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

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217 **Key points**

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

222 **Abstract**

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

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

228 A total of 1548 cases were included, mainly with lymphoid malignancies (1181 cases, 76%).
229 After viral genome sequencing in 753 cases (49%), Omicron variant was prevalent (517, 68.7%).
230 Most of the patients received at least two vaccine doses before COVID-19 (1419, 91%), mostly
231 mRNA-based (1377, 89%). Overall, 906 patients (59%) received specific treatment for COVID-19.
232 After 30-days follow-up from COVID-19 diagnosis, 143 patients (9%) died. The mortality rate in
233 patients with Omicron variant was of 7.9%, comparable to that reported for the other variants. The
234 30-day mortality rate was significantly lower than in the pre-vaccine era (31%). In the univariable
235 analysis, older age ($p<0.001$), active HM ($p<0.001$), severe and critical COVID-19 ($p=0.007$ and
236 $p<0.001$, respectively) were associated with mortality. Conversely, patients receiving monoclonal
237 antibodies, even for severe or critical COVID-19, had a lower mortality rate ($p<0.001$). In the
238 multivariable model, older age, active disease, critical COVID-19 and at least 2-3 comorbidities
239 were correlated with a higher mortality, whereas the administration of monoclonal antibodies, alone
240 ($p<0.001$) or combined with antivirals ($p=0.009$), was observed protective.

241 While mortality is significantly lower than in the pre-vaccination era, breakthrough COVID-
242 19 in HM is still associated with considerable mortality. Death rate was lower in patients who
243 received monoclonal antibodies, alone or in combination with antivirals.

244 **Introduction**

245 Coronavirus disease 19 (COVID-19) is a life-threatening infection in patients with
246 hematologic malignancies (HM), associated with severe clinical presentation and high risk of
247 death.¹⁻³ In April 2020, the European Hematology Association – Scientific Working Group
248 Infectious in Hematology (EHA-SWG) opened the EPICOVIDEHA registry to collect all adult
249 patients with HM that developed COVID-19. It aimed to describe the epidemiology, risk factors,
250 and reported a mortality rate of 31.2% among 3801 patients.⁴ In December 2020, nearly one year
251 after the first described COVID-19 case, vaccines against the severe acute respiratory syndrome
252 coronavirus 2 (SARS-CoV-2) were approved and became available first for high-risk patients,
253 including HM.⁵⁻⁸ The recently published recommendations from the European Conference of
254 Infections in Leukemia (ECIL-9) identify the critical role of mRNA-based vaccines in the fight
255 against COVID-19 and recommend their use in HM, although they may have more limited efficacy
256 amongst severely immunocompromised patients⁹.

257 We collected data on adult HMs who developed breakthrough COVID-19 to assess the
258 vaccine efficacy and the potential role of new emergent treatments against SARS-CoV-2. Our
259 preliminary data, regarding the first 113 patients included, showed a significant decrease in the
260 overall mortality rate in the post-vaccination era (12.4%), which was, however, still remarkably
261 higher compared to the rate observed in the overall population.¹⁰ To date, few reports have been
262 published about severity and outcomes of breakthrough COVID-19 in patients with cancer in
263 general¹¹⁻¹² and HMs specifically,¹³ all showing high rates of severe clinical presentation,
264 hospitalization and death among these patients. This suggests that HMs require close monitoring
265 and increased medical attention when COVID-19 is diagnosed, regardless of previous anti-SARS-
266 CoV-2 vaccine.

