Outcomes of patients with hematologic malignancies and COVID-19: A systematic review and meta-analysis of 3377 patients

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Abstract:

Outcomes for patients with hematologic malignancy infected with COVID-19 have not been aggregated. The objective of this study was to perform a systematic review and meta-analysis to estimate the risk of death and other important outcomes for these patients.

We searched Pubmed and EMBASE up to August 20, 2020, to identify reports of patients with hematologic malignancy and COVID-19. The primary outcome was a pooled mortality estimate, considering all patients and only hospitalized patients. Secondary outcomes included risk of ICU admission and ventilation in hospitalized patients. Subgroup analyses included mortality stratified by age, treatment status, and malignancy subtype. Pooled prevalence, risk ratios (RR), and 95% confidence intervals (CI) were calculated using a random-effects model.

34 adult and 5 pediatric studies (3377 patients) from Asia, Europe, and North America were included (14/34 adult studies included only hospitalized patients). The risk of death amongst adult patients was 34% (95% CI 28-39, N=3240) in this sample of predominantly hospitalized patients. Patients aged >60 years had a significantly higher risk of death than patients <60 years (RR 1.82, 95% CI 1.45-2.27, N=1169). The risk of death in pediatric patients was 4% (95% CI 1-9, N=102). The RR of death comparing patients with recent systemic anti-cancer therapy to no treatment was 1.17 (95% CI 0.83-1.64; N=736).

Adult patients with hematologic malignancy and COVID-19, especially hospitalized patients, have a high risk of dying. Patients >60 years have significantly higher mortality, and pediatric patients appear to be relatively spared. Recent cancer treatment does not appear to significantly increase the risk of death.

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Running title: COVID-19 meta-analysis

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Key Points

- • Adult patients with hematologic malignancy and COVID-19 found a 34% risk of death, while pediatric patients had a 4% risk of death.
- • Patients on systemic anti-cancer therapy had a similar risk of death to patients on no treatment (RR 1.17, 95% CI 0.83-1.64)

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and meta-analysis to estimate the risk of death and other important outcomes for these patients.

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Introduction

A substantial number of guidance documents and review articles have been published regarding the management of patients with cancer and the novel severe acute respiratory syndrome coronavirus 2 (COVID-19)[1-10]. However, there are no systematic reviews or meta-analyses specific to patients with hematologic malignancies. These patients are recognized to be highly immunocompromised due to their underlying disease as well as the treatments they receive, causing significant concern about a risk of heightened morbidity and mortality from COVID-19 in this population. On the other hand, some authors have suggested that some patients with hematologic malignancies might be "protected" from severe COVID-19 morbidity due to an attenuated inflammatory response[11-13]. Cohort and registry studies have emerged to answer these and other questions, including the COVID-19 and Cancer Consortium (CCC19), the UK Coronavirus Cancer Monitoring Project (UKCCMP), and the American Society of Hematology Research Collaborative.

Given the rapidly evolving literature and overall limited data in patients with hematologic malignancy, aggregating data to obtain more precise estimates of the risks related to COVID-19 is essential to inform clinical decision-making. The objective of this study was to perform a systematic review and meta-analysis to quantify the outcomes (deaths, hospitalizations and complications) of patients with hematologic malignancy and COVID-19.

Methods

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Eligibility criteria

All studies published since January 1, 2019 on outcomes of patients with cancer and COVID-19 were considered for inclusion. Only studies providing data on patients with hematologic malignancy (bone marrow failure syndromes such as myelodysplastic syndromes (MDS), acute leukemias, lymphomas, plasma cell dyscrasias, and/or myeloproliferative neoplasms (MPNs)) were included. Both adult (age >18 years) and pediatric (age <18 years) studies were included. Case reports, case series, or cohort studies with less than 10 patients were excluded. Only English and Chinese language reports were included. Full inclusion criteria are available in Supplemental Data Table S1.

Information sources and search strategy

Pubmed and EMBASE databases were searched up to the week of August 17, 2020. The full search strategy is available in Supplemental Data Table S2.

Two authors (AV and IG) independently conducted the search strategy, and results were compared to ensure concordance. Differences in opinion were discussed and resolved, with a third author (LKH) available for resolution of disagreements. Titles and abstracts of articles were reviewed and any that were clearly irrelevant were excluded. Full texts of remaining articles were reviewed to find studies that met the inclusion criteria. Additionally, systematic reviews related to cancer and COVID-19 were screened to identify additional references.

Data collection

A data extraction form was used to extract relevant information from the articles. Information extracted was specific to patients with hematologic malignancy, and included geographic location of study, total number of patients, median age, gender distribution, total study duration and whether follow up was complete, death rate, death rate in inpatients, ICU admission rate, mechanical ventilation rate, non-invasive ventilation rate (continuous positive airway pressure, bi-level positive airway pressure, high-flow oxygen by nasal cannula), and death rate stratified by treatment, age, and hematologic malignancy subtype.

For treatment subgroups, “systemic anti-cancer therapy (SACT)” was defined as patients on active anti-cancer therapy (i.e. cytotoxic chemotherapy, immunotherapy, targeted agents; single-agent hydroxyurea for MPNs and steroids were excluded from this definition) within 28 days to 6 months of COVID-19 diagnosis (depending on varying definitions utilized in each study). A subgroup of SACT was defined as “cytotoxic SACT”, and included patients on cytotoxic therapy only (e.g. multi-agent systemic chemotherapy or anti-myeloma therapy; excluding single-agent immunotherapy, single- agent targeted therapy, single agent hydroxyurea for MPNs, or steroids). “Not on treatment” was defined as patients on observation or who were greater than 28 days to 6 months since their last active treatment. “Best supportive care” (BSC) was defined as patients on supportive care only such as hydroxyurea alone for acute leukemia, erythropoietin stimulating agents, or where studies indicated that patients were on BSC.

