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REVIEW

Predictors of clinical evolution of SARS-CoV-2 infection in hematological patients: A systematic review and meta-analysis

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Abstract

Main aim of this systematic review is to quantify the risk and identify predictors of clinical evolution of SARS-CoV-2 in hematological patients compared to different control populations. Two independent reviewers screened the literature assessing clinical outcomes of SARS-CoV-2 infection in adult patients with active hematological malignancies published up to June 2021. Primary outcome was COVID-19 related mortality, secondary outcomes were hospital and intensive-care admission, mechanical ventilation (MV), and thromboembolic events. Variables related to study setting, baseline patients' demographic, comorbidities, underlying hematological disease, ongoing chemotherapy, COVID-19 presentation, and treatments were extracted. A total of 67 studies including 10,061 hematological patients and 111,143 controls were included. Most of the studies were retrospective cohorts (51 studies, 76%) and only 19 (13%) provided data for a control group. A significant increased risk of clinical progression in the hematological population compared to the controls was found in terms of COVID-19 related mortality (OR, 2.12; 95% CI, 1.77–2.54), hospitalization (OR, 1.98; 95% CI, 1.15–3.43), intensive-care admission (OR, 1.77; 95% CI, 1.38–2.26), and MV (OR, 2.17; 95% CI, 1.71–2.75). The risk remained significantly higher in the subgroup analysis comparing hematological patients versus solid cancer. Meta-regression analysis of uncontrolled studies showed that older age, male sex, and hypertension were significantly related to worse clinical outcomes of COVID-19 in hematological population. Older age and hypertension were found to be associated also to thromboembolic events. In conclusion, hematological patients have a higher risk of COVID-19 clinical progression compared to both the general population and to patients with solid cancer.

KEYWORDS
COVID-19, determinants, hematological malignancies, mortality, severity

1 | INTRODUCTION

Two years after the start of the COVID-19 pandemic in March 2020, SARS-CoV-2 has caused over 250 million confirmed cases and more than 5 million deaths.[1] So far, several predictors of clinical evolution have been identified and widely used to identify patients at risk of worse outcomes and prioritize the access to preventive and therapeutic resources.[2–5] Among those risk factors, age, and chronic health conditions (diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, dementia, mental disorders, chronic kidney disease, immunosuppression, obesity, and cancer) have been reported with strong associations since the early phases of the pandemic.[6]

SARS-CoV-2 causes severe lymphocyte T depletion, and at the same time works as a trigger to both the innate and the adaptive immune response, leading to an excessive and prolonged cytokine/chemokine response associated with critical and fatal COVID-19. Therefore, several therapeutic options have shown their efficacy in preventing disease progression thanks to their ability of inhibiting the inflammatory response.[7–11]

Based on this rationale, some authors hypothesized that patients with hematologic malignancies might be at lower risk of severe COVID-19 due to an attenuated inflammatory response and concomitant immunosuppressive therapies.[12] On the other hand, several studies have reported an actual risk of COVID-19 related serious events in patients with hematological malignancy compared to COVID-19 patients without cancer.[13,14] As of today, though, precise mechanisms triggering disease progression remain largely unknown. Moreover, patients with hematological malignancies represent a highly heterogeneous population with several kind of disease- or therapy-induced immunosuppression, hence requiring a more customized clinical approach for COVID-19 management and treatment.[15]

Main aim of this systematic review is to summarize existing evidence on clinical evolution of SARS-CoV-2 in hematological patients compared to non-hematological and identify major risk factors for disease progression.

2 | METHODS

This systematic review was conducted according to the PRISMA 2020 guidelines. The protocol was registered on the PROSPERO database on 25 August 2021 (CRD42021262398).

2.1 | Literature search

A literature search was performed using PubMed and LOVE Database (Epistemonikos Foundation) with pre-defined COVID-19 filters using the following search strategy: (hematol* OR haematol*) AND (cancer OR malignancy OR neoplasm OR lymphoma OR leukemia OR transplant). The search was run on 30 June 2021.

2.2 | Exclusion criteria

Studies focusing on pediatric populations, studies including patients in clinical remission (i.e., not undergoing treatment in the last 6 months), small case series (less than 10 patients), and non-English studies were excluded.