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

269 **Methods**

270 *Study design, patients, and procedures*

271 From January 1st, 2021, until March 10th, 2022, participating institutions documented
272 episodes of COVID-19 in their HMs that received anti-SARS-CoV-2 vaccination. Our analysis
273 comprised data from the EPICOVIDEHA registry. EPICOVIDEHA (www.clinicaltrials.gov; National
274 Clinical Trials identifier NCT04733729) is an international open web-based registry for patients with
275 HMs infected with SARS-CoV-2.¹⁴ EPICOVIDEHA was approved by the local ethics committee of
276 the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro
277 Cuore of Rome, Italy (Study ID: 3226). When applicable, the respective local ethics committee of
278 each participating institution have approved the project. EPICOVIDEHA methods have been
279 described elsewhere.^{4,14} The electronic case report form (eCRF) is accessible online at
280 www.clinicalsurveys.net (EFS Summer 2021, TIVIAN, Cologne, Germany). Each documented
281 patient was reviewed and validated by infectious diseases and hematology experts from the
282 coordination team. Inclusion criteria were: a) active HMs within the last five years before COVID-19
283 diagnosis, b) patients ≥ 18 years old, c) laboratory-based diagnosis of SARS-CoV-2 infection, and
284 d) last vaccine dose 15 or more days before PCR confirmed SARS-CoV-2 infection. Data on
285 baseline conditions pre-COVID-19 (i.e., age, sex, status of HM at COVID-19 diagnosis, factors
286 predisposing for COVID-19), HM clinical management (i.e., last HM treatment strategy, vaccine
287 type, spike protein concentration at diagnosis of COVID-19, COVID-19 diagnosis and management
288 (i.e., reason for diagnostic test, symptoms at onset, stay during infection, treatments received for
289 infection) and outcome (i.e., mortality, attributable mortality [assessed by the medical team in
290 charge of the patient], last day of follow-up) were collected. Status of HM at COVID-19 onset and
291 last follow up was defined as active (onset and refractory/resistant), stable disease or controlled
292 (complete and partial response) based on the reports from the respective participating institution.

293 *Study objectives*

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

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

303 *Sample size and statistical analysis*

304 No *a priori* sample size calculation was performed for this analysis. Categorical variables are
305 presented with frequencies and percentages, and continuous variables with median, interquartile
306 range (IQR) and absolute range. Univariable Cox regression model was performed with variables
307 suspected to play a role in the mortality of HM patients with COVID-19. Variables with a p-value \leq
308 0.1 were considered for multivariable analysis. A multivariable Cox regression model was
309 calculated with the Wald backward method. Mortality was analyzed by using Kaplan–Meier survival
310 plots. Log-rank test was used to compare the survival probability of the patients included in the
311 different models. A p-value ≤ 0.05 was considered statistically significant. No *a priori* sample size
312 calculation was done for this exploratory study. SPSSv25.0 was employed for statistical analyses
313 (SPSS, IBM Corp., Chicago, IL, United States). Patients with missing data in essential fields (i.e.
314 HM, chemotherapeutic program, vaccination status, COVID-19 management or survival status)
315 were considered as not valid and, then, excluded from the final analysis. Among the valid cases, if
316 a value in a specific variable was missing or unknown, it is indicated as such in the descriptive
317 analysis. Patients with missing data in a certain variable were excluded from regression analyses
318 in case that variable was included into such analyses.

319 *Data sharing statement*

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

321 **Results**

322 *Study population*

323 A total of 94 centers in 26 countries, mainly from Europe, participated and registered 1583
324 cases. A list of enrolled cases from each participating country is available in the supplemental
325 material (Fig. S1 and Fig. S2 panel A). Out of these 1583 cases, 35 were excluded since COVID-
326 19 was diagnosed within 14 days from the first vaccine dose. Clinical characteristics of 1548
327 evaluable cases are reported in Table 1. Lymphoid malignancies were the largest subgroup,
328 accounting 1181 cases (76.3%); the most frequently reported diagnosis was non-Hodgkin
329 lymphoma (NHL, 549 cases). Among myeloid malignancies, the most frequent diagnosis was
330 acute myeloid leukemia (AML, 140 cases). We found a significantly different distribution
331 lymphoid/myeloid malignancies with that reported in pre-vaccination era (pre-vaccination lymphoid
332 malignancies cases: 67.3% vs post-vaccination: 76.3%, $p < 0.001$). At the time of COVID-19
333 diagnosis, most patients had a controlled malignancy ($n=821$, 53%), 322 (20.8%) a stable disease
334 and the remaining 365 (23.6%) an active disease with 185 cases registered at HM onset. The most
335 frequently reported last HM treatment was immuno-chemotherapy or immunotherapy alone
336 ($n=708$, 42%), followed by targeted therapies ($n=311$, 20.1%) and conventional chemotherapy
337 ($n=234$, 15.1%); 92 patients (5.9%) had received HSCT within six months before COVID-19
338 (allogeneic: 76; autologous: 16) and 8 had chimeric antigen receptor T cells (CAR-T) therapy. Most
339 patients presented at least one comorbidity (60.7%) and 180 (11.6%) had a history of smoking; a
340 complete list of comorbidities and associated clinical outcomes is available in the supplemental
341 material (Table S1).