Hematologic malignancy subtypes were divided as follows: acquired bone marrow failure syndromes (e.g. MDS, aplastic anemia); acute leukemias (myeloid and lymphoid); lymphomas (non-Hodgkin and Hodgkin); plasma cell dyscrasias (multiple myeloma, amyloidosis, smoldering myeloma, monoclonal gammopathy of undetermined significance); MPNs (chronic myeloid leukemia, polycythemia vera, essential thrombocytosis, myelofibrosis). In select cases where key data were not included, authors of studies were

emailed for clarification of the published data.

Risk of bias in individual studies

As the majority of studies included were descriptive cohort studies with no comparator arm, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data was used (see Supplemental Data Table S3 for checklist)[14]. Sample size adequacy was assessed using previously described methods[15], using an estimated risk of death of 0.35 and precision of 0.05 indicating a confidence interval width of 10%. Studies scoring at least 6 out of 9 were considered low risk, as previously reported[16]. Assessment was conducted by two authors (AV and IG), while a third author (LKH) was available to resolve differences of opinion.

Outcomes

The primary outcome of the meta-analysis was the pooled risk of death amongst patients with hematologic malignancies and COVID-19, subdivided into adult and pediatric patients. Risks of death in all patients as well as within hospitalized patients are reported.

Secondary outcomes included the proportion of hospitalized patients requiring ICU admission and ventilation support (mechanical and non-invasive). Pre-specified subgroup analyses were conducted for pooled risk of death stratified by age, race (non- White versus White), treatment status, hematologic malignancy subtype, and geographic location (Asia versus Europe versus North America). Pre-specified sensitivity analyses were conducted on the primary outcomes limiting to studies with low risk of bias, to studies with complete follow up of all patients, to studies diagnosing COVID-19 based solely on real-time polymerase chain reaction (RT-PCR), and to studies that included a combination of outpatients and hospitalized patients. Due to data limitations, secondary outcomes, subgroup analyses, and sensitivity analyses were not completed for the studies reporting on pediatric patients.

Synthesis of results

The principal summary measures used were pooled prevalence and risk ratios (RR) with 95% confidence intervals (CI). Heterogeneity between estimates was assessed using the I^2 statistic, and interpreted per the Cochrane Handbook recommendations: I^2 0%-40%, heterogeneity likely not substantial; 30%-60% moderate heterogeneity; 50%- 90% substantial heterogeneity; 75%-100% considerable heterogeneity[17]. For the primary outcome, secondary outcomes, and subgroup analyses, estimates were transformed using the Freeman-Tukey double arcsine method[18], and the final pooled results were back- transformed with 95% CI for ease of interpretation. For secondary outcomes involving RR, pooled dichotomous effect measures were expressed as RR with 95% CI. Meta- analysis was performed using a random-effects model (DerSimonian and Laird) using the MetaXL (www.epigear.com) add-in for Microsoft Excel, as well as Review Manager 5.4 (Cochrane Collaboration, 2020).

Publication bias was assessed using the Doi plot and Luis Furuya-Kanamori asymmetry index (LFK index)[19]. The closer the value of the LFK index to zero, the more symmetrical the Doi plot (i.e. low risk of publication bias). LFK index values outside the interval between -1 and +1 are consistent with asymmetry (i.e. publication bias). Sensitivity testing was performed to assess the main source of asymmetry.

Data Sharing Statement

All data is reported in the paper in figures or supplemental figures. Aggregate data tables are available from the corresponding author.

Results

Figure 1 shows the flow diagram for study selection. A total of 34 adult studies (32 peer-reviewed, 1 pre-print, 1 open on-line registry) and 5 pediatric studies (4 peer- reviewed, 1 open on-line registry) comprising 3377 patients from Asia, Europe, and North America were included[20-57]. Total duration of studies ranged from 3 weeks to 15 weeks. COVID-19 was diagnosed based solely on RT-PCR in the majority of studies (27/38 sources); others did not specify (4/38) or used clinical suspicion, imaging, or external reporting in some patients (7/38). The majority of data are regarding patients followed at hospitals or cancer-centers; one study used a countrywide Ministry of Health database[52]. Table 1 lists the summary characteristics of the included studies. Table 2 lists the results of the risk of bias assessment for individual studies, and Table S4 (supplemental data) includes details of the scoring. When assessing for publication bias, major asymmetry was noted (LFK index 2.18) (Supplemental Data Figure 1); this was largely driven by the only study which used population-based data[52]. The LFK index when excluding this study due to the differences in methodology was 0.94, indicating no asymmetry and a low risk of publication bias.

COVID-19 associated mortality – adult studies

A total of 34 studies (3240 patients) had data available regarding mortality associated with a diagnosis of COVID-19 in adult patients with hematologic malignancy. The pooled risk of death was 34% (95% CI 28-39) (Figure 2a). Substantial heterogeneity was detected (I^2 87%). When limiting the analysis to mortality among inpatients only, a total of 28 studies with 2361 hospitalized patients showed a pooled risk of 39% (95% CI 34-44), with decreased heterogeneity (I^2 66%) (Figure 2b).

COVID-19 associated mortality – pediatric studies

The pooled risk of death was 4% (95% CI 1-9) in pediatric studies (5 studies, 102 patients) (Figure 2c). No statistically significant heterogeneity was detected (I^2 0%).

ICU admission and ventilation

24 studies (2192 patients) provided data regarding need for ICU admission among hospitalized patients, 21 studies (1320 patients) provided data regarding need for mechanical ventilation in hospitalized patients, and 12 studies (373 patients) provided data regarding need for non-invasive ventilation in hospitalized patients. For ICU admission, the pooled risk was 21% (95% CI` 16-27, I^2 87%); for mechanical ventilation, the pooled risk was 17% (95% CI 13-21, I^2 63%) ; for non-invasive ventilation, the pooled risk was 16% (95% CI 9-26, I^2 79%) (Supplemental Data Figure 2).

