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Breakthrough COVID-19 in vaccinated patients with hematologic malignancies: results from EPICOVIDEHA survey

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Abstract:

Limited data have been published on the epidemiology and outcomes of breakthrough COVID-19 in patients with hematological malignancy (HM) after anti-SARS-CoV-2 vaccination.

Adult HM who received at least one dose of anti-SARS-CoV-2 vaccine and diagnosed with breakthrough COVID-19 between January 2021 and March 2022 and registered in EPICOVIDEHA were included in this analysis.

A total of 1548 cases were included, mainly with lymphoid malignancies (1181 cases, 76%). After viral genome sequencing in 753 cases (49%), Omicron variant was prevalent (517, 68.7%). Most of the patients received at least two vaccine doses before COVID-19 (1419, 91%), mostly mRNA-based (1377, 89%). Overall, 906 patients (59%) received specific treatment for COVID-19. After 30-days follow-up from COVID-19 diagnosis, 143 patients (9%) died. The mortality rate in patients with Omicron variant was of 7.9%, comparable to that reported for the other variants. The 30-day mortality rate was significantly lower than in the pre-vaccine era (31%). In the univariable analysis, older age ($p<0.001$), active HM ($p<0.001$), severe and critical COVID-19 ($p=0.007$ and $p<0.001$, respectively) were associated with mortality. Conversely, patients receiving monoclonal antibodies, even for severe or critical COVID-19, had a lower mortality rate ($p<0.001$). In the multivariable model, older age, active disease, critical COVID-19 and at least 2-3 comorbidities were correlated with a higher mortality, whereas the administration of monoclonal antibodies, alone ($p<0.001$) or combined with antivirals ($p=0.009$), was observed protective.

While mortality is significantly lower than in the pre-vaccination era, breakthrough COVID-19 in HM is still associated with considerable mortality. Death rate was lower in patients who received monoclonal antibodies, alone or in combination with antivirals.

EPICOVIDEHA (www.clinicaltrials.gov; National Clinical Trials identifier NCT04733729) is an international open web-based registry for patients with HMs infected with SARS-CoV-2.

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Key points

- Mortality rate in hematologic malignancy patients with breakthrough COVID-19 is about 9%, lower than in the pre-vaccination era
- Patients who received monoclonal antibodies, alone or combined with antivirals, show a better clinical outcome

Abstract

Limited data have been published on the epidemiology and outcomes of breakthrough COVID-19 in patients with hematological malignancy (HM) after anti-SARS-CoV-2 vaccination.

Adult HM who received at least one dose of anti-SARS-CoV-2 vaccine and diagnosed with breakthrough COVID-19 between January 2021 and March 2022 and registered in EPICOVIDEHA were included in this analysis.

A total of 1548 cases were included, mainly with lymphoid malignancies (1181 cases, 76%). After viral genome sequencing in 753 cases (49%), Omicron variant was prevalent (517, 68.7%). Most of the patients received at least two vaccine doses before COVID-19 (1419, 91%), mostly mRNA-based (1377, 89%). Overall, 906 patients (59%) received specific treatment for COVID-19. After 30-days follow-up from COVID-19 diagnosis, 143 patients (9%) died. The mortality rate in patients with Omicron variant was of 7.9%, comparable to that reported for the other variants. The 30-day mortality rate was significantly lower than in the pre-vaccine era (31%). In the univariable analysis, older age ($p<0.001$), active HM ($p<0.001$), severe and critical COVID-19 ($p=0.007$ and $p<0.001$, respectively) were associated with mortality. Conversely, patients receiving monoclonal antibodies, even for severe or critical COVID-19, had a lower mortality rate ($p<0.001$). In the multivariable model, older age, active disease, critical COVID-19 and at least 2-3 comorbidities were correlated with a higher mortality, whereas the administration of monoclonal antibodies, alone ($p<0.001$) or combined with antivirals ($p=0.009$), was observed protective.

While mortality is significantly lower than in the pre-vaccination era, breakthrough COVID-19 in HM is still associated with considerable mortality. Death rate was lower in patients who received monoclonal antibodies, alone or in combination with antivirals.

Introduction

Coronavirus disease 19 (COVID-19) is a life-threatening infection in patients with hematologic malignancies (HM), associated with severe clinical presentation and high risk of death.[1-3] In April 2020, the European Hematology Association – Scientific Working Group Infectious in Hematology (EHA-SWG) opened the EPICOVIDEHA registry to collect all adult patients with HM that developed COVID-19. It aimed to describe the epidemiology, risk factors, and reported a mortality rate of 31.2% among 3801 patients.[4] In December 2020, nearly one year after the first described COVID-19 case, vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were approved and became available first for high-risk patients, including HM.[5-8] The recently published recommendations from the European Conference of Infections in Leukemia (ECIL-9) identify the critical role of mRNA-based vaccines in the fight against COVID-19 and recommend their use in HM, although they may have more limited efficacy amongst severely immunocompromised patients[9].

We collected data on adult HMs who developed breakthrough COVID-19 to assess the vaccine efficacy and the potential role of new emergent treatments against SARS-CoV-2. Our preliminary data, regarding the first 113 patients included, showed a significant decrease in the overall mortality rate in the post-vaccination era (12.4%), which was, however, still remarkably higher compared to the rate observed in the overall population.[10] To date, few reports have been published about severity and outcomes of breakthrough COVID-19 in patients with cancer in general[11-12] and HMs specifically,[13] all showing high rates of severe clinical presentation, hospitalization and death among these patients. This suggests that HMs require close monitoring and increased medical attention when COVID-19 is diagnosed, regardless of previous anti-SARS-CoV-2 vaccine.

In this study, we analyzed the epidemiology and outcome of breakthrough COVID-19 in a large cohort of HMs and evaluated anti-SARS-CoV-2 treatment received by the patients.

Methods

Study design, patients, and procedures

From January 1st, 2021, until March 10th, 2022, participating institutions documented episodes of COVID-19 in their HMs that received anti-SARS-CoV-2 vaccination. Our analysis comprised data from the EPICOVIDEHA registry. EPICOVIDEHA (www.clinicaltrials.gov; National Clinical Trials identifier NCT04733729) is an international open web-based registry for patients with HMs infected with SARS-CoV-2.[14] EPICOVIDEHA was approved by the local ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). When applicable, the respective local ethics committee of each participating institution have approved the project. EPICOVIDEHA methods have been described elsewhere.[4,14] The electronic case report form (eCRF) is accessible online at www.clinicalsurveys.net (EFS Summer 2021, TIVIAN, Cologne, Germany). Each documented patient was reviewed and validated by infectious diseases and hematology experts from the coordination team. Inclusion criteria were: a) active HMs within the last five years before COVID-19 diagnosis, b) patients ≥18 years old, c) laboratory-based diagnosis of SARS-CoV-2 infection, and d) last vaccine dose 15 or more days before PCR confirmed SARS-CoV-2 infection. Data on baseline conditions pre-COVID-19 (i.e., age, sex, status of HM at COVID-19 diagnosis, factors predisposing for COVID-19), HM clinical management (i.e., last HM treatment strategy, vaccine type, spike protein concentration at diagnosis of COVID-19, COVID-19 diagnosis and management (i.e., reason for diagnostic test, symptoms at onset, stay during infection, treatments received for infection) and outcome (i.e., mortality, attributable mortality [assessed by the medical team in charge of the patient], last day of follow-up) were collected. Status of HM at COVID-19 onset and last follow up was defined as active (onset and refractory/resistant), stable disease or controlled (complete and partial response) based on the reports from the respective participating institution.