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

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

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

362 *COVID-19 treatments and risk factors for mortality*

363 Overall, 906 patients (58.5%) received a specific treatment for COVID-19, whereas 642
364 (41.5%) were not treated, or received symptomatic therapies (non-steroidal anti-inflammatories,
365 painkillers, antipyretics). Among patients who received a specific treatment for COVID-19, 311
366 (34.3%) were treated with monoclonal antibodies only, 246 (27.1%) with corticosteroids only, 218
367 (24.1%) with antivirals only, 108 (11.9%) with antiviral plus monoclonal antibodies and the
368 remaining 23 with convalescent plasma. Details on COVID-19 treatments and outcomes are
369 displayed in the supplemental material (Table S2). Overall day-30 mortality (i.e., from COVID-19
370 diagnosis) was 9.2% (143/1548 patients died); if we consider symptomatic patients only, the day-
371 30 mortality rate was of 10.3% (130/1265 symptomatic patients died). The primary cause of death
372 was COVID-19 in 97 patients (67.8%), a combination of both, COVID-19 and progressive HM in 39
373 cases (27.2%) and HM alone or combined with other reasons in the remaining 7 patients (4.8%).
374 The mortality rate was significantly lower than that reported in pre-vaccine era (pre-vaccine 31.2%

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

401 In the multivariable model older age, active disease, ~~critical COVID-19~~ and 2-3 comorbidities
402 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.

407 **Discussion**

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

413 The current study was performed in a large cohort of vaccinated HMs to evaluate
414 epidemiology, risk factors for adverse clinical outcome and treatments of breakthrough COVID-19.
415 We found a predominance of lymphoid malignancies, higher than observed in our previous survey
416 during the pre-vaccine era; this difference might be explained by the lower efficacy of vaccines in
417 this patient population, as further suggested by the high rate of serological non-responders among
418 patients with lymphoid malignancies when evaluating anti-spike IgG levels. These data are
419 consistent with those in a recent report describing COVID-19 breakthrough infections in a large HM
420 patient cohort, mostly consisting of patients with lymphoid malignancies.¹³ Advanced age,
421 presence of comorbidities and active HM were confirmed in the present study as factors that
422 negatively influenced clinical outcome and survival; these were the same risk factors that had
423 previously been reported in the pre-vaccination era.¹⁻⁴ Interestingly, in our study, the underlying
424 malignancy did not have a significant impact on survival, which was different from our previous
425 experience in non-vaccinated patients, where AML and myelodysplastic syndrome were
426 associated with higher mortality risk.⁴ A potential explanation for this difference might be the better
427 efficacy of anti-SARS-CoV-2 vaccines in myeloid malignancies,²³⁻²⁵ than in lymphoid
428 malignancies;¹⁷⁻²² however, we may hypothesize new specific anti-SARS CoV-2 drugs and better
429 COVID-19 management to be particularly important for patients with AML at risk of increased
430 mortality if urgent chemotherapy is delayed. Similarly, as reported by other studies¹³, we did not
431 find any significant difference in terms of mortality among different treatments received for HM. As
432 expected, severe and critical COVID-19 had a worse clinical outcome than mild ones, showing a
433 strong correlation with an increased mortality rate both in univariable and multivariable analysis.
434 Given the vaccine protection, the occurrence of respiratory symptoms, hospitalization rate and

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

455 In our study, we reported an overall 30-day-mortality rate of 9.2%, mainly driven by COVID-
456 19 infection as a direct or contributing factor which is significantly lower than in the pre-vaccination
457 era.¹⁻⁴ Moreover, the 30-days mortality rate in symptomatic patients only was of 10.3%. The
458 success of vaccination strategies is likely a major factor in the reported improvement, but not the
459 only factor; ~~a better COVID-19 management and the less severity of newer variants may have~~
460 ~~played a significant role as well.~~ Previous reports suggest that COVID19 management (e.g.,
461 steroids, etc.) have also impacted outcomes. Newer variants may be less severe. Data reported in
462 our study are coincident to other recently published reports that showed a significant mortality rate

