Outcome of infection with omicron SARS-CoV-2 variant in patients with hematological malignancies: An EPICOVIDEHA survey report

To the Editor:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused high mortality in patients with hematological malignancies (HM). The newly emerged omicron variants of SARS-CoV-2 harbor multiple novel spike protein mutations that raise concerns about vaccine efficiency and antiviral efficacy of the available therapeutic monoclonal antibodies. The first published clinical data in immunocompetent patients have found that infection with omicron variants is associated with reduced vaccine efficiency compared to the delta variants, but decreased hospital admission and mortality. Preliminary, prepublished, data from a large case survey report regarding clinical outcomes are lacking. The aim of this study was to describe risk factors, antiviral treatment and outcomes of SARS-CoV-2 omicron variant infection in 593 HM patients included in the EPICOVIDEHA registry.

EPICOVIDEHA is an international open web-based registry for patients with HM infected with SARS-CoV-2. Both hospitalized and nonhospitalized patients are eligible for inclusion. The questionnaire includes data on the HM, SARS-CoV-2 vaccination status, risk factors for severe COVID-19 infection, SARS-CoV-2 virus variant, antiviral treatment, and outcomes including mortality. Classification of attributable, contributable, or nonattributable death is made by the reporting physician. All included cases are validated by experts with previous experience in research studies of hematological malignancies and infectious diseases at the University Hospital Cologne, Cologne, Germany.

Critical infection was defined as admittance to an intermediate and/or intensive care unit. Independent predictors for mortality were asssed via a Cox proportional hazard model. Risk factors for critical SARS-CoV-2 infection were determined with a logistic regression. Variables with a p-value ≤ 0.1 in the univariable models were considered for multivariable analysis. Multivariable regression models (both Cox and logistic) were calculated with the Wald backward method, and only those variables that were statistically significant displayed. Log-rank test was used to compare the survival probability of the patients included in the different models. A priori sample size calculation was not applied in this exploratory study. SPSSv25.0 was employed for statistical analyses (SPSS, IBM Corp.).

In total 593 HM patients infected with omicron were included, whereof 309 patients were admitted to hospital and 284 patients stayed home (eTable 1). Hospitalized patients were older than nonhospitalized patients, had more comorbidities, and had a higher proportion of patients with neutropenia, lymphocytopenia, active hematological malignancy, and treatment with anti-CD20 antibodies (eTable 1). At least one dose of vaccine had been administered to 83.1% of all patients, with a nonsignificant difference between nonhospitalized and hospitalized patients, 86.3% compared to 80.3% (p = 0.157) (eTable 1, eTable 2).

Overall mortality among hospitalized patients was 16.5% (51/309), of which 61% was classified as attributable to omicron, 35.3% contributable, and 3.9% unrelated. Factors associated with attributable and contributable mortality in hospitalized patients were older age (analyzed as continuous variable, hazard ratio (HR) 1.05 (95% confidence interval (CI) 1.02–1.07, p < 0.001)) and active malignancy (HR 2.5 [95% CI 1.3–4.8, p = 0.007]) (Table 1). Having received at least one dose of SARS-CoV-2 vaccine was protective in univariable analysis (HR 0.53 [95% CI 0.29–0.96, p = 0.036]), but did not reach statistical significance in multivariable analysis (HR 0.58 [95% CI 0.32–1.05, p = 0.074]) (eFigure 2a, Table 1).

Progression to critical infection occurred in 53 (17.0%) of hospitalized patients. Risk factor for progression to critical COVID-19 was pre-existent chronic pulmonary disease (odds ratio (OR) 3.2 [95% CI 1.4–7.3, p = 0.005]) (eTable 3). Baseline lymphocytes of ≥ 500 cells/mm³ were protective (OR 0.4 [95% CI 0.18–0.90, p = 0.027]) while a lymphocyte count between 200 and 499 cells/mm³ was protective in univariable analysis (OR 0.44 [95% CI 0.16–1.20, p = 0.108]). Three doses of vaccine were protective (OR 0.29 [95% CI 0.13–0.64, p = 0.003]), but not two doses (OR 0.73 [95% CI 0.33–1.66, p = 0.457]) (eTable 3). Mortality among patients with critical infection was 39.2% (20/53). Administration of antibody-based antiviral treatment with sotrovimab or fixagevimab/cilgavimab was associated with a lower risk for mortality in critical infection (HR 0.13, [95% CI 0.02–0.61, p = 0.010]) (eFigure 2b, Table 1), while administration of other SARS-CoV-2 directed monoclonal antibodies was not (data not shown).
### TABLE 1  Risk factor analysis for omicron-related mortality in hospitalized patients

