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Rossi, Giuseppe; Salmanton-García, Jon; Cattaneo, Chiara; Marchesi, Francesco; Dávila-Valls, Julio; Martín-Pérez, Sonia; Itri, Federico; López-García, Alberto; Glenthøj, Andreas; Gomes da Silva, Maria; ...

Source / Izvornik: **International Journal of Infectious Diseases, 2023, 137, 98 - 110**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1016/j.ijid.2023.10.013>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:184:513575>

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Download date / Datum preuzimanja: **2025-03-24**



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Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Age, successive waves, immunization, and mortality in elderly COVID-19 hematological patients: EPICOVIDEHA findings

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<https://doi.org/10.1016/j.ijid.2023.10.013>

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ARTICLE INFO

Article history:

Received 19 June 2023

Revised 16 September 2023

Accepted 13 October 2023

Keywords:

Elderly

SARS-CoV-2

Hematological malignancy

High-risk patient

COVID-19

ABSTRACT

Objectives: Elderly patients with hematologic malignancies face the highest risk of severe COVID-19 outcomes. The infection's impact on different age groups remains unstudied in detail.**Methods:** We analyzed elderly patients (age groups: 65–70, 71–75, 76–80, and >80 years old) with hematologic malignancies included in the EPICOVIDEHA registry between January 2020 and July 2022. Univariable and multivariable Cox regression models were conducted to identify factors influencing death in COVID-19 patients with hematological malignancy.**Results:** The study included data from 3,603 elderly patients (aged 65 or older) with hematological malignancy, with a majority being male (58.1%) and a significant proportion having comorbidities. The patients were divided into four age groups, and the analysis assessed COVID-19 outcomes, vaccination status, and other variables in relation to age and pandemic waves. The 90-day survival rate for patients with COVID-19 was 71.2%, with significant differences between groups. The pandemic waves had varying impacts, with the first wave affecting patients over 80 years old, the second being more severe in 65–70, and the third being the least severe in all age groups. Factors contributing to 90-day mortality included age, comorbidities, lymphopenia, active malignancy, acute leukemia, less than three vaccine doses, severe COVID-19, and using only corticosteroids as treatment.**Conclusion:** These data underscore the heterogeneity of elderly hematological patients, highlight the different impacts of COVID-19 waves and the pivotal importance of vaccination, and may help in planning future healthcare efforts.

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Introduction

The impact of the SARS-CoV-2 pandemic has caused excess mortality worldwide. Its severity and clinical consequences varied according to differences in the characteristics of infected subjects. Both, age [1] and hematologic malignancy [2–17] proved to be adverse prognostic factors in most studies reported, making elderly patients affected by hematological malignancy among the categories of patients most vulnerable to severe infection. A better knowledge of the clinical characteristics of COVID-19 [18] together with the availability of effective prophylactic and therapeutic agents and the benefits of widespread vaccination policies have allowed a progressive improvement in COVID-19 prognosis.

To which extent the improvement in COVID-19 prognosis and the efficacy of prophylactic interventions affects elderly patients with hematological malignancy is only partially known [9]. Also, differences in the viral strain involved [2,19–21] and in vaccination status [12,14,15,19] likely influence the risk of COVID-19 progression to severe episodes among elderly hematologic patients. The potential role of differences in the age of elderly patients with hematological malignancy on the outcome of COVID-19 and their relationship with other prognostic variables have been only partially analyzed, including time of infection [5], viral strain [2,19–21], vaccination status [12,14,15,19], and hematologic diagnosis [3,4,6–8,10,11,17].

This analysis was conducted by the collaboration of the EPICOVIDEHA registry [22] from the European Hematology Association (EHA) Infections in Hematology Scientific Working Group (SWG) and the EHA Hematology and Aging SWG. The characteristics of patients aged >65 with hematological malignancy developing COVID-19 throughout different periods of the pandemic have been analyzed in detail. Results may provide scientific knowledge useful for improved management of elderly patients and for adopt-

ing rationale interventions to face the tasks that the pandemic may present in the future. The aim of this study is to assess the impact of age, vaccination status, viral strain, and other variables on the prognosis of elderly patients with hematological malignancy who contracted COVID-19 during different phases of the pandemic, addressing a critical gap in knowledge regarding the optimal management of this vulnerable population.

Methods

Patients aged ≥ 65 registered in the EPICOVIDEHA registry [22] between March 2020 and July 31, 2022, were included in the present analysis. They were divided into four groups according to the following age ranges: 65–70 years, 71–75 years, 76–80 years, and >80 years. Additionally, the patients included in analysis had to have a laboratory-based diagnosis of COVID-19 and a documented history of active hematological malignancy within the last 5 years before COVID-19 diagnosis for participation in this study.

In addition to age, other variables were collected: sex, comorbidities, diagnosis of hematological malignancy, malignancy status at COVID-19 onset and last hematological treatment received before COVID-19 diagnosis, neutrophil and lymphocyte count at COVID-19 onset, number and type of vaccine doses received, timing of COVID-19 diagnosis subdivided according to the following pandemic waves: first wave from January to April 2020, second wave from September 2020 to March 2021, third wave from September 2021 to March 2022 and fourth wave from May to July 2022. Furthermore, COVID-19 etiology, clinical severity, need for hospitalization and intensive care unit admission, treatment, death, and cause of death were also documented.

Categorical variables are presented as frequencies and percentages and continuous variables as median, interquartile range, and absolute range. A univariable Cox regression model was built and

run with variables expected to play a role in mortality in hematological malignancy patients with COVID-19. Variables with a P -value ≤ 0.1 were included in the multivariable analysis. The multivariable Cox regression model was calculated using the Wald backward method. Survival probability was verified with Kaplan-Meier survival curves. Log-rank test was used to compare the survival probabilities of patients included in the different models. A P -value ≤ 0.05 was considered statistically significant. SPSS version 25.0 was used for statistical analysis (SPSS, IBM Corp, Chicago, IL, United States).

Results

A total of 3603 patients registered in the EPICOVIDEHA registry were studied. Median age was 74 years (interquartile range 70–80; absolute range 65–97). Males represented 58.1% ($n = 2093/3603$) of cases. Only 25.2% ($n = 909/3603$) of the patients had no comorbidities. Increasing age negatively correlated with the proportion of patients without comorbidities from 30.6% ($n = 319/1044$) in patients aged 65–70 to 20.0% ($n = 164/819$) in patients aged >80 ($P < 0.001$). The coexistence of three or more comorbidities increased with age from 12.3% ($n = 128/1044$) in patients aged 65–70 to 22.7% ($n = 186/819$) in patients >80 years old. Cardiac ($P = 0.001$) and renal ($P < 0.001$) comorbidities showed the same increasing trend, whereas the frequency of obesity ($P = 0.004$) and a history of smoking ($P = 0.003$) progressively decreased from the youngest to the eldest age group (Table 1).

Myelodysplastic syndrome was the only hematologic malignancy correlating with age ($P = 0.001$). Its frequency increased from 6.5% ($n = 68/1044$) in patients aged 65–70 to 17.3% ($n = 142/819$) in patients aged >80 . Most patients ($n = 3059/3603$, 84.9%) had received some treatment for their baseline hematological malignancy, which was active in 32.9% ($n = 1186/3603$) of patients at COVID-19 diagnosis. The proportion of patients receiving no treatment ($n = 181/819$, 22.1%), treatment with demethylating agents ($n = 67/819$, 8.2%), or best supportive/palliative care ($n = 61/819$, 7.4%) was highest above 80 years of age, whereas the proportion of patients treated with immunochemotherapy was lowest ($n = 168/819$, 20.5%, $P = 0.001$). Allogeneic or autologous stem cell transplants had been performed only in patients under the age of 75, while two patients aged 75–80 years had been treated with chimeric antigen receptor T-cell (CAR-T) cells. Peripheral blood cell counts showed severe neutropenia (absolute neutrophil count $<0.5 \times 10^9/l$) in 7.1% ($n = 256/3603$) and lymphopenia (lymphocyte count $<0.2/10^9/l$) in 9.3% ($n = 334/3603$) of cases. Both, severe neutropenia ($P = 0.017$) and lymphopenia ($P = 0.001$) were more pronounced in patients aged 65–70 and decreased in elder age groups (Table 1).