Subgroup and sensitivity analyses

Pre-specified age-stratified (<60 years and >60 years) subgroup analyses were conducted. Data with age were available from 16 studies (1169 patients). Patients under 60 years of age

had a lower pooled risk of mortality (25%, 95% CI 19-33, I^2 24%) compared to patients aged 60 years and older (47%, 95% CI 41-54, I^2 58%). The pooled RR for death for patients under 60 years versus patients aged 60 and older was 0.55 (95% CI 0.44-0.69, p<0.00001), with no statistically significant heterogeneity (I^2 0%) (Figure 3).

Subgroup analysis based on race using data from 5 studies that reported race- based outcomes (162 patients) showed that non-White patients had a significantly higher risk of death compared to White patients (RR 2.2 (95% CI 1.3-3.8, p=0.003, I^2 0%)) (Supplemental Data Figure 3).

Subgroup analyses were also conducted for patients with recent SACT (19 studies, 736 patients), the subgroup of cytotoxic SACT (13 studies, 614 patients), patients not on treatment (14 studies, 356 patients), and patients on BSC (5 studies, 21 patients). The pooled risk of mortality was 39% (95% CI 32-46, I^2 67%), 40% (95% CI 32-47, I^2 68%), 25% (95% CI 17-34, I^2 53%), and 85% (95% CI 67-97, I^2 0%) for recent SACT, the subgroup cytotoxic SACT, no treatment, and BSC, respectively. The pooled RR for death for patients with recent SACT compared to no treatment was 1.17 (95% CI 0.83- 1.64, p=0.37), with no statistically significant heterogeneity (I^2 36%, p=0.09) (Figure 4a). When restricting the analysis to the subgroup of patients with recent cytotoxic SACT versus no treatment, the pooled RR of death was 1.29 (95% CI 0.78-2.15, p=0.32), with no statistically significant heterogeneity (I^2 36%, p=0.15) (Figure 4b).

Pooled risk of death was also calculated by hematologic malignancy subtype. The risk of death for acquired bone marrow failure syndromes (14 studies, 231 patients) was 53% (95% CI 34-72, I^2 77%); for acute leukemias (18 studies, 289 patients) 41% (95% CI 30-52, I^2 57%), for plasma cell dyscrasias (23 studies, 412 patients) 33% (95% CI 25-41, I^2 58%); for lymphomas (including CLL) (20 studies, 1324 patients) 32% (95% CI 24-40, I^2 43%); for lymphomas (excluding CLL) (14 studies, 485 patients) 32% (95% CI 18-48, I^2 65%); for CLL specifically (15 studies, 517 patients) 31% (95% CI 23-40, I^2 52%); for myeloproliferative neoplasms (12 studies, 293 patients) 34% (95% CI 19-51, I^2 73%) (Supplemental Data Figure 4).

Subgroup analysis based on geographic location (Asia, Europe, or North America) was performed using data from 31 studies (2627 patients). The overall risk of death was similar between regions: 38% (95% CI 16-63, I^2 88%) in Asia, 35% (95% CI 30-40, I^2 72%) in Europe, and 31% (95% CI 18-45, I^2 81%) in North America.

Sensitivity analysis including only studies with a lower risk of bias showed a similar estimate for risk of death among all patients (33% (95% CI 27-39, I^2 89%), 28 studies with 2893 patients) compared to all studies. Sensitivity analysis including only studies with complete follow-up for all patients showed a similar risk of death compared to all studies (40% (95% CI 30-51, I^2 58%), 6 studies with 307 patients). Sensitivity analysis including only studies that diagnosed COVID-19 using RT-PCR showed a similar estimate for risk of death among all patients compared to all studies (33% (95% CI 26-39, I^2 90%), 24 studies with 2674 patients). Sensitivity analysis including only studies that reported on a combination of outpatients and hospitalized patients showed a similar estimate for risk of death among all patients (31% (95% CI 24-39, I^2 92%), 18 studies with 2407 patients) compared to all studies.

Discussion

We report the first meta-analysis to date of the risk of death in patients with hematologic malignancies and COVID-19, incorporating data from 3377 patients from three continents. The estimates of mortality are most applicable for hospitalized patients as the majority of patients included in this analysis were hospitalized (77%). The pooled risk of mortality in all adult patients was 34% (95% CI 28-39), while the pooled risk of mortality limited to hospitalized patients alone was 39% (95% CI 34-44). Furthermore, patients aged 60 years and older had a significantly higher risk of death than patients

under 60 years (47% vs. 25%, RR 1.82, 95% CI 1.45-2.27, p<0.00001), though the risk in both age groups was substantial. On the other hand, the pooled risk of death in pediatric patients was significantly lower than adult patients at 4% (95% CI 0-8), confirming previous reports that increasing age is highly correlated with risk of death from COVID- 19[58,59]. Why age is a such a powerful correlate of COVID mortality has not been determined. Theories include the possibility that children are less prone to a hyperinflammatory immune response compared to adults, as well as differences in their angiotensin converting enzyme 2 distribution that may limit viral entry and subsequent inflammation, hypoxia and tissue injury[60].

The adult mortality rate reported in this meta-analysis appears substantially higher than in patients with solid tumors, or in the general population; however, the context of these data are important. The majority (77%) of the patients in our analysis were hospitalized and 14/34 adult studies included only hospitalized patients. In cohort studies exclusively of hospitalized patients with cancer, the mortality rate ranges from 19%-42% in patients with solid tumor[38,42]. The risk of death in hospitalized patients without cancer was 21-22% in large studies from New York and Germany[61,62], including 36% in patients aged >60 years[62]. Thus, the risk of death in hospitalized patients with hematologic malignancy of 39% found in our analysis is comparable to hospitalized patients with solid tumor, but remains substantially higher than in the general population. The comparable risk of death to patients with solid tumour supports the notion that patients with hematologic malignancy should not be excluded from more intensive supportive care for COVID-19 solely on the basis of their hematologic diagnosis.