2.3 | Inclusion criteria

All studies assessing clinical outcomes of adult inpatients and outpatients with active hematological malignancies and SARS-CoV-2 infection were included. Studies with mixed patients' populations were included only if the outcome was specified for the hematological population subgroup. When subgroup analysis for hematological population was not performed, at least 80% of the included population needed to have an active hematological disease for the study to be included. Both controlled and uncontrolled studies were included. In case of case-controlled studies, to be included in the analysis, the two populations needed to be comparable for at least two among the following relevant variables: age, sex, comorbidities, COVID-19 baseline severity. No restriction was applied on publication date, and both peer-reviewed and pre-prints were included. References of all the included studies were also inspected, abstract or full text of potentially eligible articles were retrieved and examined applying the same inclusion criteria.

2.4 | Data extraction

The following predictors were included: (1) baseline conditions (i.e., age, comorbidities type of hematological malignancy, ongoing chemotherapy), (2) COVID-19 related baseline variables (prevalence of symptoms at enrollment, prevalence of confirmed pneumonia, oxygen need at baseline, need for hospitalization or intensive care unit (ICU) admission at baseline), (3) treatment related variables (modification of chemotherapy, COVID-19 administered treatments).

Primary outcome was COVID-19 related mortality at any time point. Secondary outcomes were hospital admission, ICU admission, mechanical ventilation (MV), oxygen requirement, clinical recovery (as opposite of clinical failure, both as defined by the study), bacterial or fungal superinfection, thromboembolic events, asymptomatic disease only, hematological progression, length of hospital/ICU stay.

The inclusion and exclusion process, the data extraction and the quality assessment were carried out by four reviewers working in two blinded pairs. The inclusion and exclusion process was performed with the support of the Rayyan software, data extraction was conducted using a pre-defined Excel database. Any disagreement was solved via discussion within the pair or with the involvement of a fifth reviewer.

All studies fulfilling the inclusion criteria were assessed for risk of bias via an adapted version of the Newcastle-Ottawa scale (NOS)[16] for cohort and case-control studies (details of the adapted NOS score are available in the Supplementary Material).

2.5 | Statistical analysis

Individual studies offering a comparison group were included in a first meta-analysis, where the excess risk of clinical development of the hematological population compared with the non-hematological controls was computed as pooled odds ratios with 95% CI. All studies (controlled and non-controlled) contributed to a second meta-analysis model, where the occurrence of the included clinical outcomes in the hematological population was computed as a pooled prevalence with 95% CI.

All meta-analyses were conducted using a random effects model, assuming a priori significant heterogeneity resulting from diverse study populations and different models for adjusted analyses. Heterogeneity was assessed using a chi square test of heterogeneity and the I-squared measure of inconsistency. Subgroup analysis with computation of the between-study variance was performed for the main categorical variables (i.e., study setting, main hematological disease included, study design, and type of population enrolled). Mixed effect univariate meta-regression was conducted using the unrestricted maximum likelihood method to assess the impact of the following continuous variables: patients' mean age, prevalence of female, prevalence of different race, comorbidities, proportion of patients undergoing chemotherapy, COVID-19 baseline characteristics, and COVID-19 treatments.

2.6 | Ethics approval

Since the study was designed as a systematic review and meta-analysis of published studies, ethical approval was not deemed necessary.

3 | RESULTS

From 1871 identified references, a total of 67 studies accounting for 10,061 hematological patients and 111,143 controls were included in the systematic review (Table S3 summarizes the included studies and reported outcomes).[13,15,17–81] A PRISMA flow-chart detailing the inclusion and exclusion process is available in the Supplementary Material (Figure S1).

Sample size ranged from 12 to 1389 patients per study (median 51; interquartile range (IQR), 22–164); median study duration was 66 days (IQR, 45–118). Most of the studies were cohort studies with retrospective data collection in 51 studies (76%) and prospective in 8 (12%). Whereas a control population of non-hematological patients was available in 19 (13%) studies, only eight (12%) were designed as case-control studies. Most of the studies were conducted in the USA, Europe (mostly in Italy, France, Spain, Germany, United Kingdom, Belgium), and China.