The first wave affected particularly the eldest age groups (75+ years) whereas the second wave was the youngest (65–75 years, $P < 0.001$). No further differences were observed during the subsequent pandemic waves. The viral strain causing COVID-19 was identified in 19.6% ($n = 706/3603$) of patients, with the Omicron variant accounting for COVID-19 etiology in 12.1% ($n = 437/3603$). Before developing COVID-19, 31.5% of patients had received at least one vaccine dose, in 90.6% ($n = 1025/1135$) of the cases with a messenger RNA vaccine. Many patients had received two ($n = 442/3603$, 12.3%) or three doses ($n = 570/3603$, 15.8%). Severe or critical infection was experienced by 58.5% ($n = 2109/3603$) of the patients. Vaccination rates did not change significantly with increasing age ($P = 0.172$, Table 1).

The frequency of COVID-19 diagnosis during screening was lower in the eldest patients ($P = 0.010$). Hospitalization was needed by 73.2% ($n = 2638/3603$) of the patients and intensive care was required by 21.2% ($n = 560/3603$). COVID-19 was gradually more severe based on the age of the patient, requiring

more frequent hospitalization and reporting more often pulmonary symptoms at increasing age ($P < 0.001$). The eldest patients were less commonly admitted to intensive care unit ($P < 0.001$). Potential treatment for COVID-19 was collected from 51.7% ($n = 1864/3603$) of the patients. One-fifth ($n = 752/3603$, 20.9%) of the patients did not get any treatment, and among those receiving any drug, corticosteroids alone were the most prevalent ($n = 385/3603$, 10.7%, Table 1).

At day 30 post-COVID-19 diagnosis, 23.6% ($n = 852/3603$) had died; ($n = 1038/3603$), this rose to 28.8% at day 90 (Table 2). The mortality rate raised at one year to 30.4% ($n = 1095/3603$). At day 90, mortality rate was 21.9% ($n = 229/1044$) in patients aged 65–70, 26.2% ($n = 244/932$) in those aged 71–75, 31.1% ($n = 251/808$) in those aged 76–80 and 38.3% ($n = 314/819$) in those aged >80 , respectively. In the survival probability analysis, a statistically significant difference was observed ($P < 0.001$), with an age-based gradient from younger to elder patients (Figure 1a). COVID-19 was involved in the overall mortality in 91.9% ($n = 753/1107$) of patients; hematologic malignancy contributed in 23.8% ($n = 264/1107$). These proportions did not differ in the different age groups ($P = 0.755$, Table 2).

The 90-day mortality rate was markedly higher in patients diagnosed with COVID-19 during the first wave of the pandemic ($n = 374/820$ 45.6%) than in the second ($n = 385/1198$, 37.3%, $P < 0.001$). Day 90 mortality dropped significantly for patients diagnosed during the third wave ($n = 178/1055$, 16.9%, $P < 0.001$). During the first wave, the 90-day mortality rate of patients aged 65–70 was 29.7% ($n = 310/1044$) and it progressively increased in the elder groups, being 39.6% ($n = 369/932$) in those aged 71–75, 48.7% ($n = 393/808$) in those aged 76–80 and 60.1% ($n = 492/819$) in those aged >80 ($P < 0.001$). Conversely, the increase in 90-day mortality from the youngest to the eldest age group was less marked during the second wave (27.9% ($n = 291/1044$) in patients aged 65–70 and 41.0% ($n = 336/819$) in patients aged >80 , $P < 0.001$). Association between the age of the patients and the pandemic wave was also observed in the survival probability analysis ($P < 0.001$, Figure 1b, Figure 2a, Supplementary Table 1).

Vaccination status and number of vaccine doses received significantly impacted survival probability at 90-day ($P < 0.001$), which progressively increased among patients receiving zero, one, two, three, or four doses, with differences being statistically significant for each pairwise comparison between groups (Supplementary Table 1).

Considering patients whose viral strain was genotyped, those with wild-type, Alpha, or Delta variants, had a comparable survival probability at day 90, although significantly worse than in patients with Omicron variant ($P < 0.001$, Figure 1c).

The 90-day mortality in patients receiving only corticosteroids was 35.6% ($n = 137/385$). In patients receiving antivirals with or without other treatments, 90-day mortality was significantly lower ($n = 126/438$, 25.7%) and in those receiving only monoclonal antibodies with or without other treatments, it was 12.5% ($n = 32/255$, $P < 0.001$, Figure 2b, Supplementary table 1).

In the multivariable regression analysis (Table 3), age was a significant independent risk factor for 90-day mortality. The presence of a cardiac (hazard ratio [HR] 1.262, 95% confidence interval [CI] 1.107–1.438), hepatic (HR 1.573, 95% CI 1.204–2.054), or renal (HR 1.233, 95% CI 1.029–1.476) comorbidity had a significantly negative impact on patient outcome, as well as lymphopenia at COVID-19 diagnosis. Acute leukemia had a significantly worse prognosis than any other malignancy. Moreover, an active hematologic malignancy at COVID-19 diagnosis (HR 1.651, 95% CI 1.421–1.918) also had an adverse impact on patient survival, so did baseline pulmonary involvement and critical COVID-19 (HR 2.903, 95% CI 2.517–3.347). Among COVID-19 treatments, receiving only corticosteroids increased the risk of death (HR 1.407, 95% CI 1.077–1.837),

Table 1
Demographic and clinical characteristics of the whole series of older hematologic patients with COVID-19 and of the four groups of different age.

