 (0.07–0.26) versus 0.17

[1]Department of Hematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[2]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

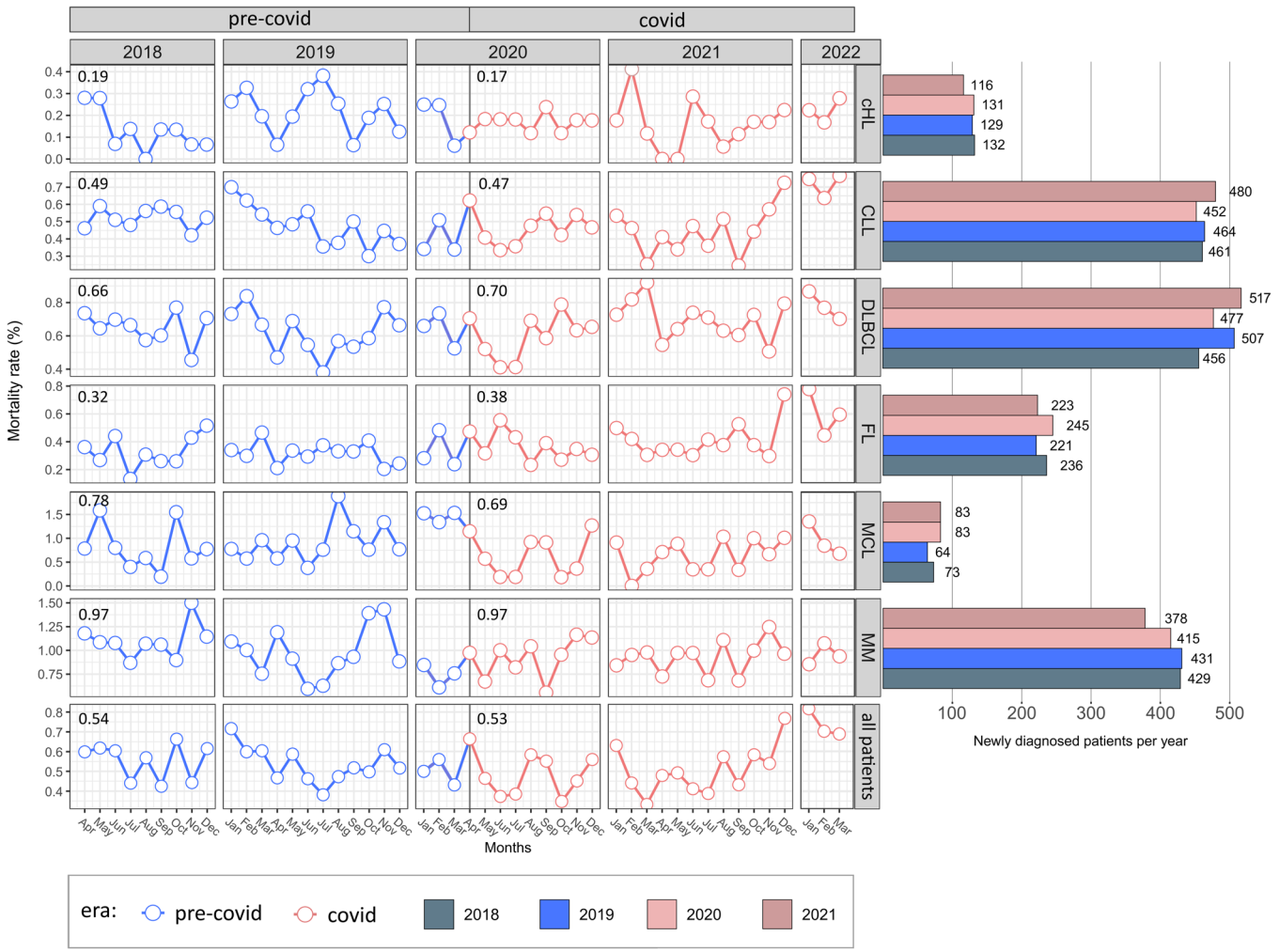

FIGURE 1 Left: Case fatality rate per disease entity per month. Median mortality rates are shown for each disease/era and for the entire cohort. Right: Bar plots illustrate the number of newly diagnosed patients per disease entity per year.

(0.12–0.19); CLL: 0.49 (0.41–0.56) versus 0.47 (0.40–0.55); DLBCL: 0.66 (0.56–0.71) versus 0.70 (0.60–0.75); FL: 0.32 (0.26–0.38) versus 0.38 (0.31–0.48); MCL: 0.78 (0.58–1.34) versus 0.69 (0.35–0.94); MM: 0.97 (0.86–1.11) versus 0.97 (0.84–1.01) (Figure 1, left). Adjusted for age at diagnosis and sex, we observed a 22% increased hazard and 25% decreased hazard of dying from any cause during the COVID-19 pandemic period compared to the pre-pandemic period in patients with FL and MCL, respectively, when comparing patients with the same time since diagnosis (Table 1). No significant changes were seen for the other disease groups.