Forty studies (59%) enrolled only hospitalized patients, while the remaining 27 included a mixed population of both in- and out-patients. Thirty-eight studies (57%) described a mixed population of hematological patients. Four studies (6%) focused on non-Hodgkin and Hodgkin lymphoma patients and two (3%) studies on central nervous system lymphoma. Five (7%) studies included only patients with multiple myeloma, eight studies (11%) included stem cell transplant (SCT) recipients, four (6%) studies focused on patients with chronic lymphocytic leukemia and one study on chronic myeloid leukemia. Two studies included patients with myeloproliferative neoplasm and one myelodysplastic syndrome. Only one study reported data on patients with acute leukemia.

Only 30 (43%) studies reported specifically on systemic anticancer chemotherapy and 35 (52%) studies reported information regarding specific COVID-19 treatment.

Study quality was considered low in 19 studies (28%; NOS score <5), 39 studies (58%) were considered as medium quality (NOS score between 6 and 7), and 9 studies (14%) were considered high quality (NOS score >8). Newcastle-Ottawa scale domains where a lower quality was found were representativeness of the cohort, selection of control and comparability (Figure 1).

3.1 | COVID-19 related mortality

Fourteen studies provided adequately matched data for COVID-19 related mortality in the hematological population compared with controls. The overall analysis showed a significant increased mortality for hematological patients (OR, 2.12; 95% CI, 1.77–2.54; $p < 0.001$). The pooled OR remained significant also when grouping the studies according to the type of control included (general population in 9 studies and other immunodeficiencies, mainly solid tumors, in 5 studies, see Figure 2). A moderate level heterogeneity (I^2, 50.3%) was measured with the meta-analysis, less heterogeneous results were found by grouping the studies by design and setting (Table 1 describes the subgroups analysis of COVID-19 related mortality).

Meta-regression analysis of continuous variables showed a significant inverse correlation between the effect size and mean age of the patients enrolled (OR, 0.77; 95% CI, 0.60–0.98; $p = 0.04$), implying that older patients had less impact of the hematological disease on the outcome. No other significant correlation was found for the other continuous variables (prevalence of female sex, diabetes, hypertension, chronic obstructive pulmonary disease, cardiovascular disease, and chemotherapy related variables).

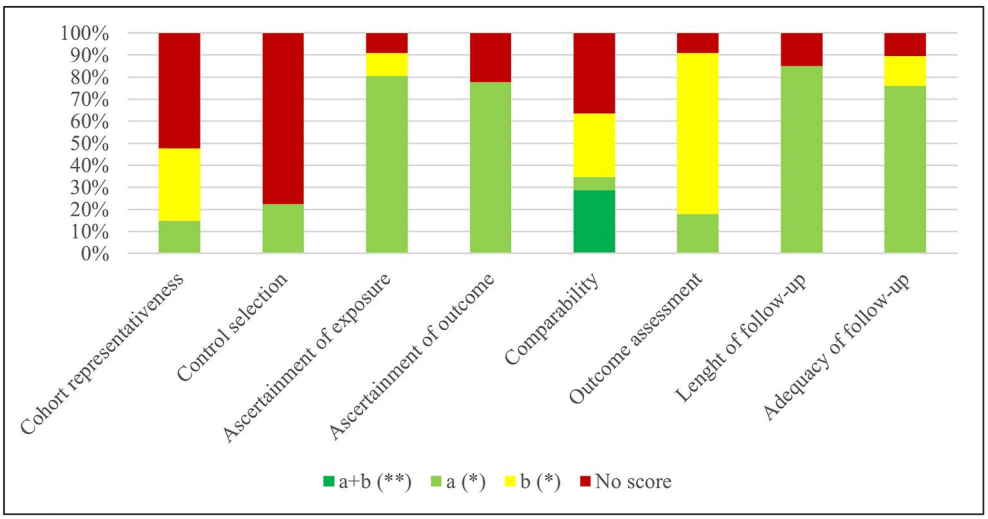

FIGURE 1 NOS score[16]