Study objectives

The primary objective of this study was to assess the epidemiology and the outcome of HMs affected by breakthrough COVID-19. Secondary objectives were: 1) to estimate the relative frequency of disease severity, graded according to international standards in our patient population;[15-16] 2) to evaluate the relative frequency of ICU admission among our patients; 3) to

evaluate the overall case-fatality rate; 4) to explore the impact of cancer treatment phase (induction, consolidation, maintenance, palliative, re-induction); 5) to explore the impact of vaccine doses administered to patient outcomes; 6) to explore the impact of COVID-19 treatment on patient outcomes. Moreover, data collected were compared with those reported in our previously published study performed in the pre-vaccine era by using the same registry.[4]

Sample size and statistical analysis

No *a priori* sample size calculation was performed for this analysis. Categorical variables are presented with frequencies and percentages, and continuous variables with median, interquartile range (IQR) and absolute range. Univariable Cox regression model was performed with variables suspected to play a role in the mortality of HM patients with COVID-19. Variables with a p-value ≤ 0.1 were considered for multivariable analysis. A multivariable Cox regression model was calculated with the Wald backward method. Mortality was analyzed by using Kaplan–Meier survival plots. Log-rank test was used to compare the survival probability of the patients included in the different models. A p-value ≤ 0.05 was considered statistically significant. No a priori sample size calculation was done for this exploratory study. SPSSv25.0 was employed for statistical analyses (SPSS, IBM Corp., Chicago, IL, United States). Patients with missing data in essential fields (i.e. HM, chemotherapeutic program, vaccination status, COVID-19 management or survival status) were considered as not valid and, then, excluded from the final analysis. Among the valid cases, if a value in a specific variable was missing or unknown, it is indicated as such in the descriptive analysis. Patients with missing data in a certain variable were excluded from regression analyses in case that variable was included into such analyses.

Data sharing statement

Requests for data sharing may be submitted to Livio Pagano (livio.pagano@unicatt.it)

Results

Study population

A total of 94 centers in 26 countries, mainly from Europe, participated and registered 1583 cases. A list of enrolled cases from each participating country is available in the supplemental material (Fig. S1 and Fig. S2 panel A). Out of these 1583 cases, 35 were excluded since COVID-19 was diagnosed within 14 days from the first vaccine dose. Clinical characteristics of 1548 evaluable cases are reported in Table 1. Lymphoid malignancies were the largest subgroup, accounting 1181 cases (76.3%); the most frequently reported diagnosis was non-Hodgkin lymphoma (NHL, 549 cases). Among myeloid malignancies, the most frequent diagnosis was acute myeloid leukemia (AML, 140 cases). We found a significantly different distribution lymphoid/myeloid malignancies with that reported in pre-vaccination era (pre-vaccination lymphoid malignancies cases: 67.3% *vs* post-vaccination: 76.3%, p<0.001). At the time of COVID-19 diagnosis, most patients had a controlled malignancy (n=821, 53%), 322 (20.8%) a stable disease and the remaining 365 (23.6%) an active disease with 185 cases registered at HM onset. The most frequently reported last HM treatment was immuno-chemotherapy or immunotherapy alone (n=708, 42%), followed by targeted therapies (n=311, 20.1%) and conventional chemotherapy (n=234, 15.1%); 92 patients (5.9%) had received HSCT within six months before COVID-19 (allogeneic: 76; autologous: 16) and 8 had chimeric antigen receptor T cells (CAR-T) therapy. Most patients presented at least one comorbidity (60.7%) and 180 (11.6%) had a history of smoking; a complete list of comorbidities and associated clinical outcomes is available in the supplemental material (Table S1).

COVID-19 severity, variants and anti-SARS-CoV-2 spike proteins

COVID-19 was mild, severe, or critical in 39%, 32.9% and 9.8% of cases, respectively. Two-hundred eighty-three patients (18.3%) were asymptomatic and in most of them the diagnosis was made in screening programs (Table 1). We found a significantly lower rate of severe or critical cases compared to that we reported in pre-vaccination era (pre-vaccination: 2425/3801, 63.8% *vs* post-vaccination: 661/1545, 42.7%; p<0.001). Overall, 823 (53.2%) patients required

hospitalization and amongst them 152 (18.1%) required admission to intensive care (ICU). The hospitalization and ICU admission rate was significantly lower than reported in the pre-vaccination era (53.2% *vs* 73%; p<0.001 and 9.8% *vs* 18.1%; p<0.001, respectively). The asymptomatic cases percentage was of 18.3% (283/1548), similar to that reported in our previous publication with data from the pre-vaccine era (17.8%, 675/3801).[4] Viral genomes were studied in 753 cases (48.6%), with the different *Omicron* variant as the most frequent viral strain (517/753, 68.7%). Most patients received two or three anti-SARS-CoV-2 vaccine doses (91%), mostly with mRNA-based technology (89%); only few patients (8.6%) received a vector-based vaccine and a minority of them an inactivated vaccine (Table 1, Fig. S2 panel B, C and D). Anti-SARS-CoV-2 spike protein IgG levels were analyzed in 244 (15.8%) fully vaccinated patients, 2-4 weeks after the last vaccine dose; among these patients, 109 (44.7%) presented an antibody response (optimal: 75, 30.7%; weak: 34, 13.9%), whereas the remaining 135 (55.3%) were non-responders. Most patients who did not have a serological response to vaccines were affected by lymphoid malignancies, as expected (126/135, 93.3%; Fig. 1).

COVID-19 treatments and risk factors for mortality

Overall, 906 patients (58.5%) received a specific treatment for COVID-19, whereas 642 (41.5%) were not treated, or received symptomatic therapies (non-steroidal anti-inflammatories, painkillers, antipyretics). Among patients who received a specific treatment for COVID-19, 311 (34.3%) were treated with monoclonal antibodies only, 246 (27.1%) with corticosteroids only, 218 (24.1%) with antivirals only, 108 (11.9%) with antiviral plus monoclonal antibodies and the remaining 23 with convalescent plasma. Details on COVID-19 treatments and outcomes are displayed in the supplemental material (Table S2). Overall day-30 mortality (i.e., from COVID-19 diagnosis) was 9.2% (143/1548 patients died); if we consider symptomatic patients only, the day-30 mortality rate was of 10.3% (130/1265 symptomatic patients died). The primary cause of death was COVID-19 in 97 patients (67.8%), a combination of both, COVID-19 and progressive HM in 39 cases (27.2%) and HM alone or combined with other reasons in the remaining 7 patients (4.8%). The mortality rate was significantly lower than that reported in pre-vaccine era (pre-vaccine 31.2%

