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Wahyuhadi J *et al.*

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Clinical outcome in hematological cancer compared to primary solid cancer patients with COVID-19 infection: a Systematic Review and Meta-Analysis
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Clinical outcome in hematological cancer compared to primary solid cancer patients with COVID-19 infection: a Systematic Review and Meta-Analysis
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Clinical outcomes of COVID-19 patients with solid and hematological cancer: a meta-analysis and systematic review

Joni Wahyuhadi[1*], Fadhillah Putri Rusdi[1], I G. M. Aswin R. Ranuh[1], Rizki Meizikri[1], Irwan Barlian Immadoel Haq[1], Rahadian Indarto Susilo[1], Makhyan Jibril Al Farabi[2]
[1]Department of Neurosurgery, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
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Abstract

Background: Previous research has consistently shown the significant difference in outcome between cancerous and non-cancerous patients with coronavirus disease 2019 (COVID-19). However, no studies have compared the clinical manifestation of COVID-19 in hematologic cancers patients and solid cancers patients. Therefore, we analyzed the outcome of COVID-19 patients with hematological cancer and primary solid cancer worldwide through a meta-analysis and systematic review.

Methods: This meta-analysis and systematic review included 20 articles with total of published between 2019 – January 2021 from Pubmed and Google Scholar which fit our inclusion criteria. Newcastle Ottawa Score was used to assess the quality and bias of included studies. The outcome measured were case-fatality rate and critical care events for COVID-19 patient with cancer and comorbidities.

Results: Critical care events and mortality were higher in the hematological than primary solid cancer group (RR (Relative Risk)=1.22 & 1.65; p <0.001). Conversely, mortality was lower in patients with two or fewer comorbidities (RR=0.57; p<0.001) and patients under the 75 year old group (RR=0.53; p< 0.05).

Conclusions: Hematologic malignancy, age, and the number of comorbidities are predictor factors for worse prognosis in COVID-19 infection.

Keywords COVID-19, cancer, outcome, oncology

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It is shown that 2.1% of patients with confirmed COVID-19 were reported also to have cancer.[2] A meta-analysis revealed that the mortality rate for COVID-19 patients with cancer was 21.1%. As many as 45.4% of cancer patients with COVID-19 have severe or critical symptoms.[2]

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Cancer patients are a uniquely susceptible population because most of these patients may be in a suboptimal physical condition while also requiring cytotoxic drugs that can reduce immunity. In addition to the symptoms of COVID-19, these patients' cancer treatment may also be delayed during the pandemic.[3]

Most observational studies have exposed that COVID-19 patients with cancer tended to have worse prognosis compared to non cancerous COVID-19 patients.[4,5] Previous research revealed that patients with hematologic cancers (HC) experienced more severe COVID-19 symptoms and higher CFR (case fatality rate) side to those with solid cancers (SC).[6] More severe manifestation and higher CFR are found in hematologic cancer patients compared to solid cancer patients.

Previous research suggested that the presence of haematological malignancies may reduce COVID-19 severity progression due to an attenuated inflammatory response.[7,8] Other studies have reported that solid tumors were a worse prognosis predictor.[10,11] The variation between studies and the lack of publications have encouraged us to analyze if patients with hematologic cancer and those with solid tumors would fare differently in the setting of COVID-19 infection.

METHODS

Study design

The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol) guidelines were used to guide this study.

Eligibility criteria

This review included clinical studies (clinical trial, retrospective, or prospective) of all cancer patients who had COVID-19 infection based on polymerase chain reaction (PCR) test. The article's year of publication was from 2019 to 2021 with English language. For inclusion, the published articles must have had documentation of COVID-19 infection in both solid cancer and hematological cancer patients. Proceeding, commentaries, and editorials without a peer-review process were excluded.

Search strategy and database source

We systematically searched databases to identify eligible articles using PubMed and Google Scholar for articles published from December 2019 to January 2021 using

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keywords our search strategy below (Table 1). We also researched references lists of relevant articles to identify additional primary studies and minimize bias.

Table 1. Search strategy for All Database

1	(COVID-19)
2	((COVID19) OR (coronavirus disease-19) OR (COVID-19 pandemic) OR (2019-SarSCoV infection) OR (coronavirus disease 2019) OR (COVID-19 virus disease)
3	#1 OR #2
4	(Cancer)
5	((Neoplasm) OR (Neoplasm, Malignant) OR (Malignant Neoplasms) OR (Malignant Neoplasm) OR (Neoplasms, Malignant) OR (Cancers) OR (Malignancy) OR (Malignancies) OR (Tumor) OR (Tumors) OR (Cancer))
6	#4 OR #5
7	#3 AND #6
8	((Outcome) OR (Outcomes) OR (Clinical Outcome) OR (Clinical Outcomes) OR (COVID-19-related Outcome) OR (coronavirus disease-19-related outcome) OR (COVID-19-related Outcomes) OR (Coronavirus Disease-19-related Outcomes))
9	#7 AND #8

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Study selection

All articles from the search strategy were screened further for eligibility. The titles and abstracts were independently screened and reviewed by three authors (FP, AR, RM). The workflow of the study selection can be seen on Figure 1. The article's technical uncertainties were resolved through discussion between all authors (FP, AR, RM, JH, RI, IB, MJ). Study assessment was based on the following criteria: 1) published in English, 2) prospective or prospective study on cancer patients with COVD-19 infection; 3) sufficient data relating to PICO (participants/interventions/comparisons/outcomes) criteria (Table 2) from COVID-19 patients with hematological and primary solid cancer.

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Data collection & study quality assessment

The data collected were demographic details (e.g., age, race, comorbidities), type of cancer (primary solid tumors and hematological malignancy), patient's anti-cancer therapies (described as surgery, chemotherapy, radiotherapy of immunotherapy), clinical outcomes (developing severe events, hospitalization rates, intensive care unit (ICU) admission rates, 30-days mortality rate and case-fatality rate). Three authors (FP, AR, RM) extracted the data, jointly reconciled, and discussed technical uncertainties. The authors then appraise the studies using the Newcastle-Ottawa scale (NOS) for cohort studies (Table 3).[2]

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Table 2. PICO (participants/interventions/comparisons/outcomes) criteria. COVID-19=coronavirus disease 2019.