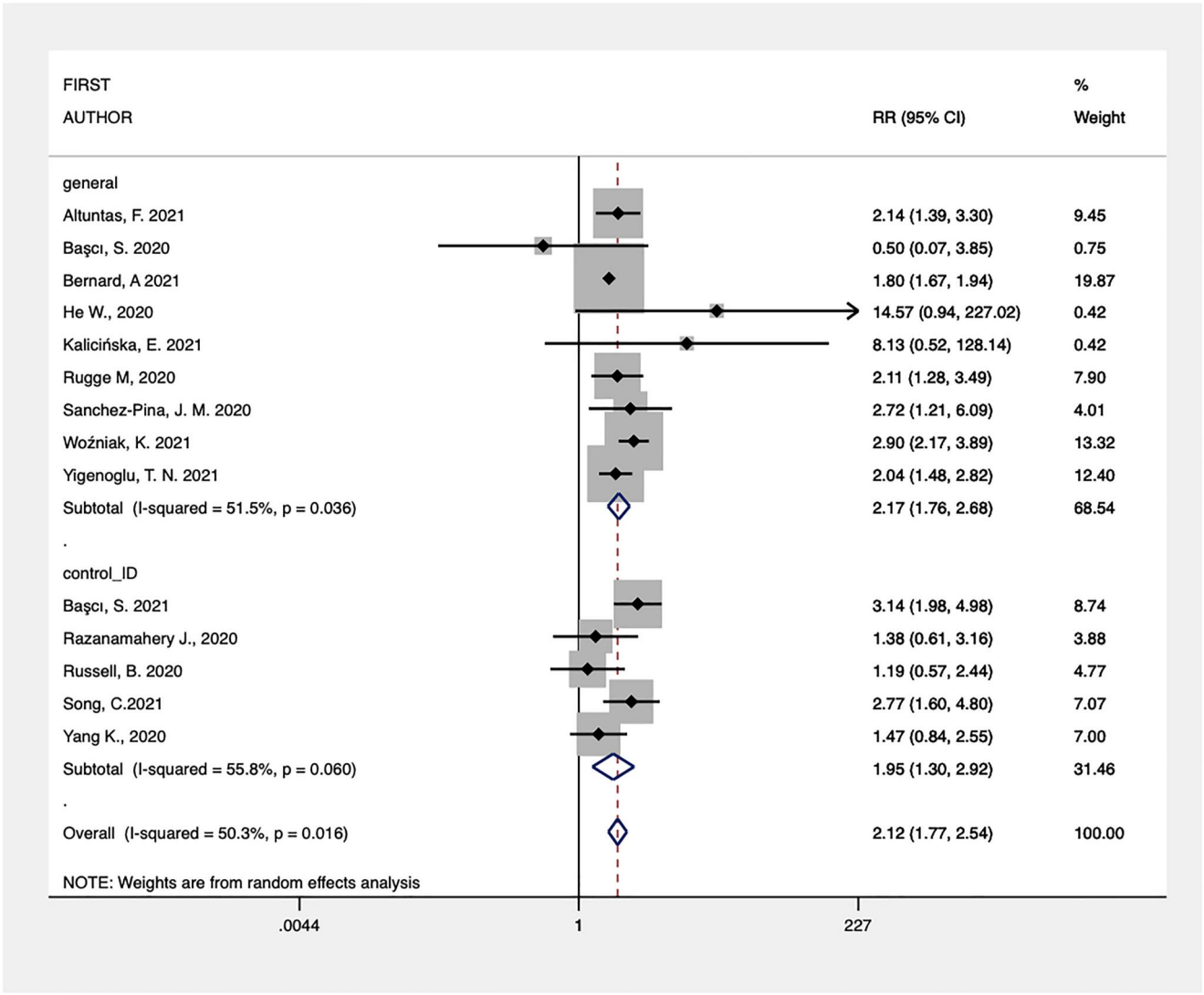

FIGURE 2 Forest-plot of controlled studies assessing COVID-19 related mortality grouped by type of control (general population or other immunosuppressive conditions)

The overall analysis of uncontrolled studies (66 studies) showed a pooled prevalence of COVID-19 related mortality of 30% (95% CI, 26%–34%) with a very high heterogeneity (I^2, 96%). As expected, a lower mortality was found in studies enrolling only outpatients or in studies with a mixed setting at enrollment (both in- and outpatients). For this reason, subgroup analysis and meta-regression to assess heterogeneity were conducted including studies where at least 80% of the population was hospitalized (46 studies). In the subgroups analysis on hospitalized patients, lower mortality rates were found in SCT patients. All subgroups showed a remarkable heterogeneity except for studies including patients with lymphoma.