| | Overall | | 65–70 years old | | 71–75 years old | | 76–80 years old | | >80 years old | | P-value |
|--|---------|-------|-----------------|--------|-----------------|--------|-----------------|--------|---------------|--------|------------------|
| | n | % | n | % | n | % | n | % | n | % | |
| Sex | | | | | | | | | | | |
| Female | 1510 | 41.9% | 432 | 41.4% | 344 | 36.9% | 345 | 42.7% | 389 | 47.5% | <0.001 |
| Male | 2093 | 58.1% | 612 | 58.6% | 588 | 63.1% | 463 | 57.3% | 430 | 52.5% | |
| Age | | | | | | | | | | | |
| <71 years old | 1044 | 29.0% | 1044 | 100.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | |
| 71–75 years old | 932 | 25.9% | 0 | 0.0% | 932 | 100.0% | 0 | 0.0% | 0 | 0.0% | |
| 76–80 years old | 808 | 22.4% | 0 | 0.0% | 0 | 0.0% | 808 | 100.0% | 0 | 0.0% | |
| >80 years old | 819 | 22.7% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 819 | 100.0% | |
| Comorbidities | | | | | | | | | | | |
| No comorbidities | 909 | 25.2% | 319 | 30.6% | 247 | 26.5% | 179 | 22.2% | 164 | 20.0% | <0.001 |
| 1 comorbidity | 1241 | 34.4% | 355 | 34.0% | 327 | 35.1% | 296 | 36.6% | 263 | 32.1% | |
| 2 comorbidities | 834 | 23.1% | 242 | 23.2% | 195 | 20.9% | 191 | 23.6% | 206 | 25.2% | |
| 3 or more comorbidities | 619 | 17.2% | 128 | 12.3% | 163 | 17.5% | 142 | 17.6% | 186 | 22.7% | |
| Chronic cardiopathy | | | | | | | | | | | |
| Chronic pulmonary disease | 1826 | 50.7% | 419 | 40.1% | 436 | 46.8% | 449 | 55.6% | 522 | 63.7% | 0.001 |
| Diabetes mellitus | | | | | | | | | | | |
| Diabetes mellitus | 654 | 18.2% | 150 | 14.4% | 171 | 18.3% | 143 | 17.7% | 190 | 23.2% | <0.001 |
| Liver disease | | | | | | | | | | | |
| Liver disease | 706 | 19.6% | 168 | 16.1% | 197 | 21.1% | 189 | 23.4% | 152 | 18.6% | <0.001 |
| Obesity | | | | | | | | | | | |
| Obesity | 156 | 4.3% | 49 | 4.7% | 45 | 4.8% | 34 | 4.2% | 28 | 3.4% | 0.465 |
| Renal impairment | | | | | | | | | | | |
| Renal impairment | 244 | 6.8% | 89 | 8.5% | 69 | 7.4% | 50 | 6.2% | 36 | 4.4% | 0.004 |
| Smoking history | | | | | | | | | | | |
| Smoking history | 388 | 10.8% | 80 | 7.7% | 92 | 9.9% | 85 | 10.5% | 131 | 16.0% | <0.001 |
| No risk factor | 453 | 12.6% | 157 | 15.0% | 122 | 13.1% | 97 | 12.0% | 77 | 9.4% | 0.003 |
| identified | 900 | 25.0% | 316 | 30.3% | 246 | 26.4% | 176 | 21.8% | 162 | 19.8% | <0.001 |
| Hematological malignancies | | | | | | | | | | | |
| Leukemia | 1456 | 40.4% | 405 | 38.8% | 342 | 36.7% | 325 | 40.2% | 384 | 46.9% | 0.001 |
| Acute lymphoid leukemia | 47 | 1.3% | 22 | 2.1% | 8 | 0.9% | 11 | 1.4% | 6 | 0.7% | |
| Chronic lymphoid leukemia | 616 | 17.1% | 154 | 14.8% | 166 | 17.8% | 146 | 18.1% | 150 | 18.3% | |
| Acute myeloid leukemia | 328 | 9.1% | 127 | 12.2% | 76 | 8.2% | 64 | 7.9% | 61 | 7.4% | |
| Chronic myeloid leukemia | 95 | 2.6% | 27 | 2.6% | 27 | 2.9% | 17 | 2.1% | 24 | 2.9% | |
| Myelodysplastic syndrome | 353 | 9.8% | 68 | 6.5% | 63 | 6.8% | 80 | 9.9% | 142 | 17.3% | |
| Hairy cell leukemia | 17 | 0.5% | 7 | 0.7% | 2 | 0.2% | 7 | 0.9% | 1 | 0.1% | |
| Lymphoma | 1128 | 31.3% | 346 | 33.1% | 318 | 34.1% | 249 | 30.8% | 215 | 26.3% | |
| Hodgkin lymphoma | 45 | 1.2% | 23 | 2.2% | 10 | 1.1% | 9 | 1.1% | 3 | 0.4% | |
| Non-Hodgkin lymphoma | 1083 | 30.1% | 323 | 30.9% | 308 | 33.0% | 240 | 29.7% | 212 | 25.9% | |
| PH negative myeloproliferative diseases | 264 | 7.3% | 69 | 6.6% | 72 | 7.7% | 58 | 7.2% | 65 | 7.9% | |
| Essential thrombocythemia | 65 | 1.8% | 8 | 0.8% | 16 | 1.7% | 19 | 2.4% | 22 | 2.7% | |
| Myelofibrosis | 126 | 3.5% | 41 | 3.9% | 36 | 3.9% | 22 | 2.7% | 27 | 3.3% | |
| Polycythemia vera | 66 | 1.8% | 16 | 1.5% | 19 | 2.0% | 16 | 2.0% | 15 | 1.8% | |
| Systemic mastocytosis | 7 | 0.2% | 4 | 0.4% | 1 | 0.1% | 1 | 0.1% | 1 | 0.1% | |
| Plasma cell disorders | 740 | 20.5% | 219 | 21.0% | 197 | 21.1% | 174 | 21.5% | 150 | 18.3% | |
| Multiple myeloma | 725 | 20.1% | 215 | 20.6% | 190 | 20.4% | 171 | 21.2% | 149 | 18.2% | |
| Amyloid light-chain amyloidosis | 15 | 0.4% | 4 | 0.4% | 7 | 0.8% | 3 | 0.4% | 1 | 0.1% | |
| Other hematological malignancies | 15 | 0.4% | 5 | 0.5% | 3 | 0.3% | 2 | 0.2% | 5 | 0.6% | |
| Aplastic anemia | 15 | 0.4% | 5 | 0.5% | 3 | 0.3% | 2 | 0.2% | 5 | 0.6% | |
| Last haematological treatment before COVID-19 | | | | | | | | | | | |
| No treatment | 574 | 15.9% | 138 | 13.2% | 138 | 14.8% | 117 | 14.5% | 181 | 22.1% | 0.001 |
| alloHSCT | 53 | 1.5% | 41 | 3.9% | 12 | 1.3% | 0 | 0.0% | 0 | 0.0% | |
| autoHSCT | 34 | 0.9% | 26 | 2.5% | 8 | 0.9% | 0 | 0.0% | 0 | 0.0% | |
| Chimeric antigen receptor T-cell | 16 | 0.4% | 10 | 1.0% | 4 | 0.4% | 2 | 0.2% | 0 | 0.0% | |

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Table 1 (continued)