Patient	Patients with COVID-19 infection
Intervention	Hematological Cancer Patients
Comparison/ Control	Primary Solid Cancer Patients
Outcome	Death Rate or Case-fatality Rate in COVID-19 Patients with Cancer, Critical Care Events Rate in COVID-19 Patients with Cancer, Death Rate in COVID-19 Patients with Cancer and Multiple Comorbidities, Death Rate in Elderly COVID-19 Patients with Cancer

Table 3. The Newcastle-Ottawa scale for quality assessment of included studies

Author	Selection	Comparability	Exposure/outcome	Total
Antrim 2020	★★	★★	★	★★★★★
Kuderer 2020	★★	★★★	★★★	★★★★★★★★
Dai 2020	★★	★★	★★	★★★★★★
deMelo 2020	★★	★	★★★	★★★★★★
Ferrari 2021	★	★★	★	★★★★
Fillmore 2020	★★	★★	★★	★★★★★★
Jazieh 2020	★★	★★	★	★★★★★
Lennard 2020	★★	★★	★	★★★★★
Li 2020	★★	★★	★★	★★★★★★
Rivera 2020	★	★	★	★★★
Rüthrich 2020	★★	★★★	★★	★★★★★★★★
Shoumariyeh 2020	★★	★★	★★	★★★★★★
Wang 2020	★★	★	★★	★★★★★
Yang 2020	★★	★★	★★	★★★★★★
Robilotti 2020	★	★	★	★★★
de Joode 2020	★	★★	★★	★★★★★
Meng 2020	★★	★★★	★★	★★★★★★★
Elkrief 2020	★★	★	★	★★★★
Tremblay 2020	★★	★	★	★★★★
Stroppa 2020	★★	★★	★★	★★★★★★

Statistical analysis

The statistical analysis, including Cochran–Mantel–Haenszel test (CMH), Risk Ratio, Heterogenicity test, and funnel plotting were done using Statistical Package for the Social Sciences (SPSS) 25, MedCalc Statistical Software version 19.3, and RevMan version 5.4.

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RESULTS

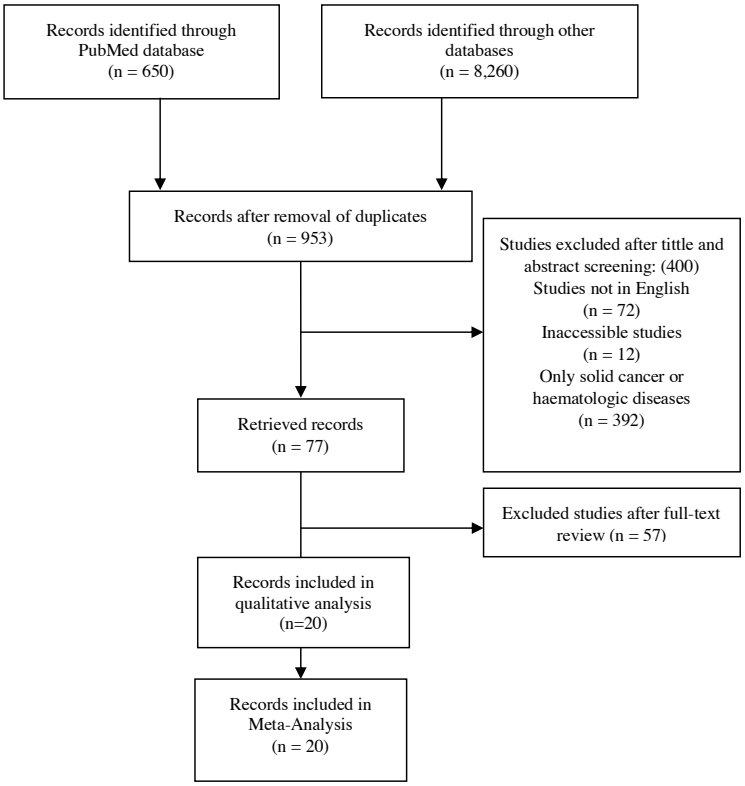

Figure 1 PRISMA flowchart on search, screening, eligibility, and literature inclusion cascade

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SYSTEMATIC REVIEW

COVID-19 severity and mortality in cancer patients

In 2020, DeMelo et al. reported that age, advanced malignancy stage, and number of metastases were associated with clinical fragility and higher risk of death in COVID-19 patients[10].

A previous study explained that COVID-19 symptoms in cancer patients ranged from mild symptoms (55% of cases), which required outpatient management only (fever, cough, fatigue, myalgia, etc.) to moderate to severe symptoms (45% of cases).

From these patients, 42% were admitted to the ICU.[10] According to a study, a complication such as secondary infection and acute respiratory distress syndrome occurred in a majority of cancer patients (63%).[4] Another study in 2020 found that patients with malignancy were prone to having COVID-19 with severe manifestation (54% vs. 35%; P=0.003). The study mentioned that severe COVID-19 symptoms upon admission are a significant risk of in-hospital death (Hazard Ratio=28.2).[11] Two other studies reported similar findings which support that cancer is associated with worse outcome.[12,13]

Regarding type of cancer, Dai and colleagues reported the hematologic cancer and lung cancer group had the highest and second highest severity and death rates compared to other cancer groups. The patients with hematological malignancy have reduced immunity and are more prone to infection, which can exacerbate COVID-19 infection[8]. Previous studies showed that leukemia, lymphoma, and myeloma as hematological cancer groups could increase death rate, ICU admission, critical manifestation, and invasive mechanical ventilation requirement.[8]

Previous study showed that patients with and without cancer had similar COVID-19 severity. In the said study, the hematological and solid tumors groups showed non-significant trends for immediate manifestation of severe events (hematological group cohort = 30% vs. solid group cohort = 61.4%).[16] However, another study from Canada investigated 252 cancer patients with COVID-19 and showed that 28% of adult patients had a high mortality rate, whereas none of the patients in the pediatric cohort had a significant illness. In hospital-acquired patients with COVID-19, overall survival (OS) was shorter than those with community-acquired infection.[17] Similarly, study from the UK reported that patients with hematological cancer have a greater risk of severe COVID-19 clinical manifestation, which needs more intensive supportive interventions and poses a greater risk of death than non-cancer patients.[5] Tremblay and colleagues explained that the hematologic malignancies group of patients might be vulnerable to COVID-19. The preliminary study also suggests that hematological cancer patients have higher mortality than the general population.[18]

Anti-cancer treatment-related outcome

Different cancer treatments including surgical, radiotherapy and COVID-19-specific medication done within 60 days before COVID-19 infection did not affect the death risk.[10] Two studies reported an increased death rate in patients who received

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immunotherapy, surgery and chemotherapy [8,19]. Robilloti demonstrated that lung cancer patients treated with immune checkpoint inhibitors (ICI) correlated with worse COVID-19 infection outcomes.[17] On the other hand, patients with lung cancer who had COVID-19 had better outcomes despite having immunotherapy.[13]

COVID-19 treatment-related outcome

Rivera et al. analyzed the treatments of COVID-19 in patients with cancer. High-dose corticosteroids combined with other therapies were correlated to higher mortality than positive and negative controls. Hydroxychloroquine combined with other drugs also demonstrated similar results, in which when combined, the risk of all-cause mortality every 30-day was increased when compared with the positive control (OR=2.15). On the other hand, remdesivir showed potential benefit as lower 30-day all-cause mortality compared to positive group (OR=0.41)[19].