To ascertain the true risk of mortality among all patients with hematologic malignancy and COVID-19 (including all outpatients), it will be important for studies to collect data on an unselected population of patients. The largest study included in this meta-analysis by Yigenoglu and colleagues from Turkey [52] likely has the best estimate for the true population mortality risk for patients with hematologic malignancy infected with COVID-19 (14%), as they used population-based data from a countrywide Ministry of Health Database. This estimate remains higher than the risk of death for a control population in their study (7%)[52], and the risk reported in a previous meta-analysis including non-cancer inpatients and outpatients with COVID-19 (8%)[5]. The risk estimate of 14% reported by Yigenoglu is also comparable to the estimated risk of death of 13% in patients with all cancers[5].

There is concern that recent SACT may result in inferior outcomes in patients with COVID-19. However, our analysis did not show evidence that recent SACT conferred a statistically significant excess risk of death compared to no treatment (RR 1.22 (95% CI 0.84-1.78,

p=0.29). This finding persisted even when limiting the analysis to a subgroup of patients on recent cytotoxic SACT (RR 1.29 (95% CI 0.78-2.15, p=0.32)). This is consistent with reports from other large studies of patients with cancer[32,34,63]. This finding may be related to recent observations that patients with therapy-induced anergy of the immune system might have a milder form of COVID-19. In fact, some therapies tested in treating COVID-19 are hematologic/immunosuppressive drugs[64]. While it is sensible to withhold or delay SACT where disease kinetics permit, these data suggest that in patients who require urgent therapy for their hematologic malignancy, treatment can be delivered despite the risks of COVID-19.

However, the analysis should be considered with caution given the heterogeneity of definitions of "recent treatment" among included studies. Clinicians should make decisions on a case- by-case with their patients, considering the community prevalence of COVID-19 in their region and the availability of health care resources.

Finally, we did find that race was an important contributor to mortality, with non- White patients having a significantly higher risk of mortality than White patients, consistent with previous reports[65,66]. We do not know whether the differences in mortality reflect an inherent biologic risk of poor outcome, impact of comorbidities, impact of social determinants of health, versus implicit bias in the provision of health care.

Following the outbreak of COVID-19, many hospitals particularly in Europe, opened clinical areas where high-level care interventions such as non-invasive ventilation could be delivered to mitigate shortages of ICU beds. The establishment of such high- dependency areas outside of a traditional ICU setting made the risk of ICU admission difficult to quantify and introduced substantial heterogeneity in our analysis. A previous meta-analysis showed a risk of ICU admission of 38% amongst all patients with cancer, utilizing a modified definition of ICU admission to include these high dependency clinical areas[5].

This study has several important limitations. First, there is the possibility of duplicate patients within studies. We are aware of two studies with overlap of 3 patients[24,33], and three studies from centres[20,22,28] that report data to the UKCCMP; thus duplicate patients may potentially have been reported by Lee et al[34]. Although it is not known which centres contributed to the ASH registry, the registry was not accepting batch data until recently, making it unlikely that there is overlap between other large aggregate data efforts (personal communication, LKH, Sept 19, 2020). Additionally, the majority of studies included were from different centres, different regions, or described differing diagnoses—thus we feel that duplicate reporting is unlikely to be a major factor in our meta-analysis.

A more important limitation of our work is the significant heterogeneity that was observed in many of the reported pooled estimates of mortality. In particular, the pooled overall mortality estimate had substantial heterogeneity (I^2 87%). This likely reflects the diverse nature of included patients including inpatients versus outpatients, wide age ranges, diverse hematologic diagnoses, and varied treatment practices across geographic areass. We sought to explore the observed heterogeneity through subgroup analyses. Our findings suggest that age is an important contributor to heterogeneity. When patients <60 years versus >60 years were analyzed separately or pediatric patients were analysed, heterogeneity substantially decreased. It is also likely that the primary hematologic diagnosis contributed to heterogeneity, as stratified analyses by diagnosis also decreased heterogeneity. Thus, our

pooled estimates of overall mortality should be interpreted with caution pending the publication of additional primary data.

An additional limitation of this report is the possibility that mortality maybe overestimated due to the included cohort studies being enriched with hospitalized patients and patients with frequent medical visits. 14 of the 34 adult reports in this meta-analysis included exclusively hospitalized patients. Moreover, even in those studies that included ambulatory patients, case ascertainment was usually dependent on the patients intersecting with the medical system – healthier, asymptomatic or pauci-symptomatic patients may thus be underrepresented in the included sample. This bias may result in an

overestimate of the risk of dying from COVID-19 among patients with hematologic malignancy. Additionally, many of the included studies report outcomes from the earliest phases of the pandemic; it is possible that mortality rates will improve due to increasing experience, expanding therapeutic options, and improved capacity of health systems to manage an influx of patients. On the other hand, several studies included in this sample had insufficient follow-up to determine the final vital status of all patients in their sample (Table 1), introducing potential bias in the other direction.

A final limitation of our study relates to the fact that mortality reported in the included studies was assumed to be related to the diagnosis of COVID-19 given the short interval follow-up and highest risk of death from COVID-19 within weeks of the diagnosis; however we acknowledge that certain hematologic malignancies (e.g. acute leukemia) are also immediately life-threatening. However, a previous study found that the risk of mortality in inpatients with hematologic malignancy increases by 50% if they are infected with COVID-19[21].

It is more important than ever during the COVID-19 pandemic, to gather, analyse and report outcome data for specific at-risk patient populations. The rate at which data on clinical outcomes of COVID-19 in cancer patients is being collected and published is remarkable; within a 10-week period between our initial and final search strategy execution, over 1600 new studies were published. This pace of publication presents a challenge for clinicians, researchers, and guideline committees to assimilate the latest findings. Meta-analyses such as this are critical in order to analyse outcomes in larger cohorts of patients and to assess trends across specific at-risk groups.