| | Overall | | 65–70 years old | | 71–75 years old | | 76–80 years old | | >80 years old | | P-value |
|--|---------|-------|-----------------|-------|-----------------|-------|-----------------|-------|---------------|-------|---------|
| | n | % | n | % | n | % | n | % | n | % | |
| Conventional chemotherapy | 512 | 14.2% | 173 | 16.6% | 112 | 12.0% | 111 | 13.7% | 116 | 14.2% | |
| Demethylating agents | 246 | 6.8% | 52 | 5.0% | 65 | 7.0% | 62 | 7.7% | 67 | 8.2% | |
| Immuno-chemotherapy | 987 | 27.4% | 295 | 28.3% | 291 | 31.2% | 233 | 28.8% | 168 | 20.5% | |
| Immunotherapy | 197 | 5.5% | 60 | 5.7% | 42 | 4.5% | 51 | 6.3% | 44 | 5.4% | |
| Supportive/Palliative | 149 | 4.1% | 23 | 2.2% | 30 | 3.2% | 35 | 4.3% | 61 | 7.4% | |
| Targeted therapy | 835 | 23.2% | 226 | 21.6% | 230 | 24.7% | 197 | 24.4% | 182 | 22.2% | |
| Status malignancy before COVID-19 | | | | | | | | | | | |
| Controlled disease | 1462 | 40.6% | 485 | 46.5% | 380 | 40.8% | 337 | 41.7% | 260 | 31.7% | <0.001 |
| Stable disease | 839 | 23.3% | 186 | 17.8% | 212 | 22.7% | 186 | 23.0% | 255 | 31.1% | |
| Active disease | 1186 | 32.9% | 334 | 32.0% | 307 | 32.9% | 266 | 32.9% | 279 | 34.1% | |
| Unknown | 116 | 3.2% | 39 | 3.7% | 33 | 3.5% | 19 | 2.4% | 25 | 3.1% | |
| Neutrophils at COVID-19 onset | | | | | | | | | | | |
| <501 | 256 | 7.1% | 93 | 8.9% | 63 | 6.8% | 56 | 6.9% | 44 | 5.4% | 0.017 |
| 501 - 999 | 191 | 5.3% | 64 | 6.1% | 50 | 5.4% | 37 | 4.6% | 40 | 4.9% | |
| >999 | 2665 | 74.0% | 726 | 69.5% | 678 | 72.7% | 613 | 75.9% | 648 | 79.1% | |
| Lymphocytes at COVID-19 onset | | | | | | | | | | | |
| <201 | 334 | 9.3% | 125 | 12.0% | 82 | 8.8% | 72 | 8.9% | 55 | 6.7% | 0.001 |
| 201 - 499 | 538 | 14.9% | 149 | 14.3% | 137 | 14.7% | 133 | 16.5% | 119 | 14.5% | |
| >499 | 2265 | 62.9% | 615 | 58.9% | 589 | 63.2% | 502 | 62.1% | 559 | 68.3% | |
| Vaccine doses before COVID-19 | | | | | | | | | | | |
| Not vaccinated | 2468 | 68.5% | 721 | 69.1% | 629 | 67.5% | 541 | 67.0% | 577 | 70.5% | 0.172 |
| One dose | 81 | 2.2% | 29 | 2.8% | 23 | 2.5% | 16 | 2.0% | 13 | 1.6% | |
| Two doses | 442 | 12.3% | 135 | 12.9% | 115 | 12.3% | 107 | 13.2% | 85 | 10.4% | |
| Three doses | 570 | 15.8% | 148 | 14.2% | 148 | 15.9% | 139 | 17.2% | 135 | 16.5% | |
| Four doses | 42 | 1.2% | 11 | 1.1% | 17 | 1.8% | 5 | 0.6% | 9 | 1.1% | |
| Last vaccination before COVID-19 | | | | | | | | | | | |
| mRNA | 1025 | 28.4% | 272 | 26.1% | 278 | 29.8% | 242 | 30.0% | 233 | 28.4% | <0.001 |
| Vector-based | 66 | 1.8% | 35 | 3.4% | 15 | 1.6% | 13 | 1.6% | 3 | 0.4% | |
| Inactivated | 40 | 1.1% | 16 | 1.5% | 8 | 0.9% | 10 | 1.2% | 6 | 0.7% | |
| Time of COVID-19 diagnosis | | | | | | | | | | | |
| 1st wave | 820 | 22.8% | 192 | 18.4% | 192 | 20.6% | 183 | 22.6% | 253 | 30.9% | <0.001 |
| January-April 2020 | | | | | | | | | | | |
| 1st interwaves | 185 | 5.1% | 66 | 6.3% | 50 | 5.4% | 31 | 3.8% | 38 | 4.6% | |
| 2nd wave | 1198 | 33.3% | 384 | 36.8% | 316 | 33.9% | 269 | 33.3% | 229 | 28.0% | |
| September 2020-March 2021 | | | | | | | | | | | |
| 2nd interwaves | 230 | 6.4% | 70 | 6.7% | 52 | 5.6% | 60 | 7.4% | 48 | 5.9% | |
| 3rd wave | 1055 | 29.3% | 298 | 28.5% | 292 | 31.3% | 245 | 30.3% | 220 | 26.9% | |
| September 2021-March 2022 | | | | | | | | | | | |
| 3rd interwaves | 68 | 1.9% | 19 | 1.8% | 20 | 2.1% | 10 | 1.2% | 19 | 2.3% | |
| 4th wave | 47 | 1.3% | 15 | 1.4% | 10 | 1.1% | 10 | 1.2% | 12 | 1.5% | |
| May-July 2022 | | | | | | | | | | | |
| SARS-CoV-2 variant | | | | | | | | | | | |
| Wild type | 113 | 3.1% | 37 | 3.5% | 31 | 3.3% | 27 | 3.3% | 18 | 2.2% | 0.001 |
| Alpha | 45 | 1.2% | 13 | 1.2% | 8 | 0.9% | 13 | 1.6% | 11 | 1.3% | |
| Delta | 111 | 3.1% | 32 | 3.1% | 32 | 3.4% | 31 | 3.8% | 16 | 2.0% | |
| Omicron | 437 | 12.1% | 120 | 11.5% | 115 | 12.3% | 104 | 12.9% | 98 | 12.0% | |
| Not tested | 2897 | 80.4% | 842 | 80.7% | 746 | 80.0% | 633 | 78.3% | 676 | 82.5% | |
| COVID-19 severity | | | | | | | | | | | |
| Asymptomatic | 557 | 15.5% | 187 | 17.9% | 144 | 15.5% | 116 | 14.4% | 110 | 13.4% | <0.001 |
| Mild infection | 937 | 26.0% | 276 | 26.4% | 227 | 24.4% | 210 | 26.0% | 224 | 27.4% | |
| Severe infection | 1554 | 43.1% | 377 | 36.1% | 389 | 41.7% | 369 | 45.7% | 419 | 51.2% | |
| Critical infection | 555 | 15.4% | 204 | 19.5% | 172 | 18.5% | 113 | 14.0% | 66 | 8.1% | |
| COVID-19 symptoms at onset | | | | | | | | | | | |
| Pulmonary | 1429 | 39.7% | 379 | 36.3% | 369 | 39.6% | 327 | 40.5% | 354 | 43.2% | 0.010 |

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Table 1 (continued)

| | Overall | | 65–70 years old | | 71–75 years old | | 76–80 years old | | >80 years old | | P-value |
|---|-------------------|-------|-------------------|-------|-------------------|-------|-------------------|-------|-------------------|-------|------------------|
| | n | % | n | % | n | % | n | % | n | % | |
| Pulmonary + extrapulmonary | 912 | 25.3% | 250 | 23.9% | 235 | 25.2% | 210 | 26.0% | 217 | 26.5% | |
| Extrapulmonary | 605 | 16.8% | 195 | 18.7% | 152 | 16.3% | 129 | 16.0% | 129 | 15.8% | |
| Screening | 657 | 18.2% | 220 | 21.1% | 176 | 18.9% | 142 | 17.6% | 119 | 14.5% | |
| Stay during COVID-19 episode | | | | | | | | | | | |
| Home | 965 | 26.8% | 309 | 29.6% | 251 | 26.9% | 217 | 26.9% | 188 | 23.0% | 0.016 |
| Hospital | 2638 | 73.2% | 735 | 70.4% | 681 | 73.1% | 591 | 73.1% | 631 | 77.0% | |
| Duration of the stay in hospital | 14 (7–23) [1–190] | | 15 (8–27) [1–155] | | 14 (8–23) [1–179] | | 14 (7–23) [1–190] | | 12 (7–20) [1–135] | | |
| Intensive care unit stay | 560 | 21.2% | 205 | 27.9% | 174 | 25.6% | 115 | 19.5% | 66 | 10.5% | <0.001 |
| Duration of the intensive care unit stay | 10 (5–18) [1–115] | | 11 (6–20) [1–74] | | 10 (5–16) [1–80] | | 9 (4–15) [1–115] | | 7 (3–14) [1–68] | | |
| COVID-19 treatment | | | | | | | | | | | |
| No specific treatment reported | 752 | 20.9% | 201 | 19.3% | 204 | 21.9% | 157 | 19.4% | 190 | 23.2% | 0.002 |
| Antivirals ± corticosteroids ± plasma | 332 | 9.2% | 97 | 9.3% | 104 | 11.2% | 67 | 8.3% | 64 | 7.8% | |
| Antivirals + monoclonal antibodies ± corticosteroids ± plasma | 106 | 2.9% | 34 | 3.3% | 34 | 3.6% | 23 | 2.8% | 15 | 1.8% | |
| Monoclonal antibodies ± corticosteroids ± plasma | 255 | 7.1% | 89 | 8.5% | 64 | 6.9% | 64 | 7.9% | 38 | 4.6% | |
| Plasma ± corticosteroids | 34 | 0.9% | 11 | 1.1% | 10 | 1.1% | 9 | 1.1% | 4 | 0.5% | |
| Corticosteroids | 385 | 10.7% | 94 | 9.0% | 88 | 9.4% | 97 | 12.0% | 106 | 12.9% | |
| Unknown | 1739 | 48.3% | 518 | 49.6% | 428 | 45.9% | 391 | 48.4% | 402 | 49.1% | |