The meta-regression analysis found that age was directly associated with increased mortality ($p = 0.001$; Adj R^2 46%; Figure 3). No other variables were found to be significantly related to COVID-19 related mortality (details in supplementary Table S1).

3.2 | Hospital admission

Controlled studies assessing hospital admission showed an increased odds of hospitalization in patients with hematological malignancies compared to either the general population or to patients with other

TABLE 1 Subgroup analysis of COVID-19 related mortality in controlled and uncontrolled studies

		Studies with control				Uncontrolled studies			
Variables	**Subgroup**	***N***	**Pooled OR**	**95% CI**	**I^2 (%)**	***N***	**Pooled prevalence**	**95% CI**	**I^2 (%)**
Setting	Hospitalized	9	1.91	1.5–2.3	18	44	0.34	0.29–0.39	91
	Mix	5	2.32	1.7–3.0	48	21	0.24	0.20–0.28	89
	Outpatients	-	-	-	-	2	0.18	0.03–0.32	0
Study design[a]	Cohort retrospective	8	1.80	1.7–1.9	0	38	0.33	0.26–0.39	97
	Cohort prospective	-	-	-	-	2	0.36	0.28–0.44	0
	Case-control	6	2.58	1.9–3.4	32	6	0.29	0.16–0.42	78
Hematological malignancy[a]	Hematopoietic cell transplantation	-	-	-	-	7	0.21	0.07–0.36	79
	Mix	13	2.14	1.8–2.6	51	31	0.36	0.31–0.41	88
	Leukemia	1	0.50	0.1–3.8	0	4	0.23	0.12–0.34	82
	Myeloma	-	-	-	-	5	0.26	0.01–0.51	98
	Myeloproliferative neoplasm	-	-	-	-	2	0.48	0.37–0.58	0
	Lymphoma	-	-	-	-	5	0.30	0.25–0.34	8

[a]Only studies reporting hospitalized patients were included in this analysis.

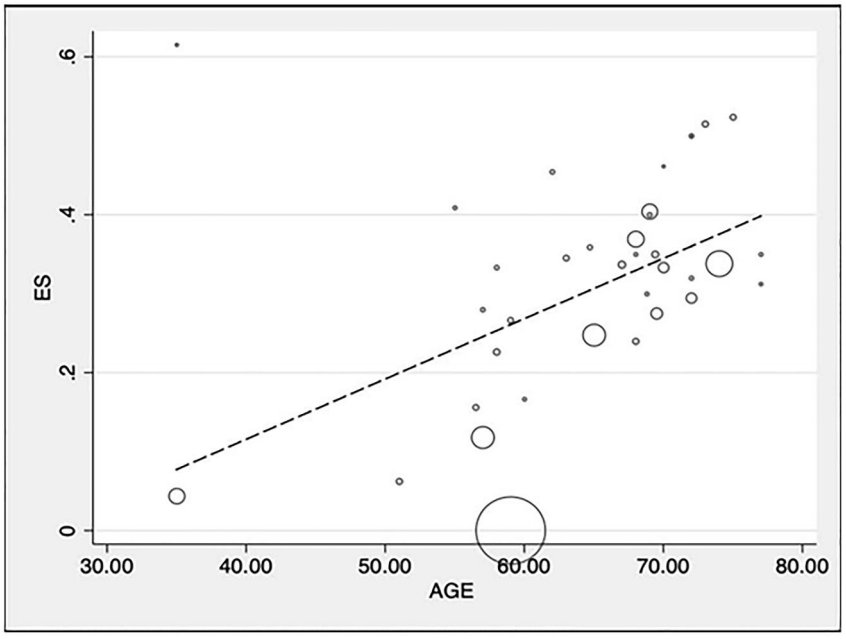

FIGURE 3 Meta-regression of COVID-19 related mortality and mean age in cohort studies

immunodeficiencies (pooled OR 1.98; 95% CI, 1.15–3.43; I^2 94%; $p = 0.014$).