vs post-vaccine 9.2%; p<0.001). Looking at two of the largest patient cohorts (i.e. chronic lymphocytic leukemia, CLL and NHL) we evaluated the potential role of chemotherapeutic treatment type on mortality rate. In CLL patients, we did not observe any significant difference in terms of 30-days mortality rate among patients who had received immune-chemotherapy (13.4%), immunotherapy alone (12.5%) or new targeted therapies (16.1%). On the contrary, in NHL we did observe a slightly higher mortality rate for patients recently treated with CAR-T (20%), compared to those treated with immune-chemotherapy (8%), immunotherapy alone (14.3%) or targeted therapies (9.5%). The outcome of patients according to clinical characteristics, vaccine received and specific treatments against SARS-CoV-2 is detailed in Table 2. As shown in Fig. 2, we did not find any significant difference in terms of 30-day mortality rate among the different HM (p=0.693), in contrast to that observed in the pre-vaccination era in which we reported a higher number of fatalities in acute myeloid leukemia/myelodysplastic syndrome patients. In univariable analysis, the factors associated with a worse mortality rate were older age (p<0.001), active HM disease (p<0.001), and presence of 2-3 comorbidities (p<0.001) ~~severe and critical COVID-19 (p=0.007 and p<0.001, respectively)~~ (Table 3). Referring to the age, patients younger than 60 years showed a more favorable outcome (30-days mortality rate: 2.6%), compared with patients aged 60-69 years (7%), 70-79 years (14.8%) and 80 years or more (19.6%) (p<0.001). Conversely, we observed a better clinical outcome for patients who received monoclonal antibodies (with or without antivirals; Fig. 3). Analyzing the severity of COVID-19 presentation, a better clinical outcome was observed in patients treated with monoclonal antibodies alone for asymptomatic, mild, or severe disease and with monoclonal antibodies combined with antivirals in critical cases (Fig. 4). We did not find differences in terms of outcome according to the number of vaccine doses received; however, a slightly better clinical outcome was evident among patients who received three to four doses versus one to two doses (p=0.040, Table 3). We did not observe differences in survival when sorting patients according to viral strain detected (p=0.664; Fig. 5), or post-vaccine anti-spike IgG levels (Table 2).

In the multivariable model older age, active disease, ~~critical COVID-19~~ and 2-3 comorbidities were the factors significantly correlated with a higher mortality, whereas receiving anti-SARS-CoV-

403 2 treatment with monoclonal antibodies alone or combined with antivirals was independently
404 associated with a lower mortality (HR: 0.155, 95%CI: 0.077-0.313; p<0.001 - HR: 0.407, 95%CI:
405 0.206-0.803; p=0.010, respectively) (Table 3). Survival and severity according to vaccine doses
406 administration and post-vaccine anti-spike IgG levels are shown in Fig. 6 and Fig. 1, respectively.

Discussion

In the pre-vaccination era, several studies reported a high COVID-19 mortality in HM.[1-4] From December 2020, anti-SARS-CoV-2 vaccines have been administered in cancer patients, including those with HM.[7-8] Most published studies in HMs confirmed the efficacy and safety of vaccines, particularly those using mRNA, however, most showing less efficacy in patients with lymphoid malignancies treated with immunosuppressive drugs.[17-22]

The current study was performed in a large cohort of vaccinated HMs to evaluate epidemiology, risk factors for adverse clinical outcome and treatments of breakthrough COVID-19. We found a predominance of lymphoid malignancies, higher than observed in our previous survey during the pre-vaccine era; this difference might be explained by the lower efficacy of vaccines in this patient population, as further suggested by the high rate of serological non-responders among patients with lymphoid malignancies when evaluating anti-spike IgG levels These data are consistent with those in a recent report describing COVID-19 breakthrough infections in a large HM patient cohort, mostly consisting of patients with lymphoid malignancies.[13] Advanced age, presence of comorbidities and active HM were confirmed in the present study as factors that negatively influenced clinical outcome and survival; these were the same risk factors that had previously been reported in the pre-vaccination era.[1-4] Interestingly, in our study, the underlying malignancy did not have a significant impact on survival, which was different from our previous experience in non-vaccinated patients, where AML and myelodysplastic syndrome were associated with higher mortality risk.[4] A potential explanation for this difference might be the better efficacy of anti-SARS-CoV-2 vaccines in myeloid malignancies,[23-25] than in lymphoid malignancies;[17-22] however, we may hypothesize new specific anti-SARS CoV-2 drugs and better COVID-19 management to be particularly important for patients with AML at risk of increased mortality if urgent chemotherapy is delayed. Similarly, as reported by other studies[13], we did not find any significant difference in terms of mortality among different treatments received for HM. As expected, severe and critical COVID-19 had a worse clinical outcome than mild ones, showing a strong correlation with an increased mortality rate both in univariable and multivariable analysis. Given the vaccine protection, the occurrence of respiratory symptoms, hospitalization rate and

severe-critical clinical presentations were significantly lower than in the pre-vaccination era, even though still strongly higher compared to the overall population.[26-29] However, it is worth underlining that about 20% of patients were asymptomatic and SARS-CoV-2 infection was detected in screening programs. Interestingly, this percentage is analogous to that reported in our published study referring to the pre-vaccination era.[4] Unfortunately, it is not possible to estimate the true incidence of breakthrough infections nor the true number of asymptomatic patients with our data as only patients with COVID19 were included in the registry: ~~we are of course aware~~ this is a potential selection bias, hypothetically hampering the reliability of our results. To the best of our knowledge, only few studies evaluated the incidence and cumulative COVID-19 risk among vaccinated cancer patients, thus showing an increased risk in HM patients compared with the overall population.[30-32] In particular, Lee and coworkers recently published a nice population-based test-negative case-control study in the United Kingdom, evaluating COVID-19 breakthrough infections among a huge number of vaccinated cancer patients and healthy controls. The authors showed that the vaccine effectiveness at 3-6 months after the second dose was lower in the cancer cohort than in the control population and among cancer patients was lower in HM patients, especially those affected by leukemia and lymphoma. Very recently, an Italian study evaluated the immunogenicity and clinical efficacy of anti-SARS-CoV-2 vaccine in HM patients on 365 patients. The authors showed an overall incidence of breakthrough infections of 2.98 per 10000 person-days, significantly lower in post-vaccine seropositive patients, whereas a clear correlation between T-cellular immunity response and risk of post-vaccine infection has not been found.[33]

In our study, we reported an overall 30-day-mortality rate of 9.2%, mainly driven by COVID-19 infection as a direct or contributing factor which is significantly lower than in the pre-vaccination era.[1-4] Moreover, the 30-days mortality rate in symptomatic patients only was of 10.3%. The success of vaccination strategies is likely a major factor in the reported improvement, but not the only factor~~; a better COVID-19 management and the less severity of newer variants may have played a significant role as well.~~ Previous reports suggest that COVID19 management (e.g., steroids, etc.) have also impacted outcomes. Newer variants may be less severe. Data reported in our study are coincident to other recently published reports that showed a significant mortality rate

of COVID-19 breakthrough infections amongst cancer patients[11-12] or more specifically among those affected by HM.[13]