Table 2

Outcome of the whole series of older hematologic patients with COVID-19 and of the four groups of different ages.

| | Overall | | 65–70 years old | | 71–75 years old | | 76–80 years old | | >80 years old | | P-value |
|--|-----------------------|-------|---------------------|-------|---------------------|-------|-----------------------|-------|---------------------|-------|------------------|
| | n | % | n | % | n | % | n | % | n | % | |
| Follow up time | 39 (14–133.5) [0–792] | | 50 (19–152) [0–792] | | 45 (17–139) [0–733] | | 35 (13–121) [0–760] | | 27 (10–103) [0–627] | | <0.001 |
| Follow-up time, alive | 75.5 (26–191) [0–792] | | 82 (29–199) [0–792] | | 81 (27–206) [0–733] | | 69 (23–174.5) [0–760] | | 63 (23–191) [0–627] | | 0.099 |
| Follow-up time, dead | 15 (7–33) [0–657] | | 19 (10–37) [0–528] | | 16 (10–38) [0–657] | | 15 (7–30) [0–577] | | 12 (5–27) [0–584] | | <0.001 |
| Overall | | | | | | | | | | | |
| Mortality | 1107 | 30.7% | 252 | 24.1% | 258 | 27.7% | 261 | 32.3% | 336 | 41.0% | |
| Reason for death | | | | | | | | | | | |
| COVID-19 | 753 | 20.9% | 164 | 15.7% | 176 | 18.9% | 184 | 22.8% | 229 | 28.0% | |
| COVID-19 + hematological malignancy | 264 | 23.8% | 66 | 6.3% | 57 | 6.1% | 59 | 7.3% | 82 | 10.0% | |
| Hematological malignancies ± other reasons | 90 | 2.5% | 22 | 2.1% | 25 | 2.7% | 18 | 2.2% | 25 | 3.1% | |
| Day 30 | | | | | | | | | | | <0.001 |
| Mortality | 852 | 23.6% | 175 | 16.8% | 194 | 20.8% | 209 | 25.9% | 274 | 33.5% | |
| Reason for death | | | | | | | | | | | |
| COVID-19 | 598 | 16.6% | 113 | 10.8% | 138 | 14.8% | 151 | 18.7% | 196 | 23.9% | |
| COVID-19 + hematological malignancy | 208 | 5.8% | 49 | 4.7% | 44 | 4.7% | 47 | 5.8% | 68 | 8.3% | |
| Hematological malignancies ± other reasons | 46 | 1.3% | 13 | 1.2% | 12 | 1.3% | 11 | 1.4% | 10 | 1.2% | |
| Day 90 | | | | | | | | | | | <0.001 |
| Mortality | 1038 | 28.8% | 229 | 21.9% | 244 | 26.2% | 251 | 31.1% | 314 | 38.3% | |
| Reason for death | | | | | | | | | | | |
| COVID-19 | 723 | 20.1% | 152 | 14.6% | 171 | 18.3% | 179 | 22.2% | 221 | 27.0% | |
| COVID-19 + hematological malignancy | 252 | 7.0% | 61 | 5.8% | 55 | 5.9% | 57 | 7.1% | 79 | 9.6% | |
| Hematological malignancies ± other reasons | 63 | 1.7% | 16 | 1.5% | 18 | 1.9% | 15 | 1.9% | 14 | 1.7% | |
| Day 365 | | | | | | | | | | | <0.001 |
| Mortality | 1095 | 30.4% | 249 | 23.9% | 256 | 27.5% | 260 | 32.2% | 330 | 40.3% | |
| Reason for death | | | | | | | | | | | |
| COVID-19 | 745 | 20.7% | 162 | 15.5% | 175 | 18.8% | 183 | 22.6% | 225 | 27.5% | |
| COVID-19 + hematological malignancy | 262 | 7.3% | 65 | 6.2% | 57 | 6.1% | 59 | 7.3% | 81 | 9.9% | |
| Hematological malignancies ± other reasons | 88 | 2.4% | 22 | 2.1% | 24 | 2.6% | 18 | 2.2% | 24 | 2.9% | |

Table 3
Univariable and multivariable regression analysis on the effect of different parameters on 90-day mortality.