The overall analysis of 11 uncontrolled studies showed an overall hospital admission rate of 56% (95% CI, 43%–69%) with a very high heterogeneity (I^2, 99%). No significant reduction in heterogeneity was seen by grouping the studies according to setting and hematological population. Meta-regression analysis found a positive association between hospital admission and diabetes, hypertension, chronic pulmonary disease, and cardiovascular disease (details in supplementary Tables S1 and S2).

3.3 | Intensive care unit admission

The meta-analysis of controlled studies showed that hematological patients compared to general population and patients with other immunodeficiencies have a significant higher risk of being admitted to ICU (9 studies included, overall OR, 1.77; 95% CI, 1.38–2.26; $p = 0.04$; I^2, 52.8%). The overall analysis of 31 studies not displaying a control group showed a pooled prevalence of ICU admission of 18% (95% CI, 15%–21%) with a high heterogeneity (I^2, 89%). No significant variations in the effect size were detected in the subgroup analysis by study design, hematological disease or study setting. The only factor associated with ICU admission rates was sex, with studies displaying higher percentages of females enrolled showing a decreased rate of ICU admission ($p = 0.01$; adjusted R^2: 24.8%) (details in supplementary Tables S1 and S2).

3.4 | Mechanical ventilation

Only five studies displayed rates of hematological patients undergoing mechanical ventilation (MV) compared to controls. When considering both control groups (general population and patients with other immunocompromizing conditions), hematological patients showed higher odds of undergoing MV with a low heterogeneity among included studies (pooled OR, 2.17; 95% CI, 1.71–2.75; $p = 0.005$; I^2, 6.2%).

A total of 16 studies reported on the rate of hematological patients with COVID-19 that were mechanically ventilated. The overall pooled prevalence was 16% (95% CI, 13%–19%) with an overall heterogeneity of 55% and no significant reduction detected via subgroup analysis. None of the continuous variables tested with the meta-regression analysis resulted significatively associated with MV (details in supplementary Tables S1 and S2).

3.5 | Thromboembolic events

No studies with a control group reported on this outcome. A total of nine uncontrolled studies analyzed the occurrence of thromboembolic events in the hematological population with a pooled prevalence of 9% (95% CI, 3%–9%; I^2, 72%). The main reported events were deep venous thrombosis, pulmonary embolism and arterial thrombosis. Age and hypertension were found to be positively correlated with thromboembolic events in the meta-regression analysis (details in supplementary Tables S1 and S2).

3.6 | Other outcomes

Among other outcomes included in the systematic review (oxygen requirement, clinical recovery, superinfection, asymptomatic disease only, hematological progression and length of hospitalization) no meta-analysis was undertaken due to the low number of studies reporting data.

4 | DISCUSSION

During the two years following the start of the pandemic, two other systematic reviews assessing the clinical outcome of hematological patients with COVID-19 have been published.[14,82] Those papers included a total of 3377 and 2316 patients respectively, and the search was conducted up to August 2020 for the first one and May 2020 for the second. Both publications reported data on overall mortality and ICU admission, and their findings are in line with our results.

Our updated analysis included studies published from the beginning of the SARS-CoV-2 pandemic up to June 2021. Overall, in our study the pooled prevalence of COVID-19 related mortality in hematological patients was 30% (95% CI, 26%–34%) with a very high heterogeneity among studies (I^2, 96%). Similarly, according to Vijenthira et al.[14] adult patients with hematologic malignancy and COVID-19 had a 34% risk of death, whereas Venkatesulu et al.[82] found that hematological malignancies patients had an all-cause in-hospital mortality rate of 33%.

Our data confirmed previous results on the ICU admission rate, which was 18% (95% CI, 15%–21%) in our analysis compared to a 21% risk (95% CI, 16%–27%) found by Vijenthira et al.[14] Very high heterogeneity was detected in both meta-analyses. As for MV, our findings showed a pooled prevalence of 16% (95% CI, 13%–19%; I^2, 55%), whereas Vijenthira et al. measured a pooled risk of 17% (95% CI, 13%–21%; I^2, 63%).[14]

We did not find any other systematic review reporting on less common outcomes such as thromboembolic events, bacterial superinfection, clinical recovery, length of hospitalization or delay of systemic anticancer chemotherapy.