METAANALYSIS

Table 4. Studies summary

Author	Country	Type of Study	Age (Median years)	Type of Cancer		Case-fatality Rate	
				Hematological Cancer (%)	Primary Solid Cancer (%)	Hematological Cancer (%)	Primary Solid Cancer (%)
Antrim 2020[23]	US	Retrospective Study	60.5	11	36	3	2
Kuderer 2020[24]	US, Canada, Spain	Retrospective Study	66	204	728	24	76
Dai 2020[8]	China	Retrospective Study	64	9	96	3	6
deMelo 2020[10]	Brazil	Retrospective Study	67.5	34	138	8	52
Ferrari 2021[11]	Brazil	Retrospective Study	61	31	167	5	33
Fillmore 2020[20]	US	Prospective Study	65	176	1483	30	200
Jazieh 2020[25]	Saudi Arab	Retrospective Study	66	9	10	9	7
Lennard 2020[5]	UK	Prospective Study	70	224	801	81	229
Li 2020[12]	China	Prospective Study	63	9	50	2	16
Rivera 2020[19]	US	Retrospective Study	67	470	1781	N/A	N/A
Rüthrich 2020[26]	Germany	Retrospective Study	N/A	124	256	31	156
Shoumariyeh 2020[15]	Germany	Retrospective Study	73	10	29	8	23
Wang 2020[27]	US	Retrospective Study	41.5	170	640	N/A	N/A
Yang 2020[4]	China	Retrospective Study	63	22	183	9	31
Robilotti 2020[17]	China, Italy	Retrospective Study	64	102	321	N/A	N/A
de Joode 2020[28]	Dutch	Prospective Study	70	111	208	43	62
Meng 2020[13]	China	Retrospective Study	64.5	16	92	8	24
Elkrief 2020[16]	Canada	Retrospective Study	73	66	179	N/A	N/A
Tremblay 2020[18]	US	Prospective Study	69	14	10	N/A	N/A
Stroppa 2020[14]	Italy	Retrospective Study	67	2	22	2	7

Case-fatality rate

In total, 14 studies included detailed case fatality rates of hematological cancer and primary solid cancer groups. Overall, the case-fatality rate in the hematological cancer group was 1.22 fold higher than the primary solid cancer group (263/976 vs. 852/4373; RR 1.22; CI 95% [1.08-1.37]; P<0.001) (Figure 2).

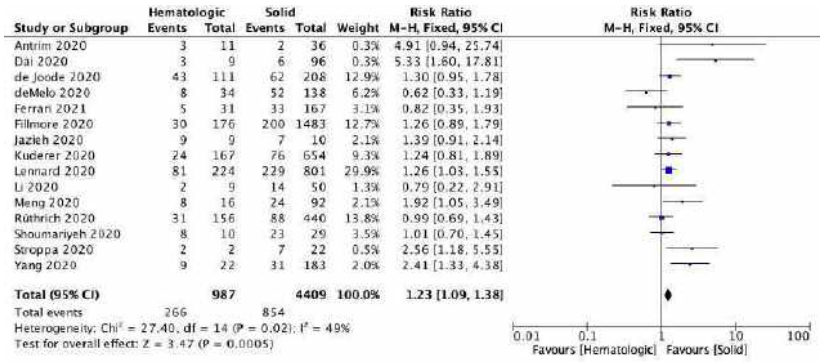

Figure 2. Case-fatality rate in hematological vs primary solid cancer patients forest plot. CI=confidence interval, df=degrees of freedom, M-H=Mantel Haenszel Method

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We performed two sub-analyses on case-fatality rate, to determine the correlation with comorbidities and age. Two studies provided data on the patients' comorbidites (two or less comorbidities and more than two comorbidities group).[10,24] Overall, the case-fatality rate in patients with two or fewer comorbidities group was 0.57 fold lower than patients with more than two comorbidities group (97/694 vs. 65/327; RR 0.57; CI 95% [0.42-0.76]; P<0.001) (Figure 3). We also calculated the pooled proportion of case-fatality rate in the cardiovascular disease group (42.5%) (Figure 4), hypertension (36.8%) (Figure 5), and diabetes mellitus (36,8%) (Figure 6), as those three were deemed the most prevalent comorbidities.

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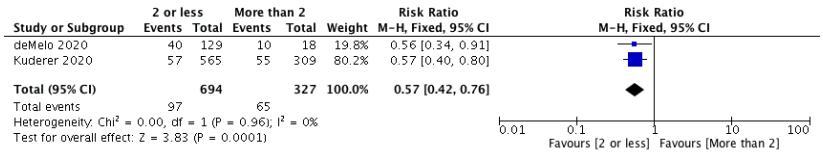

Figure 3. Case-fatality rate with multiple comorbidities in both cancer groups forest plot

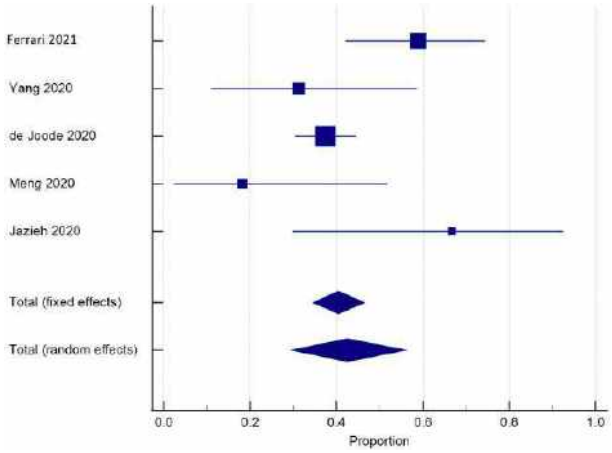

Figure 4. Case Fatality Rate in patients with cardiovascular comorbid

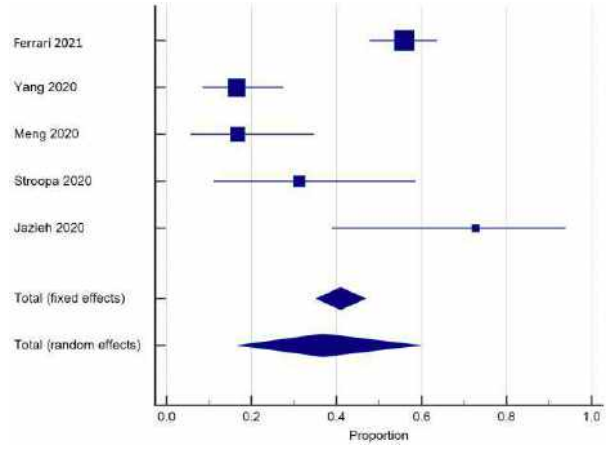

Figure 5. Case Fatality Rate in patients with hypertension

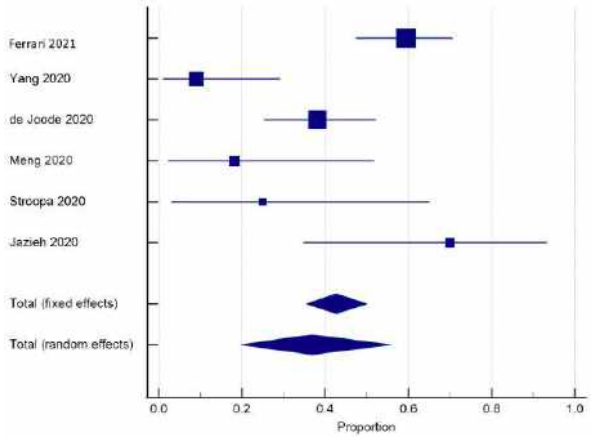

Figure 6. Death event in patients with diabetes mellitus

In total, six studies included detailed data of elderly patients (under 75 y.o. and 75 y.o. or older) in both cancer groups. Overall, the rate of death in patients under 75 y.o. group was 0.53 fold lower than patients under 75 y.o. group (250/1350 vs. 154/465; RR 0.53; CI 95% [0.36-0.80]; P=0.002) (Figure 7).