We report a systematic review and meta-analysis of the literature regarding the risk of mortality in patients with hematologic malignancy and COVID-19, current to August 20, 2020. We report a high risk of death in this population (34%), partially owing to a large percentage of hospitalized patients in studies published to date. Nonetheless, our findings highlight the importance of preventing COVID-19 among patients with hematologic malignancy. Evidence-based prevention strategies such as infection control measures, physical distancing, and appropriate shielding advice should be emphasized for hematology patients and the units in which they receive their care[67]. Importantly, despite a concerning risk of death, a majority of patients with hematologic malignancy and COVID-19 recover, even following recent SACT. As a result, we recommend that hematology patients with COVID-19 should be considered for intensive supportive interventions where appropriate and if consistent with patient preference. Finally, our data suggest that among patients who require urgent treatment of a hematologic malignancy, treatment should not be routinely withheld due to a fear of excess mortality from COVID-19.

Take-home Points for Clinical Practice - Regarding Patients with Hematologic Malignancy & COVID

• Mortality appears to be high, estimated at 34%, however, estimate may be biased by a high number of hospitalized patients in published studies
• Age is strongly associated with mortality: among those >60 years mortality is estimated at 47% (95% CI 41 – 54%), among those <18 years mortality is estimated at 4% (95% CI 1 – 9%)
• Non-white patients appear to experience higher mortality than white patients • Recent systemic anti-cancer therapy may not impact mortality
• Most patients with hematologic malignancy and COVID survive

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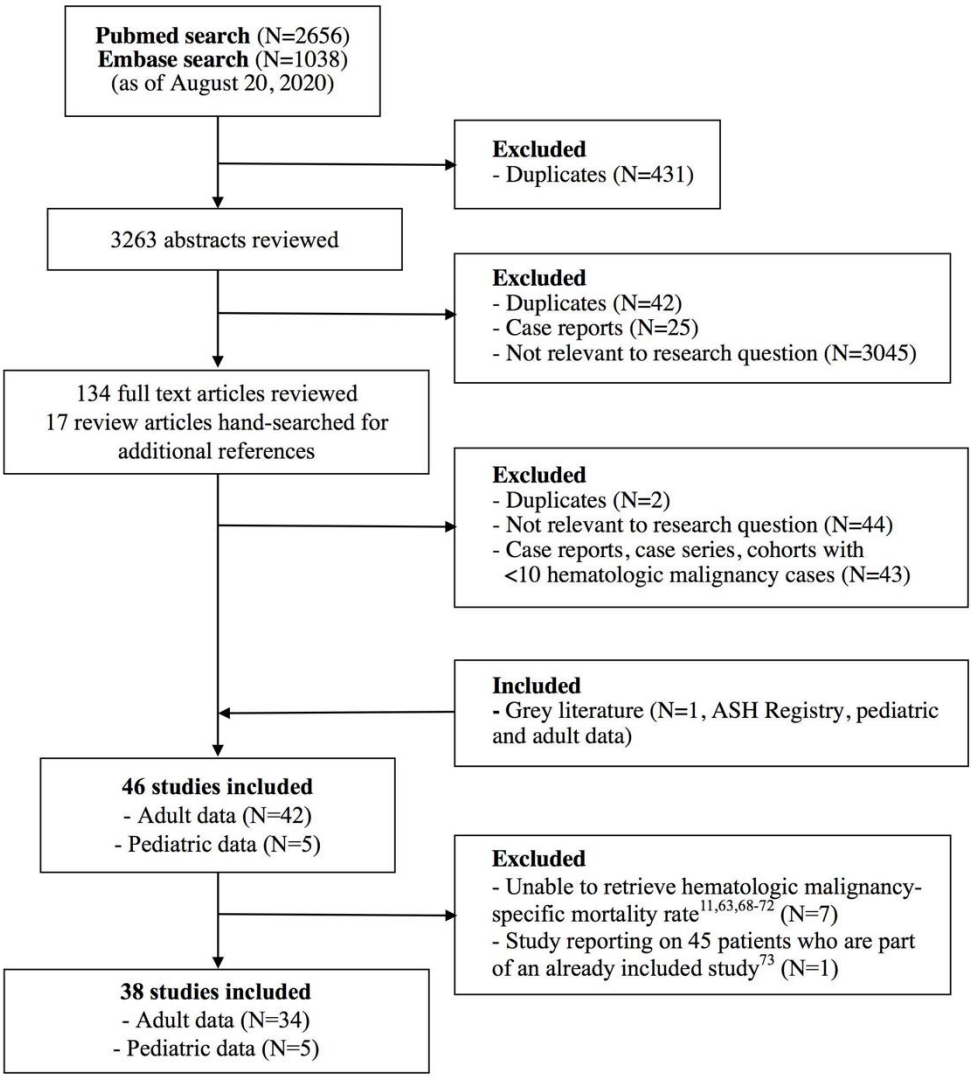

Pubmed search (N=2656)
Embase search (N=1038)
(as of August 20, 2020)
Excluded
- Duplicates (N=431)
3263 abstracts reviewed
Excluded
- Duplicates (N=42)
- Case reports (N=25)
- Not relevant to research question (N=3045)
134 full text articles reviewed
17 review articles hand-searched for additional references
Excluded
- Duplicates (N=2)
- Not relevant to research question (N=44)
- Case reports, case series, cohorts with <10 hematologic malignancy cases (N=43)
Included
- Grey literature (N=1, ASH Registry, pediatric and adult data)
46 studies included
- Adult data (N=42)
- Pediatric data (N=5)
Excluded
- Unable to retrieve hematologic malignancy-specific mortality rate[11,63,68-72] (N=7)
- Study reporting on 45 patients who are part of an already included study[73] (N=1)
38 studies included
- Adult data (N=34)
- Pediatric data (N=5)