| | UNIVARIABLE | | | | MULTIVARIABLE | | | |
|---|-----------------|-------|----------|-------|-----------------|-------|----------|-------|
| | P-value | HR | 95% C.I. | | P-value | HR | 95% C.I. | |
| | | | Lower | Upper | | | Lower | Upper |
| Age | | | | | | | | |
| 65-70 years old | - | - | - | - | - | - | - | - |
| 71-75 years old | 0.011 | 1.258 | 1.054 | 1.502 | 0.005 | 1.308 | 1.082 | 1.582 |
| 76-80 years old | <.001 | 1.584 | 1.327 | 1.889 | <.001 | 1.706 | 1.411 | 2.063 |
| >80 years old | <.001 | 2.119 | 1.792 | 2.506 | <.001 | 2.542 | 2.107 | 3.067 |
| Sex | 0.137 | 1.097 | 0.971 | 1.239 | | | | |
| Comorbidities | | | | | | | | |
| No comorbidities | - | - | - | - | | | | |
| 1 comorbidity | 0.024 | 1.216 | 1.027 | 1.441 | | | | |
| 2 comorbidities | <.001 | 1.440 | 1.206 | 1.720 | | | | |
| 3 or more comorbidities | <.001 | 1.793 | 1.494 | 2.152 | | | | |
| Chronic cardiopathy | <.001 | 1.382 | 1.225 | 1.559 | <.001 | 1.262 | 1.107 | 1.438 |
| Chronic pulmonary disease | <.001 | 1.277 | 1.106 | 1.475 | 0.832 | 0.983 | 0.839 | 1.152 |
| Diabetes | 0.024 | 1.179 | 1.022 | 1.362 | 0.417 | 1.067 | 0.913 | 1.246 |
| Liver disease | 0.003 | 1.484 | 1.149 | 1.918 | <.001 | 1.573 | 1.204 | 2.054 |
| Obesity | 0.175 | 1.166 | 0.934 | 1.455 | | | | |
| Renal impairment | <.001 | 1.645 | 1.392 | 1.943 | 0.023 | 1.233 | 1.029 | 1.476 |
| Smoking history | 0.083 | 1.162 | 0.981 | 1.376 | 0.078 | 1.177 | 0.982 | 1.411 |
| Neutrophils | | | | | | | | |
| <501 | - | - | - | - | - | - | - | - |
| 501 - 999 | 0.312 | 0.859 | 0.639 | 1.154 | 0.890 | 1.022 | 0.756 | 1.381 |
| >999 | <.001 | 0.643 | 0.526 | 0.785 | 0.157 | 0.846 | 0.671 | 1.067 |
| Lymphocytes | | | | | | | | |
| < 201 | - | - | - | - | - | - | - | - |
| 201 - 499 | 0.013 | 0.766 | 0.620 | 0.946 | 0.019 | 0.769 | 0.618 | 0.958 |
| >499 | <.001 | 0.582 | 0.487 | 0.694 | <.001 | 0.605 | 0.501 | 0.731 |
| Type of cancer | | | | | | | | |
| Acute leukaemia | - | - | - | - | - | - | - | - |
| Chronic myeloproliferative neoplasms | <.001 | 0.494 | 0.378 | 0.645 | <.001 | 0.586 | 0.436 | 0.787 |
| Chronic lymphoid leukemia | <.001 | 0.633 | 0.510 | 0.786 | <.001 | 0.632 | 0.495 | 0.807 |
| Lymphoma | <.001 | 0.684 | 0.565 | 0.828 | <.001 | 0.665 | 0.539 | 0.822 |
| Myelodysplastic syndrome | 0.030 | 0.765 | 0.600 | 0.975 | 0.015 | 0.714 | 0.545 | 0.937 |
| Multiple myeloma | <.001 | 0.595 | 0.481 | 0.735 | <.001 | 0.607 | 0.481 | 0.765 |
| Other | 0.141 | 0.424 | 0.135 | 1.329 | 0.361 | 0.579 | 0.179 | 1.871 |
| Status malignancies | | | | | | | | |
| Controlled disease | - | - | - | - | - | - | - | - |
| Stable disease | 0.847 | 1.017 | 0.854 | 1.212 | 0.794 | 1.027 | 0.843 | 1.251 |
| Active disease | <.001 | 1.927 | 1.678 | 2.212 | <.001 | 1.651 | 1.421 | 1.918 |
| Unknown | <.001 | 2.520 | 1.887 | 3.367 | <.001 | 1.860 | 1.370 | 2.526 |
| Time last malignancy treatment before COVID-19 | | | | | | | | |
| Chemotherapy - In the last month | - | - | - | - | - | - | - | - |
| Chemotherapy - In the last 3 months | 0.798 | 1.026 | 0.843 | 1.250 | | | | |
| Chemotherapy - > 3 months | 0.134 | 0.872 | 0.729 | 1.043 | | | | |
| HSCT/Chimeric antigen receptor T-cell - In the last 6 months | 0.663 | 1.110 | 0.695 | 1.774 | | | | |
| HSCT/Chimeric antigen receptor T-cell - > 6 months | 0.053 | 0.540 | 0.289 | 1.008 | | | | |
| No treatment - Not applicable | 0.031 | 0.824 | 0.691 | 0.982 | | | | |
| Not reported | 0.077 | 0.676 | 0.437 | 1.044 | | | | |
| Vaccine doses | | | | | | | | |
| Not vaccinated | - | - | - | - | - | - | - | - |
| One dose | 0.071 | 0.658 | 0.418 | 1.037 | 0.785 | 0.932 | 0.561 | 1.548 |
| Two doses | <.001 | 0.644 | 0.519 | 0.799 | 0.684 | 0.947 | 0.727 | 1.233 |
| Three doses | <.001 | 0.439 | 0.347 | 0.555 | 0.009 | 0.683 | 0.513 | 0.910 |
| Four doses | 0.002 | 0.172 | 0.055 | 0.535 | 0.079 | 0.354 | 0.111 | 1.127 |
| Variant | | | | | | | | |
| Wild type | - | - | - | - | - | - | - | - |
| Alpha | 0.994 | 0.998 | 0.558 | 1.785 | 0.699 | 0.880 | 0.459 | 1.687 |
| Delta | 0.577 | 0.873 | 0.543 | 1.406 | 0.069 | 1.645 | 0.962 | 2.812 |
| Omicron | 0.004 | 0.559 | 0.377 | 0.828 | 0.326 | 1.247 | 0.803 | 1.939 |
| Not tested | 0.864 | 0.972 | 0.706 | 1.340 | 0.220 | 1.232 | 0.883 | 1.719 |
| Symptoms at COVID-19 onset | | | | | | | | |
| Pulmonary | - | - | - | - | - | - | - | - |
| Pulmonary + extrapulmonary | 0.304 | 0.928 | 0.805 | 1.070 | 0.358 | 0.931 | 0.799 | 1.084 |
| Extrapulmonary | <.001 | 0.507 | 0.417 | 0.618 | <.001 | 0.658 | 0.534 | 0.812 |
| Screening | <.001 | 0.550 | 0.457 | 0.662 | <.001 | 0.634 | 0.514 | 0.782 |
| Intensive care unit admission | <.001 | 3.157 | 2.782 | 3.584 | <.001 | 2.903 | 2.517 | 3.347 |
| COVID-19 treatment | | | | | | | | |
| No specific treatment reported | - | - | - | - | - | - | - | - |
| Antivirals ± corticosteroids ± plasma | <.001 | 1.968 | 1.508 | 2.569 | 0.345 | 1.152 | 0.859 | 1.544 |
| Antivirals + monoclonal antibodies ± corticosteroids ± plasma | 0.553 | 1.151 | 0.723 | 1.831 | 0.546 | 0.854 | 0.512 | 1.425 |
| Monoclonal antibodies ± corticosteroids ± plasma | 0.425 | 0.853 | 0.577 | 1.261 | 0.018 | 0.589 | 0.380 | 0.915 |
| Plasma ± corticosteroids | <.001 | 2.871 | 1.702 | 4.840 | 0.159 | 1.485 | 0.857 | 2.575 |
| Corticosteroids | <.001 | 2.303 | 1.799 | 2.947 | 0.012 | 1.407 | 1.077 | 1.837 |
| Unknown | <.001 | 2.215 | 1.819 | 2.697 | <.001 | 1.486 | 1.181 | 1.869 |

CI, confidence interval; HR, hazard ratio.