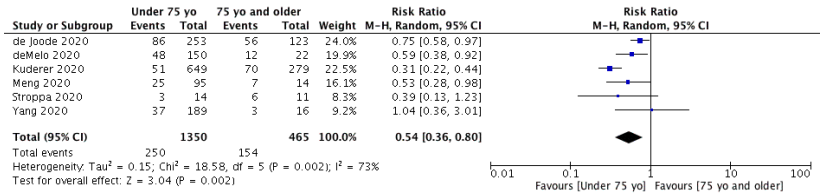

Figure 7. Case-fatality rate in elderly patients in both cancer groups forest plot

Critical care events rate

Overall, five studies included detailed data of patients who developed critical events in the hematological and primary solid cancer groups separately. Overall, the rate of critical care events in the hematological cancer group was 1.65 fold higher than the primary solid cancer group (140/371 vs. 585/2312; RR 1.65; CI 95% [1.22-2.23]; P=0.001) (Figure 8).

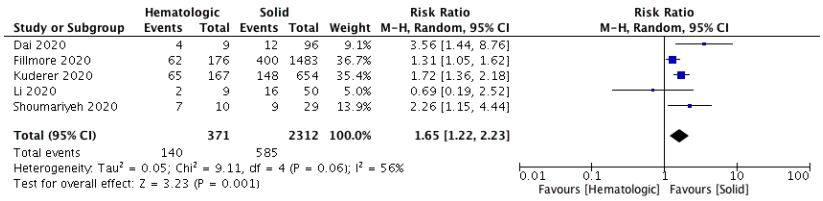

Figure 8. Critical care events rate in hematological cancer vs primary solid cancer patients forest plot

DISCUSSION

To our best knowledge, the severity of COVID-19 can be worsened by cancer. The risk of death may also increase due to cancer. Patients with hematologic malignancy have an immunocompromised state which may induce co-infection and thus aggravate COVID-19 clinical presentation.[4,5,8–14,17]. Our meta-analysis shows that the rate of mortality and critical care events were higher in the hematologic group than in the primary solid cancer group. At the same time, the case-fatality is higher in patients who had more than two comorbidities and patients aged 75 or older. Thus, our analysis showed a tendency toward publication bias for case-fatality rate (P=0.03) (Figure 9) likely to the presence of small sample size studies.

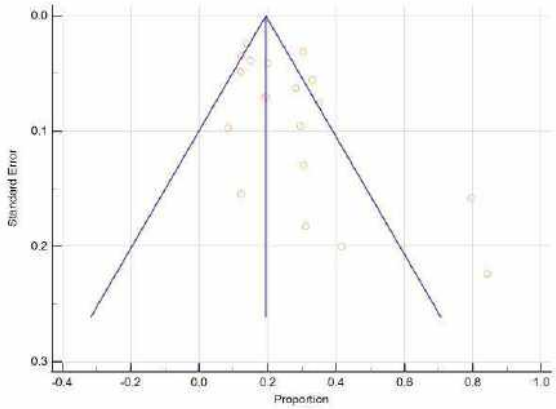

Figure 9. Case-fatality rate in both cancer groups proportional study funnel plot

Our analysis on critical care events seemed to differ from the rest of the study. The COVID-19 diagnosis test might cause this as both PCR and anti-SARS-CoV-2 IgG/IgM antibody tests[12] were used in Li's study, whereas other studies included in the

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meta-analysis only used PCR for diagnostic testing. Moreover, This was etrospective study with relatively few subjects yet with an enormous number of controls.[12]

The hematological cancer group had more severe COVID-19 manifestation.[12] However, this finding requires further verification through multi-center studies. Based on a previous study, delaying surgery or chemotherapy for patients with cancer during the COVID-19 pandemic is not required, especially in areas with fewer COVID-19 patients.[16]

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From our review, several studies from China, Europe, and North America reported that cancer patients with COVID-19 infection who received chemotherapy, immunotherapy, and ICI treatment had a higher death risk[4,5,8,17,20]. A meta-analysis in the US reported that active cytotoxic chemotherapy was associated with a high risk of adverse outcomes from COVID-19 [21]. At the same time, Stroppa et al. revealed a better prognosis of COVID-19-infected lung cancer patients treated with immunotherapy[14]. Similarly, Fillmore et al. reported a lower risk of infection was correlated with ICI treatment[14]. A meta-analysis by Yekedüz et al. revealed that cancer treatment was not associated with severity and mortality risk of COVID-19 within the last 30 days before diagnosis[22].

A COVID-19 and Cancer Consortium Cohort Study in US revealed that corticosteroids in high dose administration combined with any other therapies, and hydroxychloroquine combined with other drugs or given alone were associated with higher 30-day all-cause mortality risk in cancer patients with COVID-19 infection. While remdesivir has shown to be a potential treatment, the all-cause mortality rate in 30 days decreases [19].

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Conclusion

Hematological malignancy, elder age (75 years) and the number of comorbidities are predictors for worse prognosis in COVID-19 infection. The therapy protocol for cancer patients with COVID-19 infection and COVID-19 therapy is still debatable. Future research needs to evaluate these treatments in prospective randomized controlled trials (RCTs), address disparities, and promote studies evaluating potential anti-COVID-19 therapies.

Limitations

There were missing data points from some studies. Given these limitations, we encourage conducting multi-center registries (web/ online-based) to obtain all the data from every individual case of cancer patients with COVID-19 infection. The review section may also influenced of the authors' personal viewpoints, gaps in literature searching practices that may lead to the omission of relevant research, errors in the translation of data from the primary literature to summarization in the review.

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Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required. *Reporting guidelines*

Figshare: PRISMA checklist for 'Comparison of Clinical Outcome in Hematological Cancer Compared to Primary Solid Cancer Patients With COVID-19 Infection: a Systematic Review and Meta-Analysis, https://doi.org/10.6084/m9.figshare.17122541