463 of COVID-19 breakthrough infections amongst cancer patients¹¹⁻¹² or more specifically among
464 those affected by HM.¹³

465 In our study, we collected data about viral genotyping in about half of patients; among those,
466 the most prevalent variant was *Omicron*, accounting for more than 2/3 of patients. These data are
467 not surprising if we consider the large number of registered patients between late 2021 and early
468 2022, months in which the *Omicron* variant was rapidly spreading throughout Europe.³⁴
469 Interestingly, we did not find any significant difference in terms of severity of clinical presentation
470 and mortality rate between *Omicron* and other variants, matching to other small recently published
471 reports on HMs,³⁵⁻³⁶ but different to reports in immunocompetent patients in which *Omicron*
472 presents with better outcome than other variants.^{34,37}

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

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

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

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516 **Author contribution**

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

525 **Disclosure of conflicts of interest**

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

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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		
<i>Lymphoid malignancies</i>	<i>1181</i>	<i>76.3</i>
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
<i>Myeloid malignancies</i>	<i>356</i>	<i>23.0</i>
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
<i>Aplastic anemia</i>	<i>11</i>	<i>0.7</i>
Malignancy status before COVID-19		
Controlled disease	821	53.0
<i>Complete remission</i>	524	33.9
<i>Partial remission</i>	297	19.2
Stable disease	322	20.8
Active disease	365	23.6
<i>Onset</i>	185	12.0
<i>Refractory/Resistant</i>	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
<i>BioNTech/Pfizer</i>	1121	72.4
<i>Moderna COVE</i>	256	16.5
Vector-based	133	8.6
<i>AstraZeneca Oxford</i>	99	6.4
<i>Sputnik</i>	13	0.8
<i>J&J – Janssen</i>	21	1.4
Inactivated	38	2.5
<i>CoronaVac Sinovac</i>	21	1.4
<i>Sinopharm</i>	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 (\omicron)	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
<i>ICU</i>	152	9.8
Home	800	51.7

653 **HM:** hematologic malignancy; **IQR:** interquartile range; **HSCT:** hematopoietic stem cell
654 transplantation; **CART:** chimeric antigen receptor T-cells; **ICU:** intensive care unit.
655 (*) Referring to World Health Organization international standards, BAU/mL
656 ([https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-](https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirusdisease-covid-19)
657 [coronavirusdisease-covid-19](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	
<i>Reason for death</i>					
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	<0.001
26-50 years old	250	98.0	5	2.0	
51-69 years old	585	94.2	36	5.8	
Over 70 years old	524	83.7	102	16.3	
Comorbidities					
No comorbidities	581	95.6	27	4.4	<0.001
1 comorbidity	471	91.5	44	8.5	
2 comorbidities	223	84.8	40	15.2	
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	ns
<i>Acute lymphoid leukemia</i>	62	96.9	2	3.1	
<i>Chronic lymphoid leukemia</i>	186	88.2	25	11.8	
<i>Hodgkin lymphoma</i>	63	96.9	2	3.1	
<i>Non-Hodgkin lymphoma</i>	497	90.5	52	9.5	
Low grade	261	90.3	28	9.7	
High grade	236	90.8	24	9.2	
<i>Multiple myeloma</i>	246	89.5	29	10.5	
<i>Amyloid light-chain amyloidosis</i>	10	100.0	0	0.0	
<i>Hairy cell leukemia</i>	6	85.7	1	14.3	
Myeloid malignancies	324	91.0	32	9.0	
<i>Acute myeloid leukemia</i>	127	90.7	13	9.3	
<i>Chronic myeloid leukemia</i>	43	97.7	1	2.3	
<i>Essential thrombocythemia</i>	18	100.0	0	0.0	
<i>Myelodysplastic syndromes</i>	81	87.1	12	12.9	
Low-intermediate risk	63	91.3	6	8.7	
High risk	18	78.3	5	21.7	
<i>Myelofibrosis</i>	34	87.2	5	12.8	
<i>Polycythemia vera</i>	15	93.8	1	6.3	
<i>Systemic mastocytosis</i>	6	100.0	0	0.0	
Aplastic anemia	11	100.0	0	0.0	
Malignancy status					
Controlled disease	768	93.5	53	6.5	<0.001
<i>Complete remission</i>	505	96.4	19	3.6	
<i>Partial remission</i>	263	88.6	34	11.4	
Stable disease	294	91.3	28	8.7	
Active disease	307	96.3	58	3.7	
<i>Onset</i>	165	89.2	20	10.8	
<i>Refractory/Resistant</i>	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	
Supportive measures	28	77.8	8	22.2	ns
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	
Four doses	10	100.0	0	0.0	ns
Type of SARS-CoV-2 vaccine					
mRNA	1250	90.8	127	9.2	
<i>BioNTech/Pfizer</i>	1011	90.2	110	9.8	
<i>Moderna COVE</i>	239	93.4	17	6.6	
Vector-based	123	92.5	10	7.5	
<i>AstraZeneca Oxford</i>	91	91.9	8	8.1	
<i>Sputnik</i>	13	100.0	0	0.0	
<i>J&J - Janssen</i>	19	90.5	2	9.5	ns
Inactivated	32	84.3	6	15.7	
<i>CoronaVac Sinovac</i>	18	85.7	3	14.3	
<i>Sinopharm</i>	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	
Optimal response	71	94.7	4	5.3	ns
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	0.002
Pulmonary + extrapulmonary	349	87.3	51	12.8	
Extrapulmonary	297	94.6	17	5.4	
Asymptomatic	286	93.5	20	6.5	