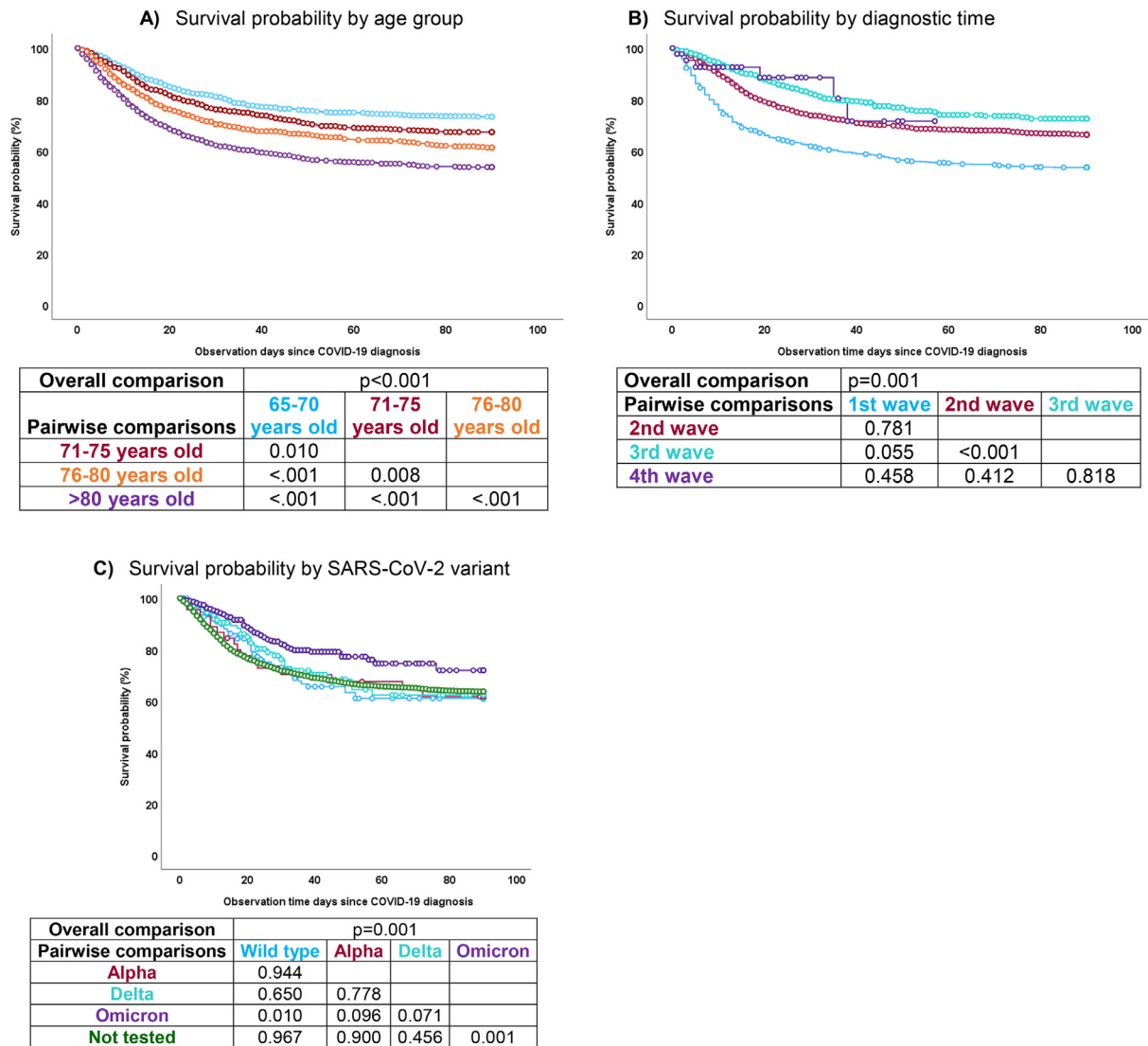


Figure 1. Survival probability by age group, diagnostic time, and SARS-CoV-2 variant.

whereas the incorporation of monoclonal antibodies significantly decreased it (HR 0.589, 95% CI 0.380-0.915). In patients >80 years old, male sex also had significantly worse prognosis (HR 1.355, 95% CI 1.074-1.709).

Discussion

Increased age was the most frequent independent risk factor for an adverse outcome of COVID-19 reported in patients with hematological malignancy. In the present study, the large number of patients analyzed allowed us to demonstrate the negative impact of increasing age even in the elderly population and to dissect the prognosis of COVID-19 according to clinical and therapeutic variables. More importantly, the duration of the study encompassing three pandemic waves from January 2020 to March 2022 enabled us to show that prognosis gradually improved, particularly during the third wave mainly sustained by the Omicron variant, and that receiving three doses of vaccine further ameliorated patient’s survival.

The present study confirms that chronological age significantly worsens the outcome of COVID-19 even within a population of

hematological malignancy selected for age ≥65 years, whose median age was 74. Overall, the 90-day survival was 71.2% and survival rates decreased with age. Survival differences were significant between each 5-year group, underscoring the prominent importance of chronological age as a predictor of adverse outcomes, even within subjects collectively defined as advanced age. In previous research, age was a significant adverse prognostic factor in 19 of 25 worldwide epidemiological studies analyzed [23]. None of those studies evaluated the impact of increasing age specifically within the elderly patient population. However, some insights have emerged from a meta-analysis involving over 600,000 patients that specifically assessed the impact of advancing age on mortality within the elderly demographic [24].

The characteristics of elderly patients studied were similar to those of patients with hematological malignancy and COVID-19 of any age reported in larger studies. As expected, the frequency of comorbidities, particularly cardiac, was higher, and there were relatively more patients with chronic lymphoid leukemia and myelodysplastic syndrome and fewer with acute lymphoid leukemia, chronic myeloid leukemia and Hodgkin’s lymphoma, reflecting the epidemiology of the general population.

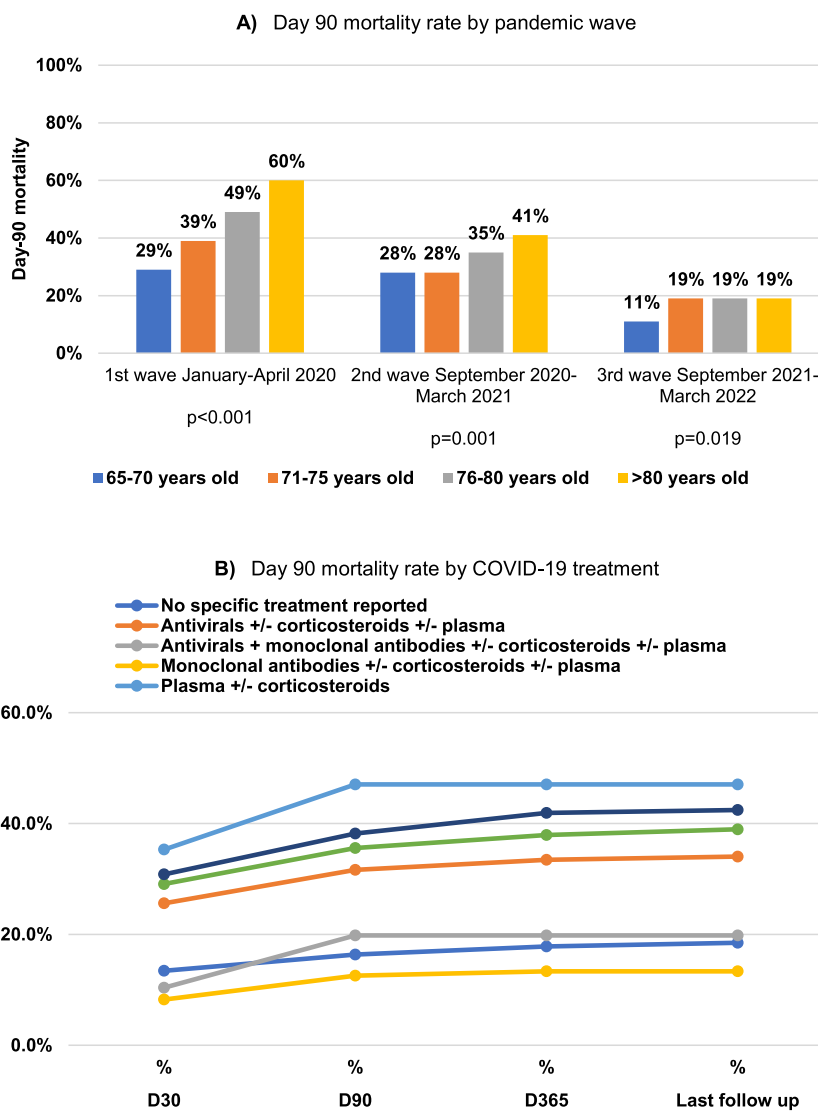


Figure 2. Day 90 mortality rate by pandemic wave and COVID-19 treatment.

In our elderly patients, there were significant differences associated with increasing age in variables potentially impacting survival. The eldest patients had more comorbidities but less severe neutropenia and lymphopenia. More importantly, they were less likely to receive targeted antivirals and monoclonal antibodies for COVID-19 or to receive intensive care when hospitalized for severe disease. Nevertheless, multivariable analysis confirmed that age *per se* remains one of the most powerful independent predictors of adverse outcomes among elderly patients with COVID-19.