In our study, we collected data about viral genotyping in about half of patients; among those, the most prevalent variant was *Omicron*, accounting for more than 2/3 of patients. These data are not surprising if we consider the large number of registered patients between late 2021 and early 2022, months in which the *Omicron* variant was rapidly spreading throughout Europe.[34] Interestingly, we did not find any significant difference in terms of severity of clinical presentation and mortality rate between *Omicron* and other variants, matching to other small recently published reports on HMs,[35-36] but different to reports in immunocompetent patients in which *Omicron* presents with better outcome than other variants.[34,37]

The vast majority of patients enrolled in our study received two or three vaccine doses; comparing clinical presentation and outcomes, we did not find consistent data supporting a better clinical outcome for patients who had received a higher number of vaccine doses, even though a slight difference in deaths proportion was observed comparing those who received 1-2 *vs* 3-4 doses. However, in multivariable analysis, the number of doses did not significantly impact on the overall 30-day-mortality. Several studies highlighted the role of a third vaccine dose as capable of restoring the immune response in serologically less responsive HM patients.[38-39] However, there are insufficient data to consider patients with low anti-spike antibody titers at high risk of worse outcomes. Indeed, in our study we did not find any differences in terms of outcomes stratifying patients according to serological response after 2-4 weeks from the last vaccine dose. By using World Health Organization international standards (BAU/mL), we did not find a significantly better survival for patients with optimal response, compared to those with weak or no response, although these data were only available in a small percentage of patients (16%). This lack of direct correlation between serological response and survival might be at least in part explained by the putative role of anti-SARS-CoV-2 induced cellular immunity, as suggested by several studies,[23-24,40] since the presence of memory T-cells might control the infection and prevent severe COVID-19 even if high titers of long-lasting neutralizing antibodies are not elicited.[41] However, since a recently

published study did not find a clear correlation between post-vaccine T-cell immunity and vaccine clinical efficacy,[33] further studies are warrant to better understand this aspect. Another possible explanation is related to the role of the specific anti-SARS-CoV-2 treatments (i.e. monoclonal antibodies, antivirals) that could have partially balanced the lack of protection of serological non responders. Indeed, from our survey, monoclonal antibodies with or without antivirals showed a high clinical activity irrespective of COVID-19 severity, showing the best efficacy when administered as single agents in asymptomatic mild and severe patients, and when administered in combination with antivirals in critical ones. The role of monoclonal antibodies in mitigating the negative impact of weak vaccine responses is supported by a recent randomized trial evaluating their role in immunocompetent people without serological response.[42] Moreover, our multivariable model confirmed the positive impact on 30-day mortality risk for patients who had received monoclonal antibodies alone or combined with antivirals. We are aware that the present study has limitations due to the retrospective observational design and the possible selection bias due to the large number of participating institutions. Moreover, viral genotyping and serological data were not available for all enrolled patients and we did not know whether COVID-19 was first diagnosed in hospital or in the community, a potential key information for discriminating patient risk and infection natural history. Further prospective studies better evaluating the role of vaccine response in HM are needed.

In conclusion, our survey has shown that vaccination and novel COVID-19 treatments have brought significant improvements in terms of mortality in HMs. To further improve the prognosis of these patients, the role of additional booster vaccine doses, and the role of prophylactic monoclonal antibodies in patients with an ineffective response to vaccination should be investigated.

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Author contribution

LP served as the principal investigator. JSG and FM served as project manager and research assistant, respectively. LP, JSG, and FM contributed to study design, study supervision, and data interpretation and wrote the paper. AB, PC, MH, PK, AP, FP, AOC and LP conceived the registry idea. LP, JSG and FM did the statistical plan, analysis and interpreted the data. All the authors recruited participants and collected and interpreted data. All authors contributed to manuscript writing and review of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure of conflicts of interest

All the authors have no disclosures to declare for this submitted paper.

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652 # Tables

Table 1. Clinical characteristics of 1548 vaccinated HM patients who developed COVID-19

	n	%
Sex		
Female/male	661/887	42.7/57.3
Age		
Median (y.o.) (IQR) [range]	66 (55 - 75) [18 - 96]	
<50/>50 y.o.	301/1247	19.5/80.5
Comorbidities		
None/ 1-2-3 comorbidities	608/940	39.3/60.7
Smoking history	180	11.6
Malignancy		
Lymphoid malignancies	*1181*	*76.3*
Acute lymphoid leukemia	64	4.1
Chronic lymphoid leukemia	211	13.6
Hodgkin lymphoma	65	4.2
Non-Hodgkin lymphoma	549	35.5
Low grade	289	18.7
High grade	260	16.8
Multiple myeloma	275	17.8
Amyloid light-chain amyloidosis	10	0.6
Hairy cell leukemia	7	0.5
Myeloid malignancies	*356*	*23.0*
Acute myeloid leukemia	140	9.0
Chronic myeloid leukemia	44	2.8
Essential thrombocythemia	18	1.2
Myelodysplastic syndromes	93	6.0
Low-intermediate risk	69	4.5
High risk	23	1.5
Myelofibrosis	39	2.5
Polycythemia vera	16	1.0
Systemic mastocytosis	6	0.4
Aplastic anemia	*11*	*0.7*
Malignancy status before COVID-19		
Controlled disease	821	53.0
Complete remission	524	33.9
Partial remission	297	19.2
Stable disease	322	20.8
Active disease	365	23.6
Onset	185	12.0
Refractory/Resistant	180	11.6
Unknown	40	2.6
Last malignancy treatment		
alloHSCT	76	4.9
autoHSCT	16	1
CAR-T	8	0.5
Chemotherapy		
Conventional chemotherapy	234	15.1
Demethylating agents	80	5.2
Immunotherapy	146	5.7
Immuno-chemotherapy	562	36.3
Targeted therapy	311	20.1
Supportive measures	36	2.3

Table 1. Clinical characteristics of 1548 vaccinated HM patients who developed COVID-19

	n	%
No treatment	136	8.8
Vaccination		
One dose	129	8.3
Two doses (or J&J)	770	49.7
Three doses	639	41.3
Four doses	10	0.6
Type of vaccine		
mRNA	1377	89.0
BioNTech/Pfizer	1121	72.4
Moderna COVE	256	16.5
Vector-based	133	8.6
AstraZeneca Oxford	99	6.4
Sputnik	13	0.8
J&J – Janssen	21	1.4
Inactivated	38	2.5
CoronaVac | Sinovac	21	1.4
Sinopharm	17	1.1
Spike protein dosage after vaccination (*)		
No response	135	8.7
Weak response	34	2.2
Optimal response	75	4.8
Not tested	1304	84.2
COVID-19 infection		
Wild type	40	2.6
Alpha (α)	34	2.2
Beta (β)	1	0.1
Delta (δ)	161	10.4
Omicron (o)	517	33.4
Not tested	795	51.4
Severity		
Asymptomatic	283	18.3
Mild infection	604	39.0
Severe infection	509	32.9
Critical infection	152	9.8
Symptomatology at onset		
Asymptomatic	306	19.8
Pulmonary	528	34.1
Pulmonary + extrapulmonary	400	25.8
Extrapulmonary	314	20.3
Stay during COVID-19		
Hospital	823	53.2
ICU	152	9.8
Home	800	51.7