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

661 (*) 1-2 doses vs 3-4 doses p-value: 0.040

662 (**) Referring to World Health Organization international standards, BAU/mL

663 ([https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-](https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirusdisease-covid-19)
664 [coronavirusdisease-covid-19](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		p value	HR	95 CI	
			Lower	Upper			Lower	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

665 **Figure legends**

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

669 **Figure 2.** Survival probability by most prevalent underlying condition.

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

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

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

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

Figure 1

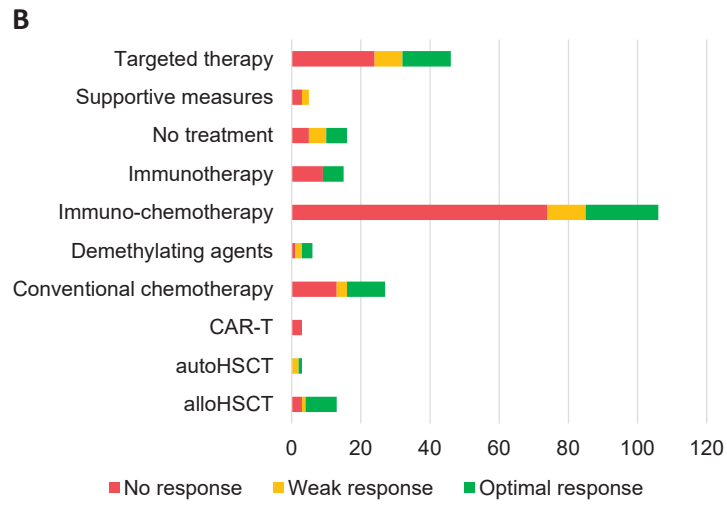
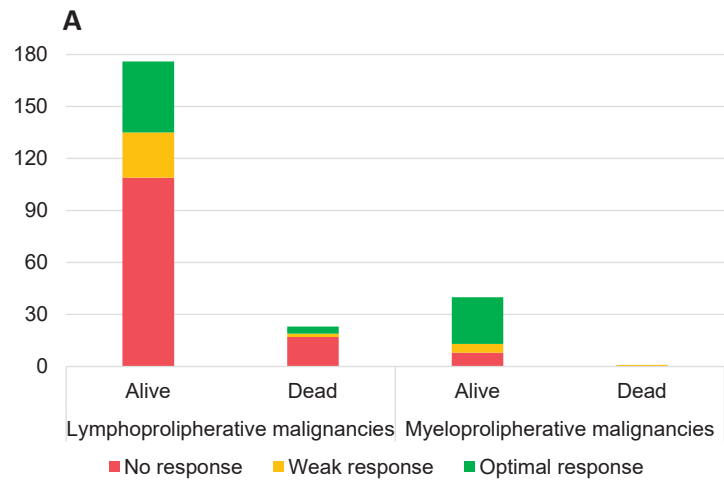
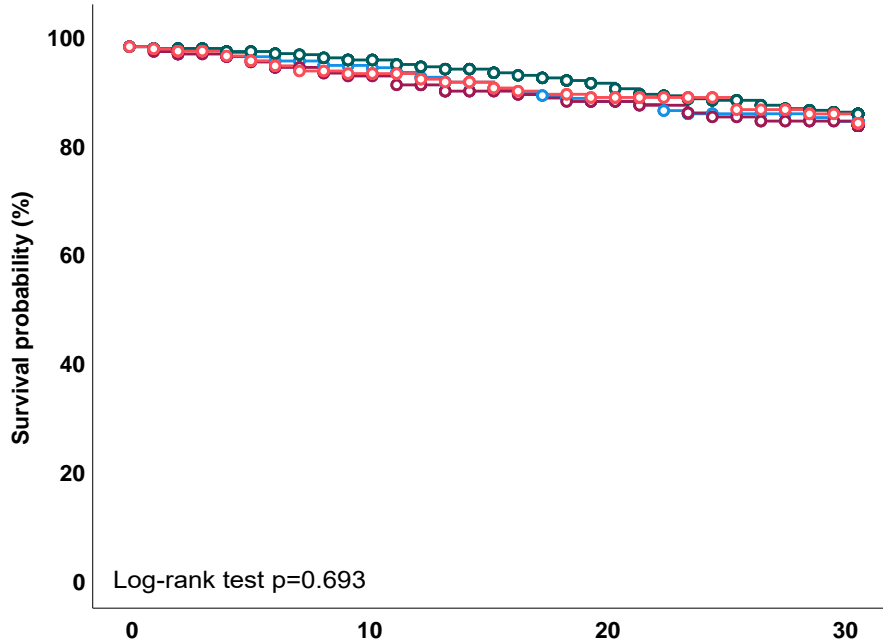
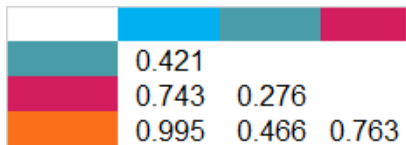