Competing interests

No competing interests were disclosed

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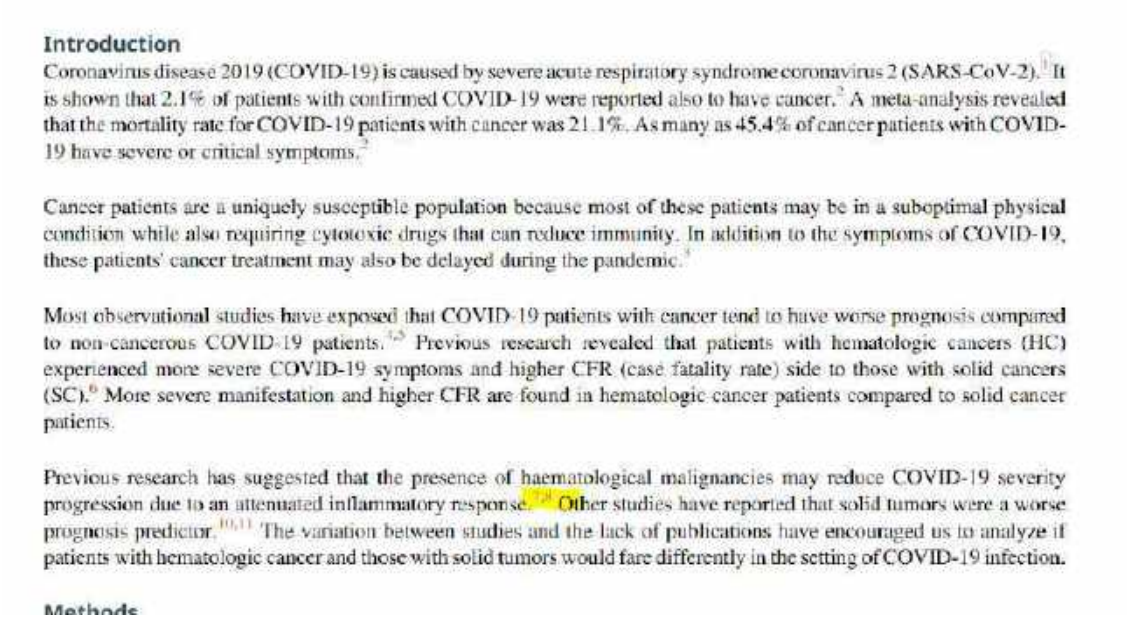

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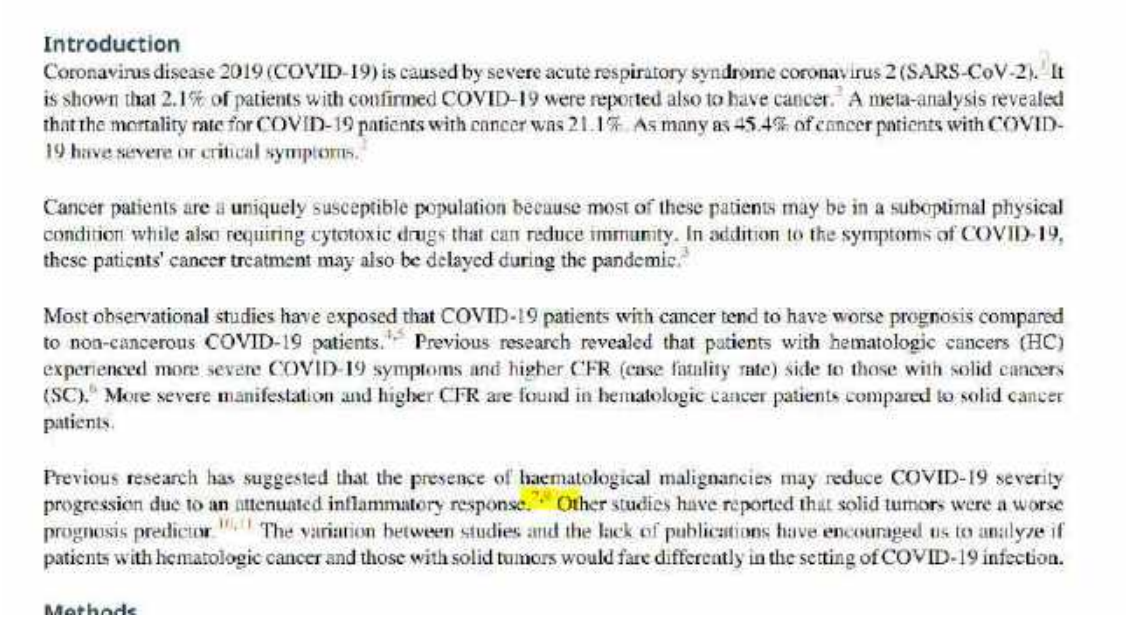

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Comparison of Clinical Outcome in Hematological Cancer Compared to Primary Solid Cancer Patients With COVID-19 Infection: a Systematic Review and Meta-Analysis

Joni Wahyuhadi[1*], Fadhillah Putri Rusdi[1], I G. M. Aswin R. Ranuh[1], Rizki Meizikri[1], Irwan Barlian Immadoel Haq[1], Rahadian Indarto Susilo[1], Makhyan Jibril Al-Farabi[2]
[1]Department of Neurosurgery, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Corresponding Author: Joni Wahyuhadi : joniwahyuhadi.rsudsoetomo@gmail.com

Background Reports have consistently shown the significant outcome difference between cancerous and non-cancerous COVID-19-infected patients. The majority of observational studies reported worse outcomes in patients with Cancer. However, studies comparing the clinical course of COVID-19 in patients with hematologic cancers to patients with solid cancers are still limited. Therefore, the authors decided to study the overall outcome of COVID-19 patients with hematological Cancer and primary solid Cancer all around the world through a systematic review and meta-analysis

Methods This systematic review and meta-analysis included articles published between 2019 – January 2021 from PubMed, Medline, Embase, and Google Scholar. The outcome measured was death rate or case-fatality rate and critical care rate in COVID-19 patients with cancer, multiple comorbities and elderly.

Results mortality and critical care events were higher in the hematological than primary solid cancer group (RR=1.22 & 1.65). Conversely, mortality was lower in patients with 2 or fewer comorbidities group (RR=0.57) and in patients under 75 y.o. group (RR=0.53).

Conclusion Hematologic malignancy, age and number of comorbidities are predictor factors for worse prognosis in COVID-19 infection.

Keywords COVID-19, Cancer, outcome, oncology

INTRODUCTION

Coronavirus disease 2019 (COVID-19) Pneumonia is an infectious disease caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2).[1] A proportion of 2.1% of patients with confirmed COVID-19 were reported to have Cancer. A meta-analysis reported that the mortality in cancer patients with COVID-19 was 21.1%. As

many as 45.4% of cancer patients with COVID-19 experience severe or critical symptoms.[2]

Cancer patients are a uniquely susceptible population because most of these patients may be in a suboptimal physical condition while also requiring cytotoxic drugs that can reduce immunity. In addition to the problem of COVID-19, these patients may also receive cancer treatment delays during this pandemic.[3]

The majority of observational studies have shown that COVID-19 patients with Cancer tended to fare worse.[4,5] Previous research revealed that patients with hematologic cancers (HC) have more severe COVID-19 symptoms and higher CFR (Case Fatality Rate) compared to those with solid cancers (SC).[6] Some authors, however, have suggested that some patients with hematologic malignancies might be "protected" from severe COVID-19 morbidity due to an attenuated inflammatory response.[7,8] Other studies have reported that solid tumors were a worse prognosis predictor.[9,10] The variation between studies and the lack of publications have encouraged us to develop prognosis for the patient with hematologic Cancer and the solid tumor with COVID-19 infection.

MATERIAL AND METHODS

General information and literature search strategy

Study selection was carried out based on PRISMA (*Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol*) method guideline. The data was collected from *PubMed*, *Medline*, *Embase* and *Google Scholar*.