HM: hematologic malignancy; **IQR:** interquartile range; **HSCT:** hematopoietic stem cell transplantation; **CART:** chimeric antigen receptor T-cells; **ICU:** intensive care unit.
(*) Referring to World Health Organization international standards, BAU/mL (https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirusdisease-covid-19)

Table 2. Outcome of vaccinated HM patients who developed COVID-19

	Alive		Dead		p-value
	n	%	n		%
Outcome at 30 days					
Alive	1405	90.8			
Dead			143	9.2	
Reason for death					
COVID-19			97	67.8	
COVID-19 + HM			39	27.2	
HMs +/- other reasons			7	4.8	
Sex					
Female	591	89.4	70	10.6	ns
Male	814	91.8	73	8.2	
Age					
18-25 years old	46	100.0	0	0.0	
26-50 years old	250	98.0	5	2.0	
51-69 years old	585	94.2	36	5.8	<0.001
Over 70 years old	524	83.7	102	16.3	
Comorbidities					
No comorbidities	581	95.6	27	4.4	
1 comorbidity	471	91.5	44	8.5	
2 comorbidities	223	84.8	40	15.2	<0.001
3 or more comorbidities	130	80.2	32	19.8	
Smoker or ex-smokers	158	87.8	22	12.2	
Malignancies					
Lymphoid malignancies	1070	92.8	111	7.2	
Acute lymphoid leukemia	62	96.9	2	3.1	
Chronic lymphoid leukemia	186	88.2	25	11.8	
Hodgkin lymphoma	63	96.9	2	3.1	
Non-Hodgkin lymphoma	497	90.5	52	9.5	
Low grade	261	90.3	28	9.7	
High grade	236	90.8	24	9.2	
Multiple myeloma	246	89.5	29	10.5	
Amyloid light-chain amyloidosis	10	100.0	0	0.0	
Hairy cell leukemia	6	85.7	1	14.3	
Myeloid malignancies	324	91.0	32	9.0	
Acute myeloid leukemia	127	90.7	13	9.3	
Chronic myeloid leukemia	43	97.7	1	2.3	
Essential thrombocythemia	18	100.0	0	0.0	
Myelodysplastic syndromes	81	87.1	12	12.9	
Low-intermediate risk	63	91.3	6	8.7	
High risk	18	78.3	5	21.7	
Myelofibrosis	34	87.2	5	12.8	ns
Polycythemia vera	15	93.8	1	6.3	
Systemic mastocytosis	6	100.0	0	0.0	
Aplastic anemia	11	100.0	0	0.0	
Malignancy status					
Controlled disease	768	93.5	53	6.5	
Complete remission	505	96.4	19	3.6	
Partial remission	263	88.6	34	11.4	
Stable disease	294	91.3	28	8.7	
Active disease	307	96.3	58	3.7	
Onset	165	89.2	20	10.8	<0.001
Refractory/Resistant	142	78.9	38	21.1	

Table 2. Outcome of vaccinated HM patients who developed COVID-19

	Alive		Dead		p-value
	n	%	n		%
Unknown	36	90.0	4	10.0	
Last malignancy treatment before COVID-19					
alloHSCT	72	94.8	4	5.2	
autoHSCT	16	100.0	0	0.0	
CAR-T	6	75.0	2	25.0	
Conventional chemotherapy	215	90.6	91.9	8.1	
Demethylating agents	73	90.5	7	9.5	
Immuno-chemotherapy	512	91.2	50	8.8	
Immunotherapy	78	87.6	11	12.3	
Targeted therapy	279	89.8	32	10.2	ns
Supportive measures	28	77.8	8	22.2	
No treatment	126	92.6	10	7.4	
SARS-CoV-2 vaccination before COVID-19 (*)					
One dose	115	89.1	14	10.9	
Two doses	689	89.5	81	10.5	
Three doses	591	91.9	48	8.1	ns
Four doses	10	100.0	0	0.0	
Type of SARS-CoV-2 vaccine					
mRNA	1250	90.8	127	9.2	
BioNTech/Pfizer	1011	90.2	110	9.8	
Moderna COVE	239	93.4	17	6.6	
Vector-based	123	92.5	10	7.5	
AstraZeneca Oxford	91	91.9	8	8.1	
Sputnik	13	100.0	0	0.0	
J&J - Janssen	19	90.5	2	9.5	ns
Inactivated	32	84.3	6	15.7	
CoronaVac | Sinovac	18	85.7	3	14.3	
Sinopharm	14	82.4	3	17.6	
Spike protein dosage after vaccination (**)					
No response	118	87.4	17	12.6	
Weak response	31	91.2	3	8.8	ns
Optimal response	71	94.7	4	5.3	
Not tested	1185	90.9	119	9.1	
COVID-19 variant					
Wild type	36	90.0	4	10.0	
Alpha	30	88.2	4	11.8	
Beta	1	100.0	0	0.0	
Delta	141	87.6	20	12.4	
Omicron	476	92.1	41	7.9	ns
Not tested	721	90.7	74	9.3	
COVID treatment					
No specific treatment reported	618	96.3	24	3.7	
Antivirals + monoclonal antibodies	98	90.7	10	9.3	
Antivirals	186	85.3	32	14.7	
Corticosteroids	185	75.2	61	24.8	
Monoclonal antibodies	302	97.1	9	2.9	<0.001
Plasma	16	69.6	7	30.4	
COVID-19 infection					
Asymptomatic	270	95.5	13	4.5	
Mild infection	581	96.1	23	3.9	0.002
Severe infection	456	89.6	53	10.4	

Table 2. Outcome of vaccinated HM patients who developed COVID-19

	Alive		Dead		p-value
	n	%	n		%
Critical infection	98	64.5	54	35.5	
COVID-19 symptoms					
Pulmonary	473	89.6	55	10.4	
Pulmonary + extrapulmonary	349	87.3	51	12.8	0.002
Extrapulmonary	297	94.6	17	5.4	
Asymptomatic	286	93.5	20	6.5	

HM: hematologic malignancy; **IQR:** interquartile range; **HSCT:** hematopoietic stem cell transplantation; **CART:** chimeric antigen receptor T-cells; **ICU:** intensive care unit; **ns:** not statistically significant.

(*) 1-2 doses *vs* 3-4 doses p-value: 0.040

(**) Referring to World Health Organization international standards, BAU/mL (https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirusdisease-covid-19).