The availability of a significant number of studies including a control group of COVID-19 patients without hematological malignancies allowed us to compute the excess risk of worse outcome in this specific patients' population. All outcomes (mortality, hospital admission, ICU admission and MV) were significantly worse in hematological patients when compared to the general population, and to patients with other immunocompromizing conditions (mostly solid organ cancer).

These results do not support the initial belief that immunocompromized patients might less frequently experience worse clinical outcomes compared to the general population, and provide

evidence that adequate preventive policy targeting fragile populations is essential.

We used subgroup analysis and meta-regression to test whether some of the included clinical variables could predict clinical evolution in hematological patients. Among those, we found a positive correlation between age and COVID-19 related mortality ($p = 0.001$; Adj R^2 41% coefficient 0.007), hypertension ($p = 0.03$; coefficient 0.001) and thromboembolic events ($p = 0.003$; coefficient 0.001). Once results are quantitatively summarized, one of the added values of meta-analysis is the ability to detect and try to assess between-study variance. In both our analyses (controlled and uncontrolled studies), a high heterogeneity was detected, suggesting remarkable differences among included studies. Meta-regression of continuous variables did not show remarkable reduction in heterogeneity, whereas a reduced heterogeneity was measured when grouping studies by design, and in some specific type of hematological patients' population. However, as expected when including observational studies, a significant proportion of the between-study variance could not be explained by any of the included variables.

Our work has some limitations, mostly related to the study design and the underreporting of possibly relevant outcome predictors. Most of the studies had a retrospective design and only 14 studies included an adequate control group for the mortality analysis. Some key examples of incomplete reporting of relevant variables are the type of hematological malignancies (unspecified in more than half of the studies), the setting (mixed in almost one-third of the studies), or the type and the percentage of patients undergoing systemic chemotherapy for which details were rarely provided. Also, inclusion of relevant COVID-19 related variables (from disease severity to specific pharmacological interventions) was highly heterogeneous among studies.

Among laboratory abnormalities, mostly lymphopenia, mild thrombocytopenia and elevated D-dimer values are reported among patients with COVID-19.[83] More severe abnormalities have been often associated with more severe infection; D-dimer and, to a lesser extent, lymphopenia seem to have the largest prognostic associations.[84,85] As for our selected studies, laboratory findings were seldom reported, and hard to harmonize. Thus, no estimation of their predictive value in the hematological population could be done.

Most of the studies were rated as having a medium quality, and "selection" and "comparability" were the domains with the lowest scores and at higher risk of introducing bias in the analysis.

Compared to other systematic reviews, this work constitutes a relevant update of the evidence on the topic and summarizes quite many studies including a relevant sample size. One of the strengths of our systematic review is that it provides wide and comprehensive analysis of different variables that could potentially predict clinical evolution of COVID-19 in hematological patients. However, it must be noted that the systematic search dates back to June 2021 and all the included studies were conducted before mass vaccination was available.

In conclusion, this systematic review quantifies the higher risk of death, hospitalization, ICU admission and MV in hematological patients with COVID-19 compared to the general population and to patients with other immunodeficiencies. In line with available data on the general population, older age, male sex, and hypertension are significantly related to worse clinical outcomes of COVID-19 in hematological population.

Large cohort studies, such as the recent collaborative effort of the ITA-HEMA-COV (the ITAlian HEMatology Alliance on Covid-19) on SARS-CoV-2 infection in patients with lymphoma,[86] are necessary to better analyze the role of relevant clinical determinants related to the hematological disease (i.e., type of disease, role of chemotherapy). Additionally, a further update of our data collection is needed to measure the effect of mass vaccination and use of recently approved drugs in immunocompromized patients.

AUTHOR CONTRIBUTIONS

All authors contributed to the population, intervention, control, outcome selection and the protocol draft. Elisa Razzaboni, Anna Maria Azzini, Mariana Nunes Pinho Guedes, Maria Elena De Rui performed the literature search and the data extraction. Elena Carrara performed the analysis and drafted manuscript. All authors have reviewed and approved the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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PEER REVIEW

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SUPPORTING INFORMATION

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

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