The role of hematological malignancy as a direct cause of death was limited, accounting for only 8.1% of deceased patients. This proportion was lower than that reported in hematological malignancy patients of any age suggesting that in elderly persons the clinical impact of COVID-19 was more severe than that of their underlying hematological malignancy [12–14,18,19]. Among the different hematological malignancies, the prognosis of COVID-19 was worst in patients with acute leukemia, where increasing age had a negative prognostic effect. In other hematological malignancies, this effect was less pronounced.

Similarly to the general population, the first wave of COVID-19 from January to April 2020 was more severe than the second from

September 2020 to March 2021, which in turn was more severe than the third wave, from September 2021 to March 2022. The severity of COVID-19 during the first wave was particularly evident in patients >80 years old who were the largest group and whose 90-day survival did not reach 40%. On the contrary, the second wave affected primarily the youngest age group whose outcome did not differ from the first wave, whereas in the other age groups COVID-19 burden gradually decreased and its outcome improved. The third pandemic wave did not show an age predominance within elderly patients and its prognosis was markedly better with death rates below 20% in all age groups including patients >80 years old.

The improved outcome of COVID-19, in parallel to the pandemic evolution, has been ascribed to a presumed lower virulence of the Omicron virus variant [2,19–21], mostly represented since the third wave of the pandemic. However, in hematological malignancy patients, Omicron was still associated with considerable attributable mortality [19]. Although the viral strain was known only in a limited number of patients, the present study confirms that survival with the Omicron variant was significantly higher in elderly patients. The increased survival rates were particularly evident in pa-

tients aged 65–70 years whereas in the elder groups, differences between Omicron and the other variants were less notable, suggesting that if a patient is frail due to coexisting conditions like hematological malignancy, the effects of the lower virulence of virus variant may be outbalanced by increasing age.

The vaccination status may have also played a substantial role in the better outcome of the more recent Omicron variants. An improvement both in 30-day and 90-day survival was documented in patients receiving at least one dose of vaccine compared to unvaccinated patients. The difference was highly significant despite a low vaccination rate. This result may be surprising as it is generally assumed that hematological malignancy is associated with a lack of serological response to vaccines, both against COVID-19 or other viruses, for example, influenza [25]. In addition, treatments commonly used in hematological malignancy, like anti-CD20 monoclonal antibodies and Bruton's tyrosine kinase inhibitors [7], are strong inhibitors of anti-SARS-CoV-2 antibody production after vaccination [26,27], and increasing age may contribute to a reduced response to vaccination in hematological malignancy [26], as reported already, with an age cut-off of 82 years, but not in other reports [27]. Nevertheless, our report strongly documents the paramount importance of vaccination in elderly patients with hematological malignancy as well as the increasingly favorable impact of vaccination in parallel to increasing age. The beneficial effect of vaccines was magnified by the worsening prognosis with increasing age of unvaccinated patients. In patients >80 years old, a single vaccine dose was sufficient to improve survival significantly compared to unvaccinated persons, whose 90-day survival was lower than 50%. Patients aged 75–80 required a two-dose vaccination course to have a significant survival advantage, while a third additional dose was necessary in the cohort of patients aged 71–75. Similarly, in patients aged 65–70, a third dose was associated with a marked survival improvement compared to receiving only two doses.

The efficacy of a booster dose in enhancing the serological response rate and also the cellular immune response in persistently seronegative patients has been already reported in patients with hematological malignancy, irrespective of age [28], except in those recently treated with anti-CD20 monoclonal antibodies [29]. In the present study, the importance of a third vaccine dose in elderly patients was further highlighted by the multivariable analysis showing that vaccination with three doses was the most important actionable variable conferring an independent survival advantage. A lower number of doses and infection with the Omicron virus variant did not reach statistical significance.

The potential further benefit of a fourth vaccine dose in hematological malignancy patients is still under investigation. In a small series of solid organ transplant patients, a 50% seroconversion of seronegative patients and a 100% boosting of patients with low-positive antibody levels were shown [30]. Results of the present series are to be interpreted with caution since only 42 patients had received a fourth vaccine dose. Nevertheless, survival of these patients at 90 days reached over 90% overall and 100% in those aged 65–70 and 75–80 years, and it was consistently better than that of patients receiving three doses in all age groups.

Taken together, these data highlight the key importance of vaccination in a category of patients with a combination of multiple risk factors like comorbidities and hematological malignancy, whose difficulties in coping with COVID-19 are magnified by the increase in chronological age. Of note, age was recently demonstrated as the most significant adverse risk factor for survival in vaccinated patients with breakthrough COVID-19 [12,14]. Therefore, every improvement in the ability to effectively respond to the virus, including the immune response to multiple doses of vaccine, should be actively pursued.

In multivariable analysis, also an active hematologic malignancy, a diagnosis of acute leukemia, a more severe presentation of COVID-19, as well as comorbidities and severe lymphopenia were independently associated with mortality. They have been reported as potential risk factors in other reports on adult hematological malignancy patients with COVID-19 [31]. Unlike vaccination, most of these variables can be hardly addressed to improve the prognosis of our patients. However, the use of prolonged treatments for hematological malignancy, potentially causing lymphopenia, as well as optimal management of cardiac, renal, and hepatic comorbidities should be implemented to limit the dismal consequences of COVID-19 in elderly patients with hematological malignancy. Our data show that increasing age was associated with a suboptimal management of COVID-19. The use of antivirals and monoclonal antibodies, whose efficacy was highlighted also in our series, was apparently neglected particularly in patients >80 years old, although in this category of very frail patients, better infection management may maximize therapeutic benefits.

This large registry study has some limitations in addition to its retrospective nature. Data are incomplete particularly regarding the identification of SARS-CoV-2 variants, COVID-19 treatments, and potential thromboembolic phenomena. Other relevant limitations include the absence of sample size calculation due to its exploratory aims, and the potential bias stemming from the lack of data on functionality, cognition, and the prevalence of polypharmacy among elderly patients with hematological malignancy who contracted COVID-19, which could have provided additional insights into their overall health status and outcomes. Finally, the fact that antiviral and monoclonal antibody treatments were underutilized in patients over 80, potentially limited benefits in this vulnerable group.

In conclusion, elderly COVID-19 patients with hematological malignancy are a heterogeneous group whose prognosis markedly worsens with age. Despite the above limitations, the data collected provide a framework to address the optimal healthcare management of elderly hematological malignancy patients using preventive and therapeutic strategies, including vaccination and antiviral agents, which may be modulated according to increasing chronological age. Additionally, this study underscores the significant impact of age on the prognosis of elderly COVID-19 patients with hematological malignancy, mirroring the worse vital prognosis observed in other elderly patients with COVID-19 and specific comorbidities. Furthermore, the data highlight the crucial role of monoclonal antibodies in reducing mortality among these vulnerable individuals.

CRediT authorship contribution statement

G.R., J.S.G., C.C., R.C., O.A.C. and L.P. contributed to study design, study supervision, did the statistical plan and data interpretation, and wrote the paper. J.S.G. performed the statistical analysis. All authors recruited participants and collected and interpreted data, 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, have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Declarations of competing interest

The authors have no competing interests to declare.

Funding

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).

Ethical approval

EPICOVIDEHA (www.clinicaltrials.gov; NCT04733729) is an international open web-based registry for patients with HM infected with SARS-CoV-2. This registry was centrally 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). Additionally, if applicable, the respective local ethics committee of each participating institution might have approved the EPICOVIDEHA.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2023.10.013](https://doi.org/10.1016/j.ijid.2023.10.013).

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