|                     | Hospital Overall | Hospital Critical | Abbreviations: 95% CI, 95% confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. |
|---------------------|------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                     | Unvariable       | Multivariable     |                                                                                      |                                                                                                                                  |
|                     | p value HR       | 95% CI            | p value HR       | 95% CI            |                                                                                      |                                                                                                                                  |
| Sex                 |                  |                   |                                                                                      |                                                                                                                                  |
| Female              | —                | —                 | —                        | —                 | —                        | —                                                                             |
| Male                | .609 0.866 1.501 | 0.500 3.844       | .014 1.214 3.957     | 0.055 1.287 3.826  | .604 1.491 6.738          | 0.330 1.926 6.288                                                                 |
| Age                 | <.001 1.047 1.022 1.072 | <.001 1.044 1.020 1.068 | .036 0.530 0.293 0.959 | 0.074 0.581 0.320 1.054 | 0.592 0.780 0.314 1.934 | 0.369 1.330 0.404 4.377                                                                 |
| Status of malignancy at COVID-19 onset |                  |                   |                                                                                      |                                                                                                                                  |
| Controlled malignancy | —                | —                 | —                        | —                 | —                        | —                                                                             |
| Stable malignancy   | 0.348 1.526 3.684 | 0.500 2.957       | .014 1.760 4.762       | 0.055 1.287 3.826  | .604 1.491 6.738          | 0.330 1.926 6.288                                                                 |
| Active malignancy   | 0.003 2.726 5.229 | 0.007 4.762       | 0.088 2.511 7.240      | 0.055 2.887 9.776  | .604 1.491 6.738          | 0.330 1.926 6.288                                                                 |
| Baseline malignancy |                  |                   |                                                                                      |                                                                                                                                  |
| Lymphoproliferative malignancies | — | — | —                       | — | — | —                                                                             |
| Myeloproliferative malignancies | 0.508 0.798 1.556 | — | — | — | — | —                                                                             |
| Aplastic anemia     | 0.974 0.000 0.000 | —                 | —                        | —                 | —                        | —                                                                             |
| Previous SARS-CoV-2 vaccination | 0.036 0.530 0.293 0.959 | 0.074 0.581 0.320 1.054 | 0.592 0.780 0.314 1.934 | — | — | —                                                                             |
| COVID-19 treatment |                  |                   |                                                                                      |                                                                                                                                  |
| No treatment        | —                | —                 | —                        | —                 | —                        | —                                                                             |
| Any remdesivir, minus sotrovimab | 0.857 0.941 1.817 | 0.095 0.967 0.314 2.975 | 0.200 0.452 1.34 1.521 | — | — | —                                                                             |
| Any sotrovimab + any tixagevimab/cilgavimab | 0.134 0.531 0.232 1.216 | 0.021 0.172 0.039 0.766 | 0.010 0.134 0.029 0.614 | — | — | —                                                                             |
| Plasma only + molnupiravir only | 0.639 1.330 0.404 4.377 | 0.776 1.242 0.280 5.513 | 0.604 1.491 0.330 6.738 | — | — | —                                                                             |
| Previous administration of antiCD20 | 0.760 1.090 0.626 1.898 | 0.187 0.528 0.205 1.363 | — | — | —                                                                             |

**Abbreviations:**
- 95% CI: 95% confidence interval
- COVID-19: coronavirus disease 2019
- HR: hazard ratio
- SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