Figure 2

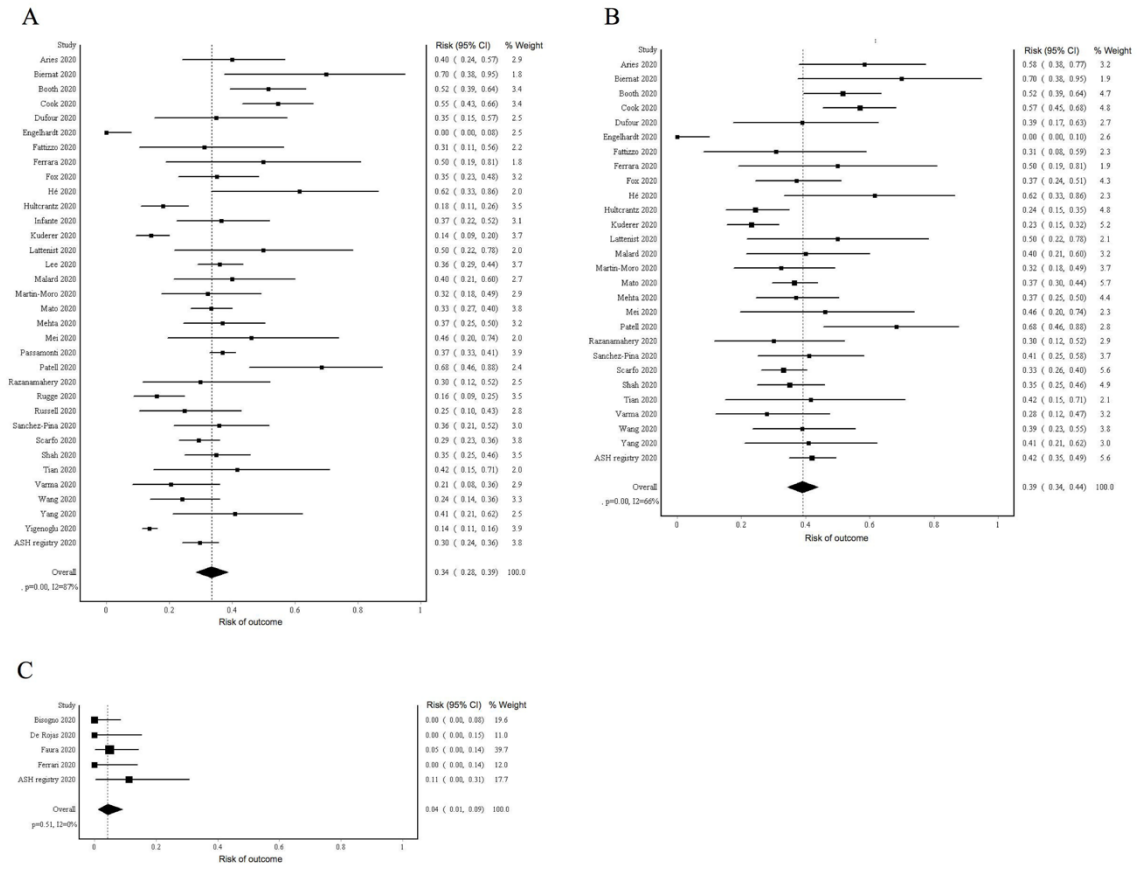

A
Study
Risk (95% CI)
% Weight
Aries 2020 0.40 (0.24, 0.57) 2.9
Biernat 2020 0.70 (0.38, 0.95) 1.8
Booth 2020 0.52 (0.39, 0.64) 3.4
Cook 2020 0.55 (0.43, 0.66) 3.4
Dufour 2020 0.35 (0.15, 0.57) 2.5
Engelhardt 2020 0.00 (0.00, 0.08) 2.5
Fattizzo 2020 0.31 (0.11, 0.56) 2.2
Ferrara 2020 0.50 (0.19, 0.81) 1.8
Fox 2020 0.35 (0.23, 0.48) 3.2
Hé 2020 0.62 (0.33, 0.86) 2.0
Hultcrantz 2020 0.18 (0.11, 0.26) 3.5
Infante 2020 0.37 (0.22, 0.52) 3.1
Kuderer 2020 0.14 (0.09, 0.20) 3.7
Lattenist 2020 0.50 (0.22, 0.78) 2.0
Lee 2020 0.36 (0.29, 0.44) 3.7
Malard 2020 0.40 (0.21, 0.60) 2.7
Martin-Moro 2020 0.32 (0.18, 0.49) 2.9
Mato 2020 0.33 (0.27, 0.40) 3.8
Mehta 2020 0.37 (0.25, 0.50) 3.2
Mei 2020 0.46 (0.20, 0.74) 2.0
Passamonti 2020 0.37 (0.33, 0.41) 3.9
Patell 2020 0.68 (0.46, 0.88) 2.4
Razanamahery 2020 0.30 (0.12, 0.52) 2.5
Rugge 2020 0.16 (0.09, 0.25) 3.5
Russell 2020 0.25 (0.10, 0.43) 2.8
Sanchez-Pina 2020 0.36 (0.21, 0.52) 3.0
Scarfo 2020 0.29 (0.23, 0.36) 3.8
Shah 2020 0.35 (0.25, 0.46) 3.5
Tian 2020 0.42 (0.15, 0.71) 2.0
Varma 2020 0.21 (0.08, 0.36) 2.9
Wang 2020 0.24 (0.14, 0.36) 3.3
Yang 2020 0.41 (0.21, 0.62) 2.5
Yigenoglu 2020 0.14 (0.11, 0.16) 3.9
ASH registry 2020 0.30 (0.24, 0.36) 3.8
Overall 0.34 (0.28, 0.39) 100.0
, p=0.00, I2=87%
0 0.2 0.4 0.6 0.8 1
Risk of outcome
B
Study
Risk (95% CI)
% Weight
Aries 2020 0.58 (0.38, 0.77) 3.2
Biernat 2020 0.70 (0.38, 0.95) 1.9