Table 3. Univariable and multivariable analysis of factors influencing mortality at 30 days

	Univariable				Multivariable			
	p value	HR	95 CI Lower	95 CI Upper	p value	HR	95 CI Lower	95 CI Upper
Sex								
Female	-	-	-	-				
Male	0.148	0.785	0.566	1.090				
Age	<0.001	1.059	1.044	1.075	<0.001	1.042	1.024	1.061
Malignancy status at COVID-19 diagnosis								
Controlled disease	-	-	-	-	-	-	-	-
Stable disease	0.183	1.364	0.863	2.157	0.767	1.081	0.647	1.806
Active disease	<0.001	2.494	1.718	3.619	0.001	1.981	1.305	3.008
Baseline malignancy								
Aplastic anemia	-	-	-	-				
Lymphoid malignancies	0.875	3032.714	0.000	.				
Myeloid malignancies	0.876	2974.523	0.000	.				
Comorbidities								
0-1 comorbidities	-	-	-	-	-	-	-	-
≥ 2 comorbidities	<0.001	2.802	2.019	3.889	0.027	1.503	1.050	2.229
Type of last vaccination								
mRNA	-	-	-	-				
Vector-based	0.359	0.740	0.389	1.409				
Inactivated	0.122	1.907	0.841	4.326				
SARS-CoV-2								
Omicron	-	-	-	-				
Alpha	0.800	1.142	0.409	3.190				
Beta	0.960	0.000	0.000	.				
Delta	0.210	1.408	0.825	2.403				
Wild type	0.758	1.175	0.421	3.281				
Not tested	0.399	1.179	0.805	1.726				
Vaccine doses before COVID-19								
One dose	-	-	-	-				
Two doses	0.870	1.049	0.595	1.849				
Three or more doses	0.637	0.866	0.478	1.572				
Serological response before COVID-19								
No response	-	-	-	-				
Weak response	0.632	0.740	0.217	2.529				
Optimal response	0.124	0.425	0.143	1.264				
COVID-19 treatment								
Corticosteroids	-	-	-	-	-	-	-	-
Antivirals + monoclonal antibodies	0.001	0.333	0.171	0.651	0.010	0.407	0.206	0.803
Antivirals	0.010	0.570	0.372	0.874	0.099	0.680	0.431	1.075
Monoclonal antibodies	<0.001	0.123	0.061	0.247	<0.001	0.155	0.077	0.313
Plasma	0.852	1.077	0.493	2.355	0.243	1.605	0.726	3.549

Figure legends

Figure 1. Patient distribution by serological response after last COVID-19 vaccination before COVID-19. Panel A) By baseline malignancy; Panel B) By last treatment for hematological malignancy immediately before COVID-19

Figure 2. Survival probability by most prevalent underlying condition.

Figure 3. Survival probability of patients by COVID-19 treatment.

Figure 4. Survival probability by COVID-19 treatment and COVID-19 severity. Panel A) Asymptomatic patients; Panel B) Mild patients; Panel C) Severe patients; Panel D) Critical patients.

Figure 5. Survival probability by SARS-CoV-2 variant.

Figure 6. Patient distribution by number of doses administered before COVID-19 and COVID-19 severity.

Figure 1

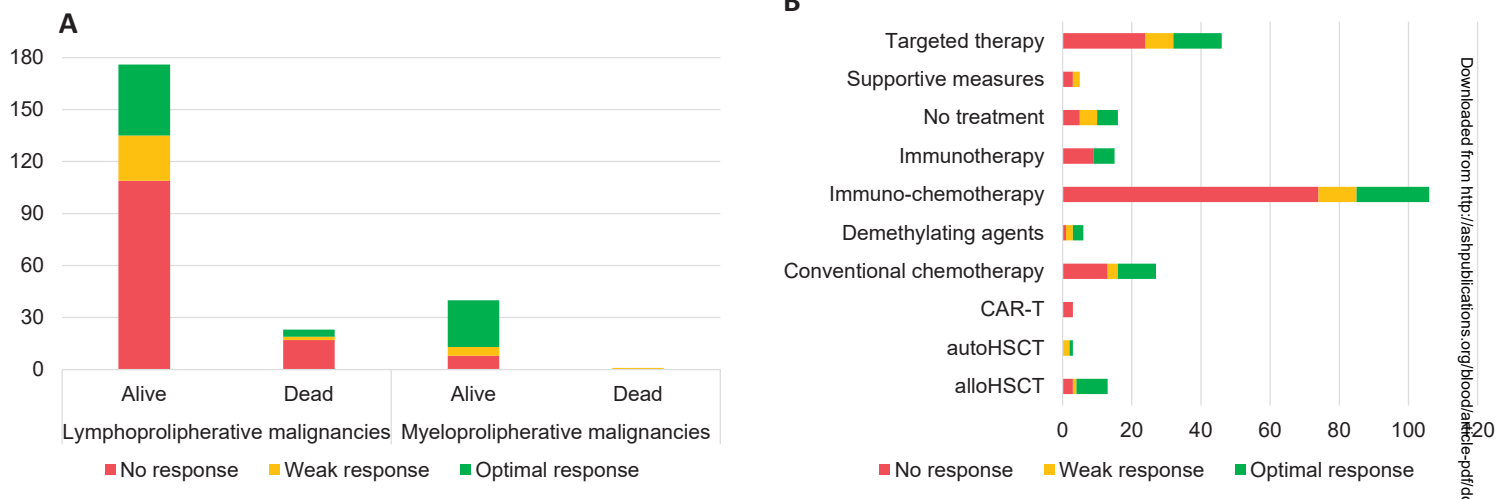
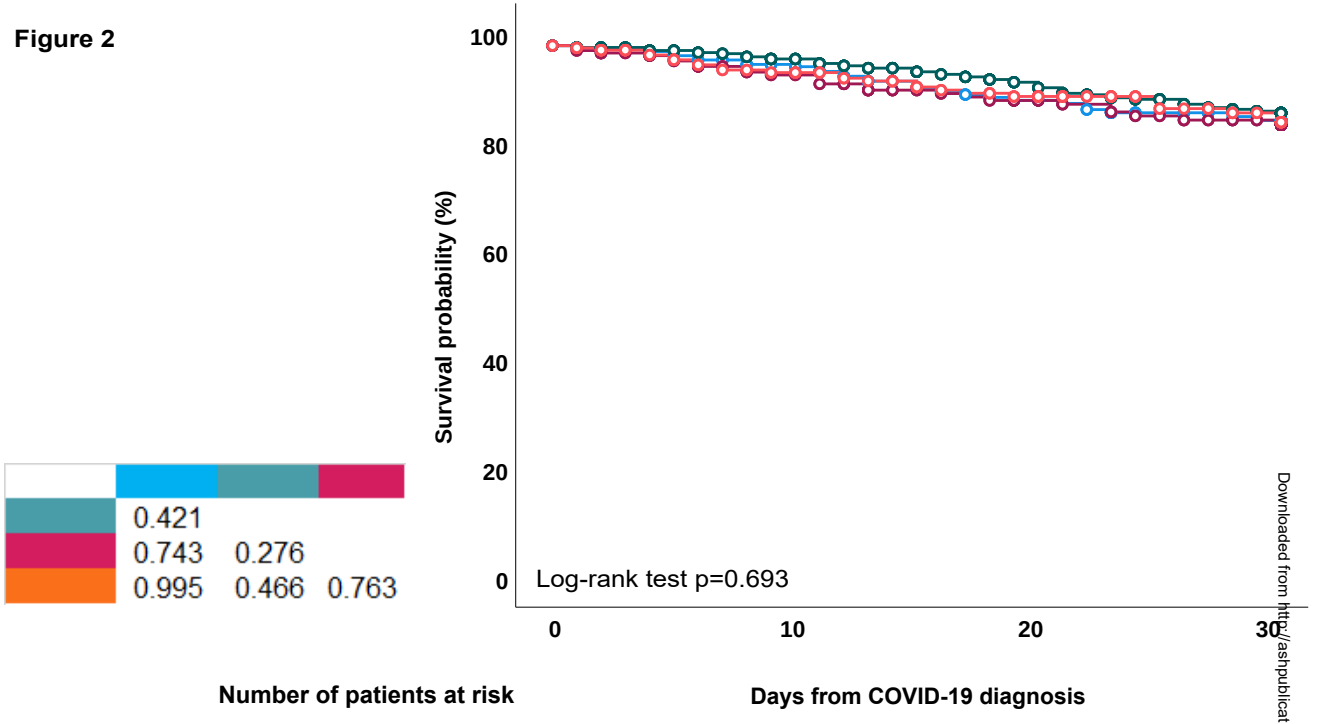