Figure 2



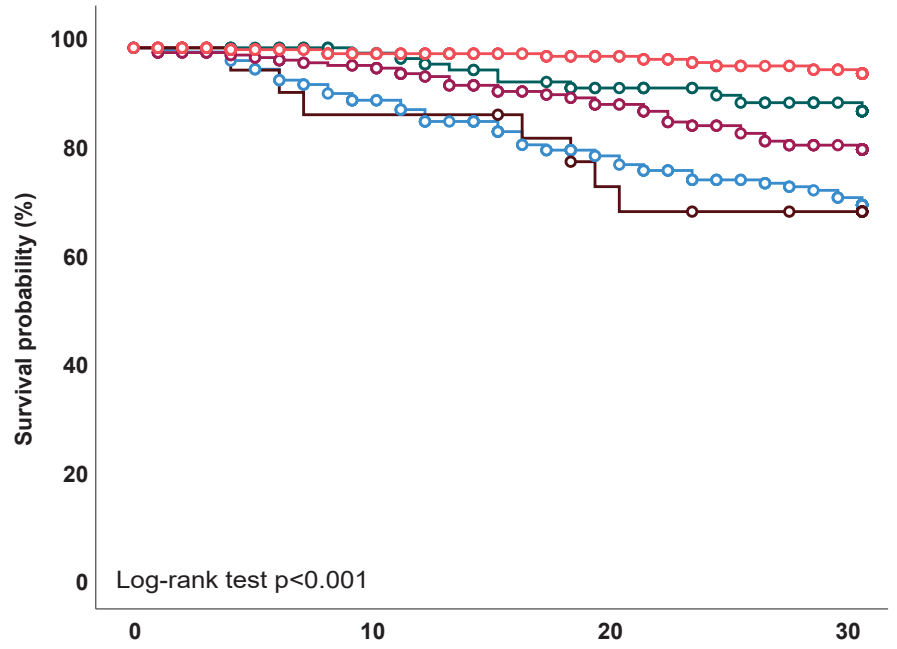
Number of patients at risk

Days from COVID-19 diagnosis

	0	10	20	30
MM	275	215	152	114
NHL	549	452	346	236
CLL	211	165	125	92
AML/MDS	233	183	141	96

Figure 3

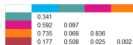
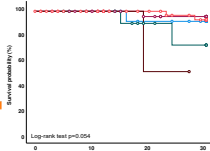
	<0.001			
	0.009	0.134		
	<0.001	0.027	<0.001	
	0.832	0.013	0.117	<0.001



	Number of patients at risk			
	0	10	20	30
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

Figures 4

Asymptomatic patients

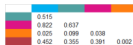
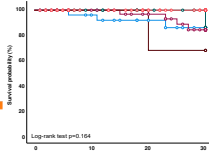


Number of patients at risk

Days from COVID-19 diagnosis

	0	10	20	30
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