Booth 2020 0.52 (0.39, 0.64) 4.7
Cook 2020 0.57 (0.45, 0.68) 4.8
Dufour 2020 0.39 (0.17, 0.63) 2.7
Engelhardt 2020 0.00 (0.00, 0.10) 2.6
Fattizzo 2020 0.31 (0.08, 0.59) 2.3
Ferrara 2020 0.50 (0.19, 0.81) 1.9
Fox 2020 0.37 (0.24, 0.51) 4.3
Hé 2020 0.62 (0.33, 0.86) 2.3
Hultcrantz 2020 0.24 (0.15, 0.35) 4.8
Kuderer 2020 0.23 (0.15, 0.32) 5.2
Lattenist 2020 0.50 (0.22, 0.78) 2.1
Malard 2020 0.40 (0.21, 0.60) 3.2
Martin-Moro 2020 0.32 (0.18, 0.49) 3.7
Mato 2020 0.37 (0.30, 0.44) 5.7
Mehta 2020 0.37 (0.25, 0.50) 4.4
Mei 2020 0.46 (0.20, 0.74) 2.3
Patell 2020 0.68 (0.46, 0.88) 2.8
Razanamahery 2020 0.30 (0.12, 0.52) 2.9
Sanchez-Pina 2020 0.41 (0.25, 0.58) 3.7
Scarfo 2020 0.33 (0.26, 0.40) 5.6
Shah 2020 0.35 (0.25, 0.46) 4.9
Tian 2020 0.42 (0.15, 0.71) 2.1
Varma 2020 0.28 (0.12, 0.47) 3.2
Wang 2020 0.39 (0.23, 0.55) 3.8
Yang 2020 0.41 (0.21, 0.62) 3.0
ASH registry 2020 0.42 (0.35, 0.49) 5.6
Overall 0.39 (0.34, 0.44) 100.0
, p=0.00, I2=66%
0 0.2 0.4 0.6 0.8 1
Risk of outcome
C
Study
Risk (95% CI)
% Weight
Bizogno 2020 0.00 (0.00, 0.08) 19.6
De Royas 2020 0.00 (0.00, 0.15) 11.0
Faura 2020 0.05 (0.00, 0.14) 39.7
Ferrari 2020 0.00 (0.00, 0.14) 12.0
ASH registry 2020 0.11 (0.00, 0.31) 17.7
Overall 0.04 (0.01, 0.09) 100.0
p=0.51, I2=0%
0 0.2 0.4 0.6 0.8 1
Risk of outcome

Figure 3

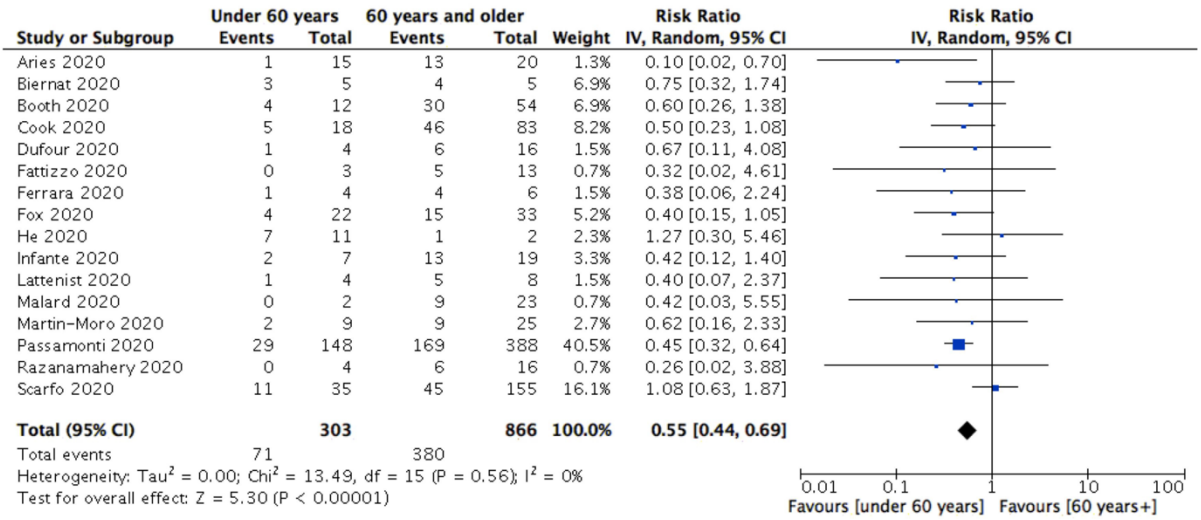
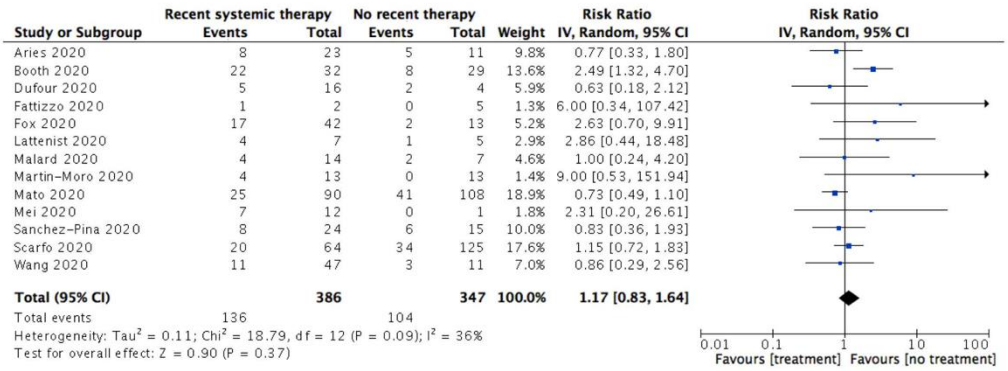
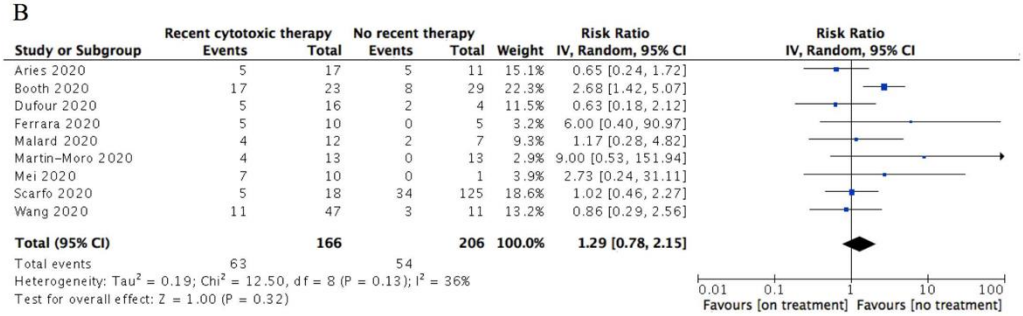