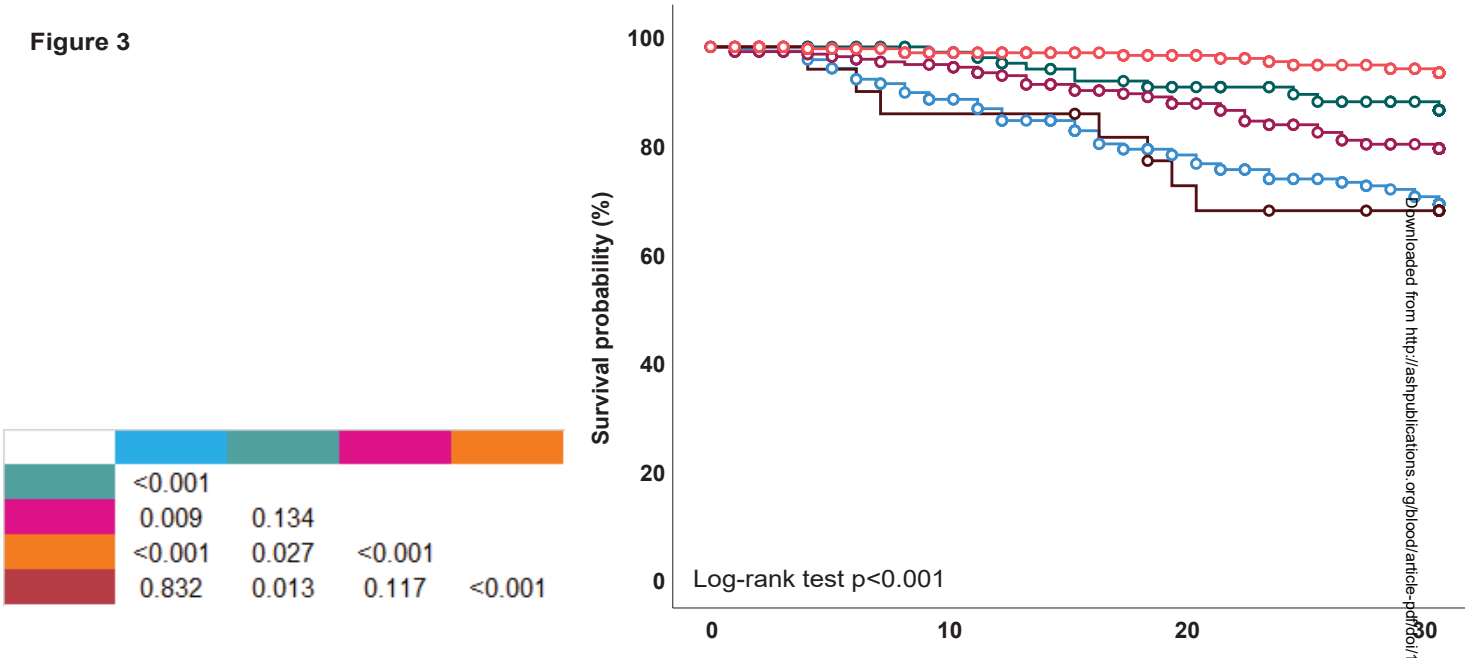
Figure 2



Number of patients at risk

MM	275	215	152	114
NHL	549	452	346	236
CLL	211	165	125	92
AML/MDS	233	183	141	96

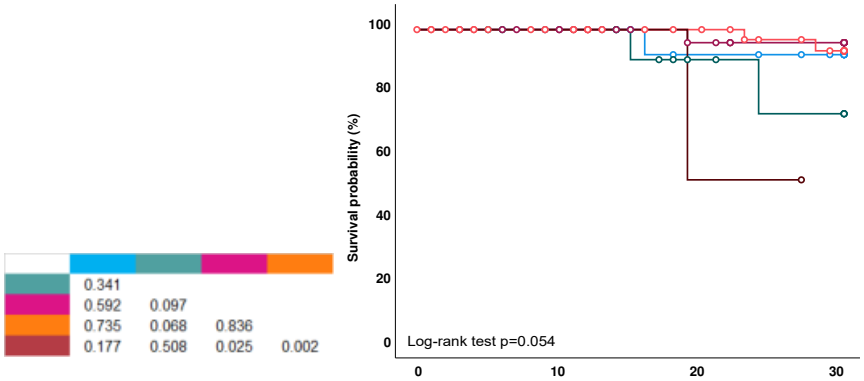
Figure 3



Number of patients at risk				
Corticosteroids	246	200	139	97
Antivirals + monoclonal antibodies	108	94	72	54
Antivirals	218	184	135	96
Monoclonal antibodies	311	233	173	124
Plasma	23	20	15	12

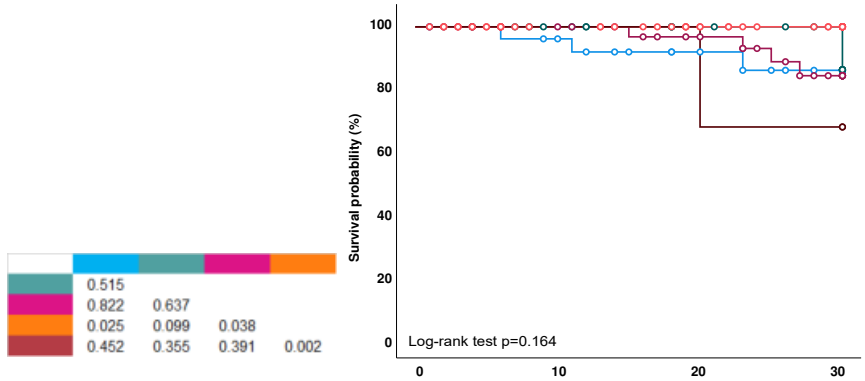
Figure 4

Asymptomatic patients



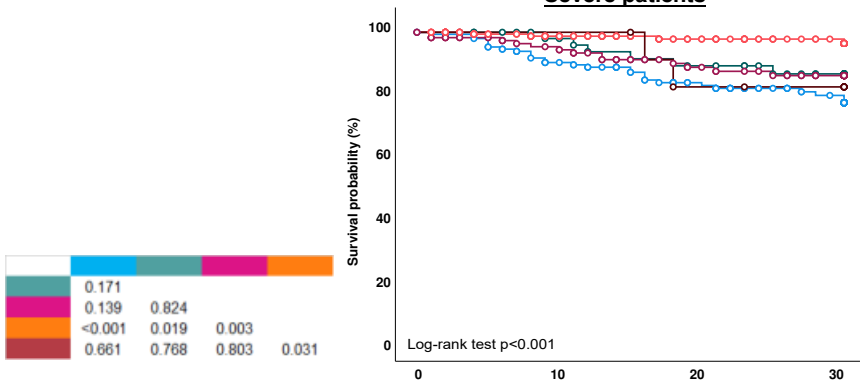
Number of patients at risk	Days from COVID-19 diagnosis			
Corticosteroids	14	13	10	7
Antivirals + monoclonal antibodies	14	12	6	4
Antivirals	33	30	21	17
Monoclonal antibodies	51	40	32	24
Plasma	2	2	1	0