Eligibility Criteria

Articles included in this review were clinical studies (Clinical trial, retrospective, or prospective) of cancer patients without the restriction of age or race who had COVID-19 infection based on polymerase chain reaction (PCR) test. All adult and pediatric patients are included in this review. Articles were accepted for this review if they were written in English or Bahasa. The article's year of publication is from 2019 to 2020. For inclusion, the published articles must have had documentation of COVID-19 infection in both solid Cancer and hematological cancer patients.

Proceeding articles, editorials, commentaries, or publications without peer-review process were excluded. Further excluded were all clinical studies on COVID-19-related outcomes in remission cancer patients.

Information Source and Search Strategy

We conducted a systematic search for the literature to identify relevant articles using PubMed, Medline, Embase and Google Scholar for articles published from December 2019 to June 2020 using keywords our search strategy below (Table 1). We also researched references listed in relevant articles to identify additional primary studies and minimal bias.

Table 1. Search strategy

1	(COVID-19)
2	((COVID19) OR (COVID-19 pandemic) OR (COVID-19 virus disease) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (coronavirus disease-19) OR (2019-nCoV disease) OR (COVID-19 virus infection))
3	#1 OR #2
4	(Cancer)
5	((Neoplasm) OR (Tumors) OR (Tumor) OR (Cancer) OR (Cancers) OR (Malignancy) OR (Malignancies) OR (Malignant Neoplasms) OR (Malignant Neoplasm) OR (Neoplasm, Malignant) OR (Neoplasms, Malignant))
6	#4 OR #5
7	#3 AND #6
8	((Outcome) OR (Outcomes) OR (Clinical Outcome) OR (Clinical Outcomes) OR (COVID-19-related Outcome) OR (coronavirus disease-19-related outcome) OR (COVID-19-related Outcomes) OR (Coronavirus Disease-19-related Outcomes))
9	#7 AND #8

Study Selection

All potentially included articles were screened in two stages for eligibility. In the first stage of assessment, the titles and abstracts of the potentially pertinent articles were screened independently by three authors. The full text was retrieved and independently reviewed by the same authors in the second stage of assessment for those abstracts that met the inclusion criteria. In addition, the article's technical uncertainties were discussed and resolved between review authors.

Data Collection & Study Quality Assessment

The data collection protocol was discussed and agreed upon before the project's start. The extracted data included bibliographic data, demographic details of the COVID-19-confirmed patients (e.g., age, race, comorbidities), type of Cancer (primary solid tumors and hematological malignancy), patient's anti-cancer therapies (described as surgery, chemotherapy, radiotherapy of immunotherapy), clinical outcomes (developing into severe events, hospitalization rates, ICU admission rates, 30-days mortality rate and case-fatality rate). All medical consequences and conclusion were

recorded. Three authors independently extracted the data from the selected studies. The data were jointly reconciled, the disputes and technical uncertainties were discussed and resolved between review authors. After collecting the data, we appraised the studies according to the evidence level using data evaluation using Newcastle-Ottawa scale (NOS) for cohort studies (Table 3). From all included studies, there are 15 retrospective studies and 5 prospective studies (Table 4). Further studies assessment was based on the following criteria: 1) published in english, 2) Retrospective, or prospective study on cancer patients with COVD-19 infection; 3) having enough data of COVID-19 patients with hematological and primary solid Cancer, the included patients characteristic datas as mention in PICO table (Table 2).

Table 2. PICO

Patient	Patients with COVID-19 infection
Intervention	Hematological Cancer Patients
Comparison/ Control	Primary Solid Cancer Patients
Outcome	Death Rate or Case-fatality Rate in COVID-19 Patients with Cancer, tical Care Events Rate in COVID-19 Patients with Cancer, Death Rate i OVID-19 Patients with Cancer and Multiple Comorbidities, Death Rate in Elderly COVID-19 Patients with Cancer

Table 3. The Newcastle-Ottawa scale for quality assessment of the studies

Author	Selection	Comparability	Exposure/outcome	Total
Antrim 2020	★★	★★	★	★★★★★
Kuderer 2020	★★	★★★	★★★	★★★★★★★★
Dai 2020	★★	★★	★★	★★★★★★
deMelo 2020	★★	★	★★★	★★★★★★
Ferrari 2021	★	★★	★	★★★★
Fillmore 2020	★★	★★	★★	★★★★★★
Jazieh 2020	★★	★★	★	★★★★★
Lennard 2020	★★	★★	★	★★★★★
Li 2020	★★	★★	★★	★★★★★★
Rivera 2020	★	★	★	★★★
Rüthrich 2020	★★	★★★	★★	★★★★★★★★
Shoumariyeh 2020	★★	★★	★★	★★★★★★
Wang 2020	★★	★	★★	★★★★★
Yang 2020	★★	★★	★★	★★★★★★
Robilotti 2020	★	★	★	★★★
de Joode 2020	★	★★	★★	★★★★★
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Statistical Analysis

This meta-analysis used Statistical Package for the Social Sciences (SPSS) version 24, MedCalc Statistical Software version 19.3, and Revman version 5.4 from the Cochrane Review for statistical analysis.

RESULTS

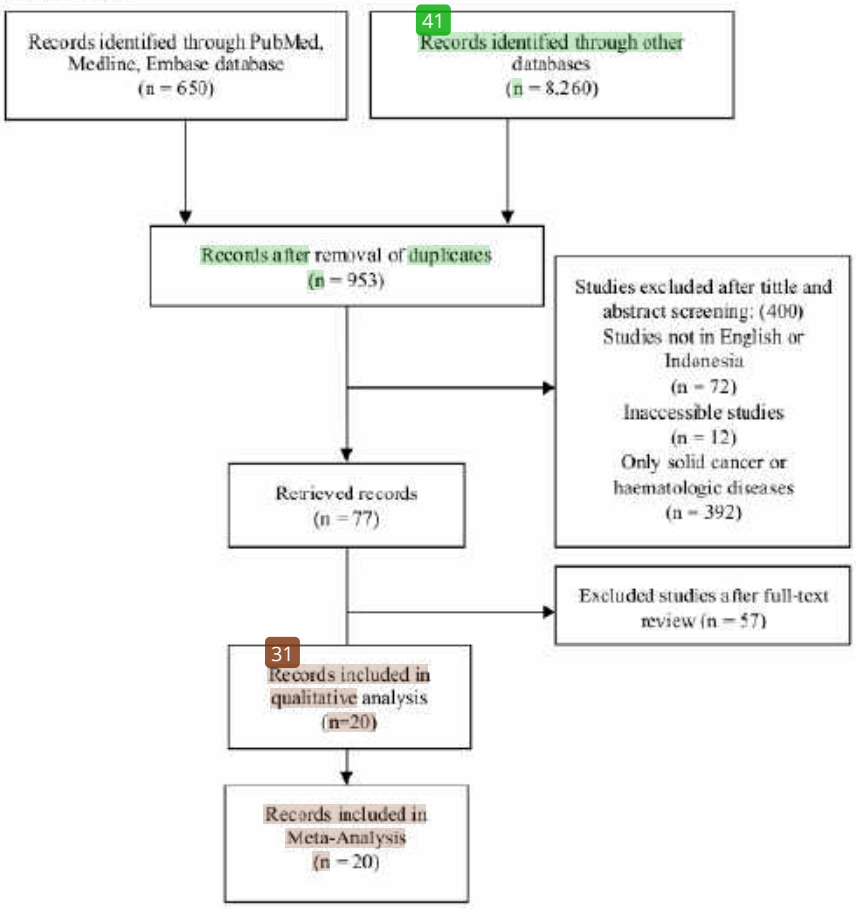

Figure 1 PRISMA flowchart on search, screening, eligibility, and literature inclusion cascade

LITERATURE REVIEW

COVID-19 Severity and Mortality in Cancer Patient

In 2020, deMelo and colleagues reported the characteristics associated with clinical fragility in COVID-19 and Cancer, such as age, advanced malignancy stage, number of metastases, non-curative treatment or supportive treatment and symptomatic

patients at hospital admission were significantly associated with a higher risk of death in COVID-19 patients[9].