Under 60 years
60 years and older
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Aries 2020 1 15 13 20 1.3% 0.10 [0.02, 0.70]
Biernat 2020 3 5 4 5 6.9% 0.75 [0.32, 1.74]
Booth 2020 4 12 30 54 6.9% 0.60 [0.26, 1.38]
Cook 2020 5 18 46 83 8.2% 0.50 [0.23, 1.08]
Dufour 2020 1 4 6 16 1.5% 0.67 [0.11, 4.08]
Fattizzo 2020 0 3 5 13 0.7% 0.32 [0.02, 4.61]
Ferrara 2020 1 4 4 6 1.5% 0.38 [0.06, 2.24]
Fox 2020 4 22 15 33 5.2% 0.40 [0.15, 1.05]
He 2020 7 11 1 2 2.3% 1.27 [0.30, 5.46]
Infante 2020 2 7 13 19 3.3% 0.42 [0.12, 1.40]
Lattenist 2020 1 4 5 8 1.5% 0.40 [0.07, 2.37]
Malard 2020 0 2 9 23 0.7% 0.42 [0.03, 5.55]
Martin-Moro 2020 2 9 9 25 2.7% 0.62 [0.16, 2.33]
Passamonti 2020 29 148 169 388 40.5% 0.45 [0.32, 0.64]
Razanamahery 2020 0 4 6 16 0.7% 0.26 [0.02, 3.88]
Scarfo 2020 11 35 45 155 16.1% 1.08 [0.63, 1.87]
Total (95% CI) 303 866 100.0% 0.55 [0.44, 0.69]
Total events 71 380
Heterogeneity: Tau² = 0.00; Chi² = 13.49, df = 15 (P = 0.56); I² = 0%
Test for overall effect: Z = 5.30 (P < 0.00001)
0.01 0.1 1 10 100
Favours [under 60 years] Favours [60 years+]

Figure 4

A


Recent systemic therapy
No recent therapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Aries 2020 8 23 5 11 9.8% 0.77 [0.33, 1.80]
Booth 2020 22 32 8 29 13.6% 2.49 [1.32, 4.70]
Dufour 2020 5 16 2 4 5.9% 0.63 [0.18, 2.12]
Fattizzo 2020 1 2 0 5 1.3% 6.00 [0.34, 107.42]
Fox 2020 17 42 2 13 5.2% 2.63 [0.70, 9.91]
Lattenist 2020 4 7 1 5 2.9% 2.86 [0.44, 18.48]
Malard 2020 4 14 2 7 4.6% 1.00 [0.24, 4.20]
Martin-Moro 2020 4 13 0 13 1.4% 9.00 [0.53, 151.94]
Mato 2020 25 90 41 108 18.9% 0.73 [0.49, 1.10]
Mei 2020 7 12 0 1 1.8% 2.31 [0.20, 26.61]
Sanchez-Pina 2020 8 24 6 15 10.0% 0.83 [0.36, 1.93]
Scarfo 2020 20 64 34 125 17.6% 1.15 [0.72, 1.83]
Wang 2020 11 47 3 11 7.0% 0.86 [0.29, 2.56]
Total (95% CI) 386 347 100.0% 1.17 [0.83, 1.64]
Total events 136 104
Heterogeneity: Tau² = 0.11; Chi² = 18.79, df = 12 (P = 0.09); I² = 36%
Test for overall effect: Z = 0.90 (P = 0.37)
0.01 0.1 1 10 100
Favours [treatment] Favours [no treatment]

B


Recent cytotoxic therapy
No recent therapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Aries 2020 5 17 5 11 15.1% 0.65 [0.24, 1.72]
Booth 2020 17 23 8 29 22.3% 2.68 [1.42, 5.07]
Dufour 2020 5 16 2 4 11.5% 0.63 [0.18, 2.12]
Ferrara 2020 5 10 0 5 3.2% 6.00 [0.40, 90.97]
Malard 2020 4 12 2 7 9.3% 1.17 [0.28, 4.82]
Martin-Moro 2020 4 13 0 13 2.9% 9.00 [0.53, 151.94]
Mei 2020 7 10 0 1 3.9% 2.73 [0.24, 31.11]
Scarfo 2020 5 18 34 125 18.6% 1.02 [0.46, 2.27]
Wang 2020 11 47 3 11 13.2% 0.86 [0.29, 2.56]
Total (95% CI) 166 206 100.0% 1.29 [0.78, 2.15]
Total events 63 54
Heterogeneity: Tau² = 0.19; Chi² = 12.50, df = 8 (P = 0.13); I² = 36%
Test for overall effect: Z = 1.00 (P = 0.32)
0.01 0.1 1 10 100
Favours [on treatment] Favours [no treatment]