In this study, we compared mortality rates for B-cell-derived malignancies before and during the COVID-19 pandemic. The stable or even decreasing mortality rates during the pandemic indicate that the partly virtual management of most Danish patients with hematologic malignancies during the pandemic did not result in an increased mortality rate and may have shielded patients from transmission of COVID-19. However, other factors impacting the mortality rate during this time period cannot be ruled out. For instance, the effect of potentially improved therapies or omission of rituximab maintenance therapy during the pandemic was not accounted for in the statistical models and may skew results. We and others have previously demonstrated that the mortality was high for hematological patients testing positive for SARS-CoV-2 during the pandemic.[9] Especially during the early pandemic, the number of COVID-19 patients may have been too few to impact all-cause mortality for an entire disease population, while mortality rates over time may have been impacted by acquired immunity from

TABLE 1 Cox's model hazard ratio, adjusted for age at diagnosis and sex, for the COVID pandemic as the time-varying covariate with prepandemic period as a reference.

	COVID-19 pandemic		
Disease	**Hazard ratio**	**95% CI**	***p* Value**
cHL	0.90	[0.64; 1.26]	0.53
CLL	0.95	[0.84; 1.09]	0.48
DLBCL	1.04	[0.93; 1.17]	0.48
FL	1.22	[1.01; 1.48]	0.04
MCL	0.75	[0.56; 0.99]	0.04
MM	0.92	[0.82; 1.03]	0.15

Abbreviations: cHL, classical Hodgkin lymphoma; CI, confidence interval; CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MM, mutliple myeloma.

vaccines/previous infections and less severe variants in the later part of the pandemic with rampant surges during the emergence of the omicron variant.[10] Even so, we were unable to demonstrate crude excess mortality during the COVID-19 pandemic as compared with the prepandemic years. With modest confidence, we showed that patients with MCL demonstrated a lower fatality rate during the pandemic, likely due to low numbers or introduction of novel therapies like novel BTK inhibitors and bispecific antibodies for later line treatment in clinical trials and decreased use of chemoimmunotherapy during the pandemic. However, our data does not allow closer analyses of changes in treatment between the two periods. Patients with FL showed higher fatality rate during the pandemic, which could hypothetically be attributed to the fact that the diagnosis of indolent lymphoid cancers like FL (and CLL) may be substantially delayed due to the changes in management during COVID. Thus, the patients diagnosed with FL (and CLL) during this period may represent patients with more progressive disease, which in part could explain the increased mortality for the FL cohort. Besides the small numbers, which could explain the changes in fatality rates observed for MCL and FL as a chance finding, it could also be a reflection of changes in the proportion of patients receiving active treatment or rituximab maintenance during the pandemic.[11] With longer follow-up, survival improvement for all diseases might have been observed.[12] Our study could not confirm such improvement, likely due to its limited 4-year follow-up. In terms of mortality, the patient cohorts with B-cell-derived malignancies were not negatively affected by either the COVID-19 pandemic itself or the transformation to telemedicine during the pandemic. However, whether the expected gradual improvement in survival reported by Hemminki et al. was masked by potential negative effect of the COVID pandemic remains unresolved.[12] Whether this experience may pave the path for future expansion of telemedicine will have to be evaluated by long-term observation of patient subcohorts, considering not only the diagnosis and mortality rates but also other quality-of-life aspects such as mental health, social functioning, and maintained patient–physician relationship.

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AUTHOR CONTRIBUTIONS

Carsten U. Niemann, Christian Brieghel, and Tereza Faitová designed the study. Tereza Faitová, Frank Eriksson, and Christian Brieghel performed the bioinformatic and statistical analyses. Tereza Faitová, Christian Brieghel, and Carsten U. Niemann wrote the first version of the manuscript, all authors read, contributed, and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

Carsten U. Niemann received research funding and/or consultancy fees outside this work from Abbvie, Janssen, AstraZeneca, Genmab, Beigene, CSL Behring, Octapharma, Eli & Lily, and Takeda. Christian Brieghel has received consultancy fees from AstraZeneca and travel grants from Octapharma outside this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The data sets generated and analyzed during this study are derived from patients treated in Denmark. Due to Danish legislation (Act No. 502 of May 23, 2018) and approvals granted by the Danish Data Protection Agency, it is not possible to upload raw data to a publicly available database. However, access to these data can be made available from the corresponding author on reasonable request.

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ORCID

Tereza Faitová http://orcid.org/0000-0003-2729-0354
Christian Brieghel http://orcid.org/0000-0002-1816-8106
Carsten U. Niemann https://orcid.org/0000-0001-9880-5242

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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