A previous study explained that Covid-19 symptoms in cancer patients ranged from mild symptoms (55% of cases) which required outpatient management only (fever, cough, fatigue, myalgia, etc.) to moderate to severe symptoms (45% of cases). from these patients, 42% was admitted to the ICU[10]. According to a study, complications such as secondary infection and acute respiratory distress syndrome occurred in a majoriy of cancer patients (63%).[4] Another study in 2020 found that patients with Cancer were more likely to have severe/critical COVID-19 on admission (54% vs 35%; P=0.003). The study mentioned that severe COVID-19 symptoms upon admission is a significant risk of in-hospital death (HR=28.2)[11]. Two other studies reported similar findings which support that Cancer is associated with worse outcome.[12,13,14]

In regards to the type of Cancer, Dai and colleagues reported that patients with hematologic Cancer and lung cancer have the highest and second-highest severity and death rates among all patients with Cancer, respectively. The patients with hematological malignancy have reduced immunity and more prone to infection, which can exacerbate COVID-19 infection[8]. Patients with hematological Cancer including leukemia, lymphoma and myeloma have relatively high death rate (3 [33.33%] of 9 patients), high ICU admission rate (4 [44.44%] of 9 patients), high risks severe/critical symptoms (6[66.67%] of 9 patients), and high chance of utilization of invasive mechanical ventilation (2 [22.22%] of 9 patients). Patients with lung cancer had the second-highest risk levels, with death rate (4 [18.18%] of 22 patients), ICU admission rate (6 [27.27%] of 22 patients), risks of severe/critical symptoms (11[50.00%] of 22 patients), and the chance of utilization of invasive mechanical ventilation (4 [18.18%] of 22 patients).[8]

A study from the UK reported that patients with hematological malignancies were at a greater risk of having more severe COVID-19 clinical phenotype, requiring more intensive supportive interventions, and suffering an increased risk of death compared with those with non-hematological malignancies.[5] Tremblay and colleagues explained that patients with hematologic malignancies may be particularly vulnerable to COVID-19, and preliminary evidence suggests that they have increased mortality as compared with the general population. In this series, all but one such patient was on active treatment, which has been associated with a more aggressive COVID-19 course.

High mortality rate (41,7%) likely reflects the severity of COVID-19 infection in patients with hematologic malignancies.[15]

In contrast, a study showed that patients with and without had no differences in severity of COVID-19. In the said study, patients with hematological malignancies showed a non-significant trend for the earlier occurrence of severe events compared to solid tumor patients (severe event free survival for hematological cohort = 30% vs severe event-free survival for solid cohort = 61.4%).[16]

A study from Canada took into account the age of the cancer patients. The study investigated 252 cancer patients with COVID-19 and found that 28% of adult patients had a high mortality rate, whereas none of the patients in the pediatric cohort had a significant illness. In hospital-acquired patients with COVID-19, overall survival (OS) was shorter than those with community-acquired infection.[17]

Anti-cancer Therapy-Related Outcome

Different modalities of cancer therapy; systemic agents (chemotherapy, hormonal therapy, targeted therapy, immunotherapy), surgery or radiotherapy within 60 days before COVID-19 and COVID-19-speficic therapy did not influence the risk of death according to a study.[9] Another study also failed to demonstrate an increased risk of worse severity nor outcome in relation to the therapy received by COVID-19 infected cancer patients.[10]

Two studies reported an increased death rate in patients who received immunotherapy[5,8,19], surgery[8], and chemotherapy.[19] Robillloti and colleagues demonstrated that lung cancer patients treated with Immune Checkpoint Inhibitor (ICI) correlated with worse COVID-19 infection outcome.[14] On the other hand, patients with lung cancer who had COVID-19 had better outcome despite getting immunotherapy according to a study.[13]

COVID-19 treatment-related Outcome

Rivera et al. (2020) analyzed the effect of COVID-19 treatments in cancer patients. High-dose corticosteroids plus any other therapy was associated with increased mortality in comparison with both the positive and negative controls, respectively. Hydrooxychloroquine combined with other drugs also demonstrated similar results, in which when combined, the risk of 30-day all-cause mortality was increased when compared with positive control (OR=2.15). On the other hand,

remdesivir showed potential benefit as decreased 30-day all-cause mortality in comparison with positive controls (OR=0.41)[18].

METAANALYSIS

Case-Fatality Rate

Fourteen studies included detailed datas of case-fatality rate in hematological Cancer and primary solid cancer groups separately. Overall, the case-fatality rate in hematological cancer group was 1.22 folds higher than primary solid cancer group (263/976 vs 852/4373; RR 1.22; CI 95% [1.08-1.37]; P<0.001) (Figure 2).

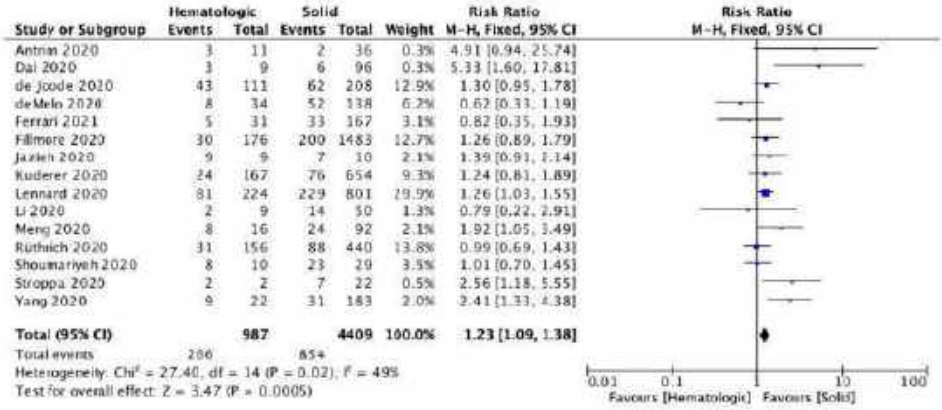

Figure 2. Case-fatality rate in hematological vs primary solid cancer patients forest plot

We performed two sub-analyses on case-fatality rate, they are case-fatality rate in relation with comorbidities and age. Two studies provided data on the patients' comorbidites (2 or less comorbidities and more than 2 comorbidities group). Overall, the case-fatality rate in patients with 2 or less comorbidities group was 0.57 folds lower than patients with more than 2 comorbidities group (97/694 vs 65/327; RR 0.57; CI 95% [0.42-0.76]; P<0.001) (Figure 3). We also calculated the pooled proportion of case-fatality rate in patients with cardiovascular disease (42.5%) (Figure 4), hypertension (36.8%) (Figure 5), and diabetes Mellitus (36.8%) (Figure 6), as those three were deemed the most prevalent comorbidities.