**Notes:**
- Controlled malignancy: Complete remission or partial remission; active malignancy: onset or refractory/resistant.
- No treatment: Includes treatment with acyclovir, favipiravir, casivirimab/imdevimab, bamlanivimab/etesevimab and regdanvimab.
- Any remdesivir, minus sotrovimab: Includes all antiviral treatment which included remdesivir except for sotrovimab and tixagevimab/cilgavimab.
- Any sotrovimab + any tixagevimab/cilgavimab: Includes all antiviral treatment which included sotrovimab or tixagevimab/cilgavimab.
- Plasma only + molnupiravir only: Includes single therapy with convalescent plasma or molnupiravir.
This observational study from the EPICOVIDEHA registry is the first report on clinical data in a large cohort of omicron-infected HM patients. The main finding is that infection with omicron is associated with considerable attributable mortality in HM patients. Additionally, we found factors associated with a potential antibody response, that is, not having severe lymphocytopenia and having received at least three doses of SARS-CoV-2 vaccine, and treatment with monoclonal antibodies with in vitro effect against omicron, to be protective against progression to critical infection and death.

The mortality among hospitalized HM patients was 16.5% which is lower than during the COVID-19 waves of 2020 and 2021, but considerably higher than previously reported mortality rates in immunocompetent patients with omicron infection.\textsuperscript{1,3,4} Data regarding outcomes in HM patients with omicron are scarce, but our finding is in agreement with a small recent preliminary report on omicron in chronic lymphoid leukemia patients, where 23% 30-day mortality was reported.\textsuperscript{7} Thus, as opposed to immunocompetent patients, infection with omicron in HM patients is still associated with a considerable mortality in hospitalized patients.

Due to serological data not being registered consistently by all participating centers, the protective effect of vaccination was analyzed according to number of doses administrated. For the whole cohort, the vaccination rate was numerically higher in non-hospitalized patients than hospitalized patients, 86.3% compared to 80.3%, respectively. Administration of at least one dose of vaccine was protective against death in all hospitalized patients in univariable analysis but not in multivariable analysis (p = .074). Three doses of vaccine were protective against progression to critical infection in hospitalized patients, while two doses were not, a finding that is well in line with the additional booster effect against omicron in immunocompetent patients.\textsuperscript{7,8} Interestingly, lymphocytopenia, which has been associated with a poor vaccine response, was also associated with progression to critical infection.\textsuperscript{9} Finally, among patients that progressed to critical infection, vaccination was not associated with a protective effect against death, contrary to treatment with monoclonal antibodies with in vitro effect against omicron.\textsuperscript{7} These findings raise the hypothesis that while vaccination appears to be protective against severe infection and death, lack of response, as manifested by progression to critical infection despite vaccination, may be at least in part compensated by passive immunization using SARS-CoV-2-antagonizing monoclonal antibodies. This hypothesis is in line with the findings from a large, randomized treatment study, reporting significantly decreased mortality with administration of monoclonal antibodies in hospitalized seronegative immunocompetent patients.\textsuperscript{10}

Important limitations of our study include the retrospective observational design and the accompanying risk for selection bias at participating sites, lack of serological data, and lack of sequencing data which would enable distinction between the different omicron variants. Due to these limitations, caution must be taken in interpretation and generalization of the results.

In conclusion, infection with omicron in patients with HM was associated with considerable morbidity and mortality, vaccination with at least three doses was protective against progression to critical infection, and treatment with monoclonal antibodies was associated with reduced mortality in patients that had progressed to critical infection.

**FUNDING INFORMATION**

EPICOVIDEHA has received funds from Optics COMMIT (COVID-19 Unmet Medical Needs and Associated Research Extension) COVID-19 RFP program by GILEAD Science, United States (Project 2020-8223).

**CONFLICT OF INTEREST**

The authors declare that they have no competing interests for this work.

**DATA AVAILABILITY STATEMENT**

The datasets used and/or analyzed during the current study are not publicly available due to individual privacy reason, but are available from the corresponding author on reasonable request.

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**SUPPORTING INFORMATION**

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