Mild patients



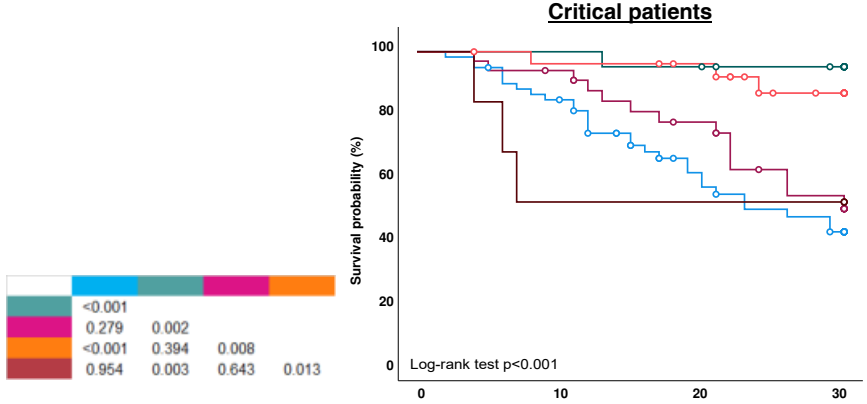
Number of patients at risk	Days from COVID-19 diagnosis			
Corticosteroids	27	23	16	10
Antivirals + monoclonal antibodies	20	16	10	7
Antivirals	39	33	26	15
Monoclonal antibodies	53	37	28	19
Plasma	3	3	3	2

Severe patients



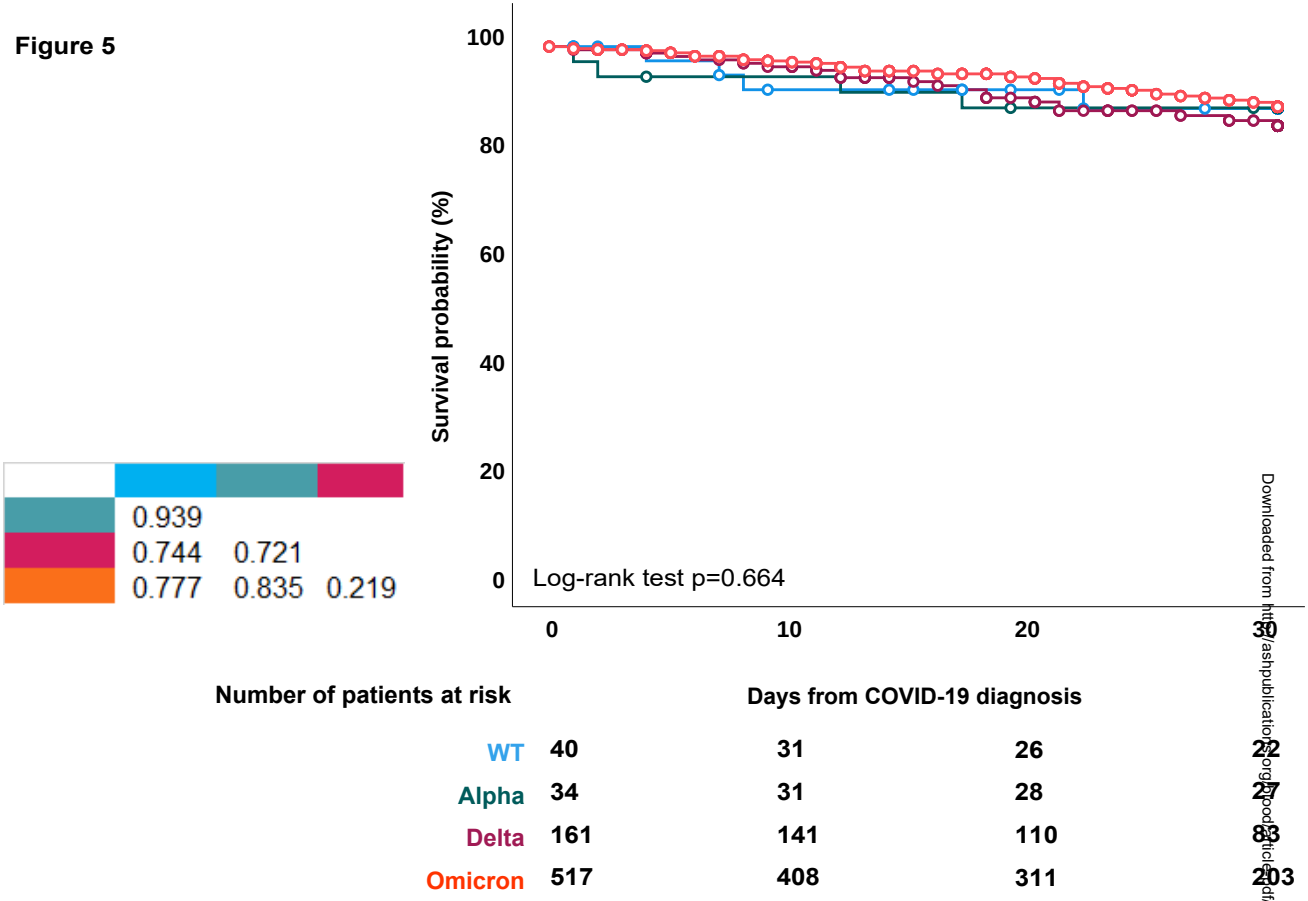
Number of patients at risk	Days from COVID-19 diagnosis			
Corticosteroids	148	117	88	65
Antivirals + monoclonal antibodies	54	46	37	27
Antivirals	114	92	67	52
Monoclonal antibodies	181	132	91	68
Plasma	12	12	8	7

Critical patients



Number of patients at risk	Days from COVID-19 diagnosis			
Corticosteroids	57	47	25	15
Antivirals + monoclonal antibodies	20	20	19	16
Antivirals	32	29	21	
Monoclonal antibodies	26	24	22	
Plasma	6	3	3	

Figure 5



Number of patients at risk — **Days from COVID-19 diagnosis**

WT	40	31	26	22
Alpha	34	31	28	27
Delta	161	141	110	83
Omicron	517	408	311	203

Figure 6