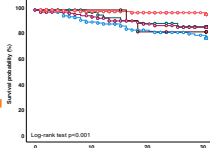


Number of patients at risk

Days from COVID-19 diagnosis

	0	10	20	30
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

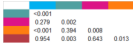
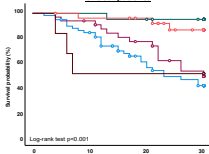


Number of patients at risk

Days from COVID-19 diagnosis

	0	10	20	30
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

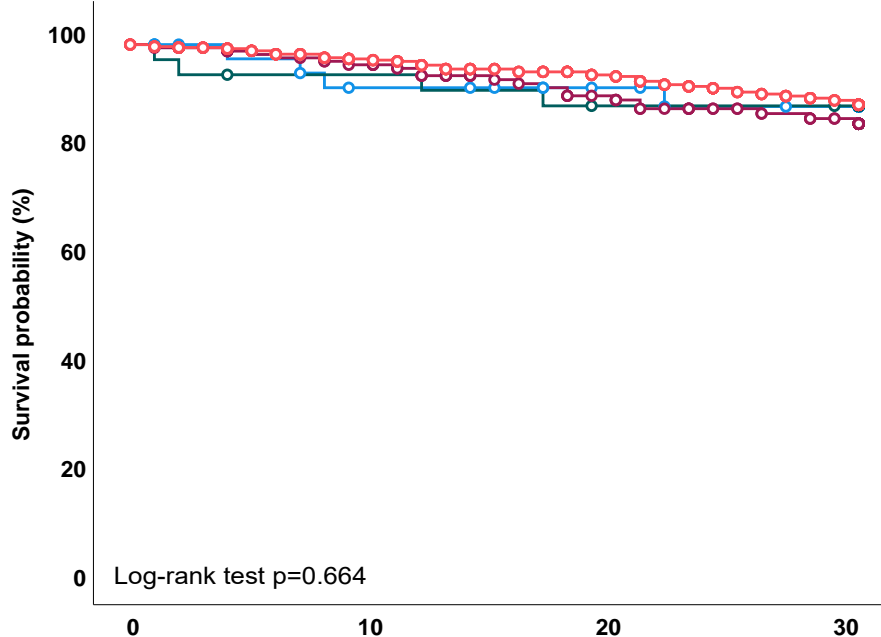
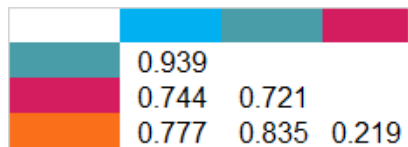


Number of patients at risk

Days from COVID-19 diagnosis

	0	10	20	30
Corticosteroids	57	47	25	15
Antivirals + monoclonal antibodies	20	20	19	16
Antivirals	32	29	21	12
Monoclonal antibodies	26	24	22	13
Plasma	6	3	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