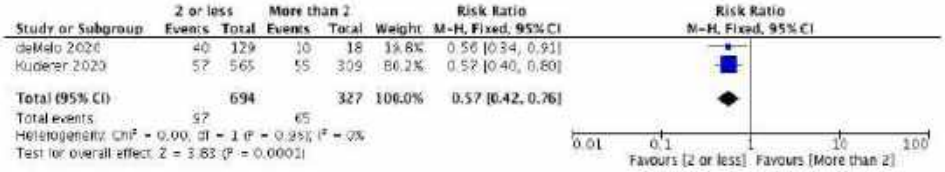

Figure 3. Case-fatality rate with multiple comorbidities in both cancer groups forest plot

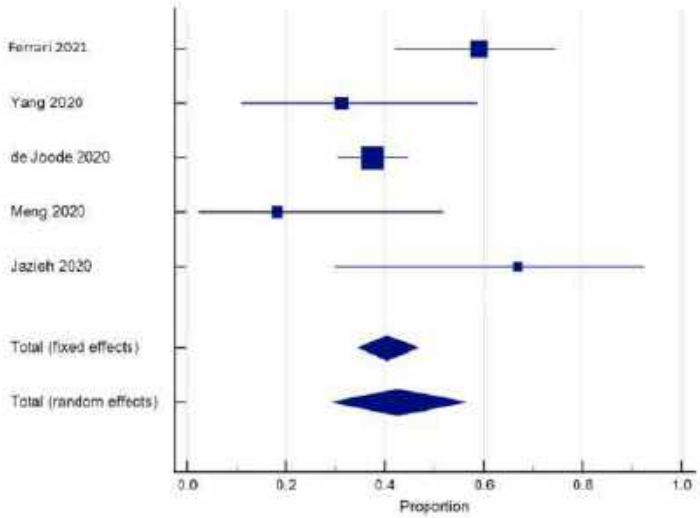

Figure 4. Death event in patients with cardiovascular comorbid

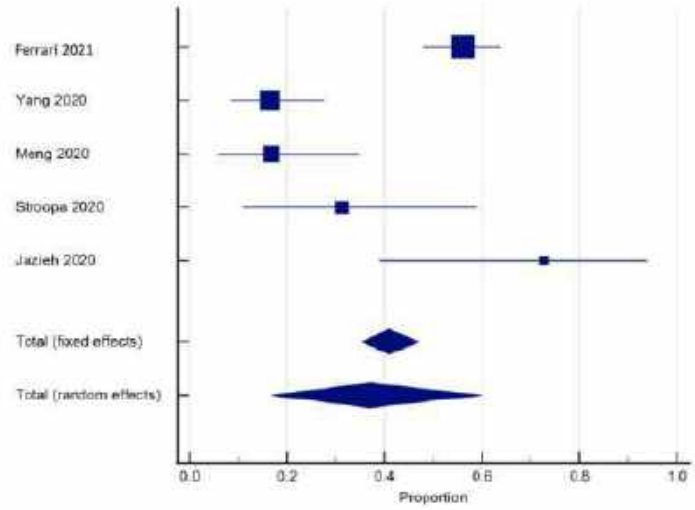

Figure 5. Death event in patients with hypertension

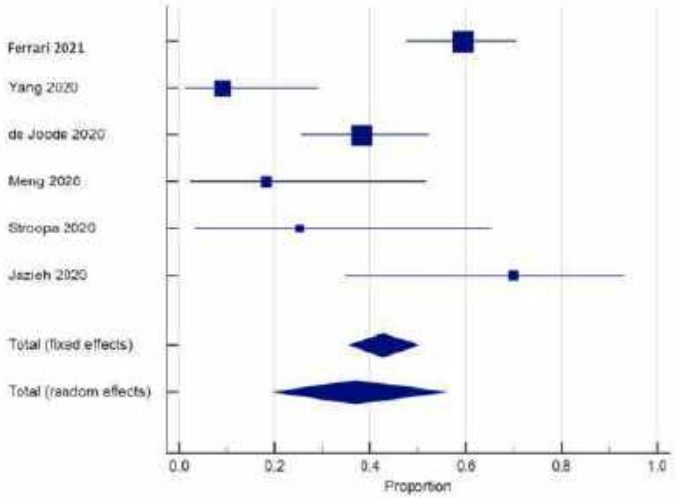

Figure 6. Death event in patients with diabetes mellitus

Six studies included detailed data of elderly patients (under 75 y.o. and 75 y.o. or older group) in both cancer groups. Overall, the rate of death in patients under 75 y.o. group was 0.53 folds lower than patients under 75 y.o. group (250/1350 vs 154/465; RR 0.53; CI 95% [0.36-0.80]; P=0.002) (Figure 7).

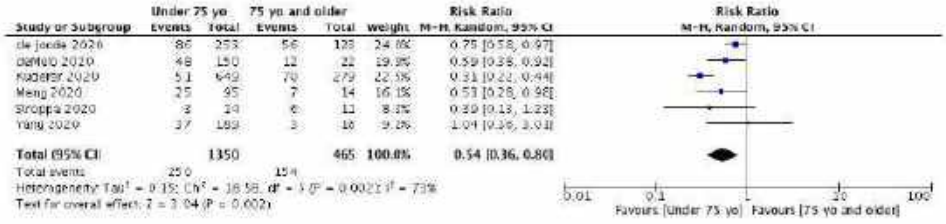

Figure 7. Case-fatality rate in elderly patients in both cancer groups forest plot

Critical Care Events Rate

Five studies included detailed data of patients progression into critical events in hematological Cancer and primary solid cancer groups separately. Overall, the rate of critical care events in hematological cancer group was 1.65 folds higher than primary solid cancer group (140/371 vs 585/2312; RR 1.65; CI 95% [1.22-2.23]; P=0.001) (Figure 8).

Figure 8. Critical care events rate in hematological Cancer vs primary solid cancer patients forest plot

DISCUSSION

To our best knowledge, Cancer can worsen COVID-19 severity and increase the risk of death. In addition, the immunocompromised state in patients with Cancer, especially in those with hematologic malignancy, may induce co-infection and thus aggravate COVID-19 clinical presentation.[4,5,8–14,17]. Our meta-analysis shows that the rate of mortality and critical care events were higher in the hematologic group than in primary solid Cancer. In comparison, the case-fatality is higher in patients with more than two comorbidities and patients aged 75 or older. Thus our analysis showed a tendency toward publication bias for case-fatality rate (P=0.03) (Figure 9) likely to the presence of small sample size studies.

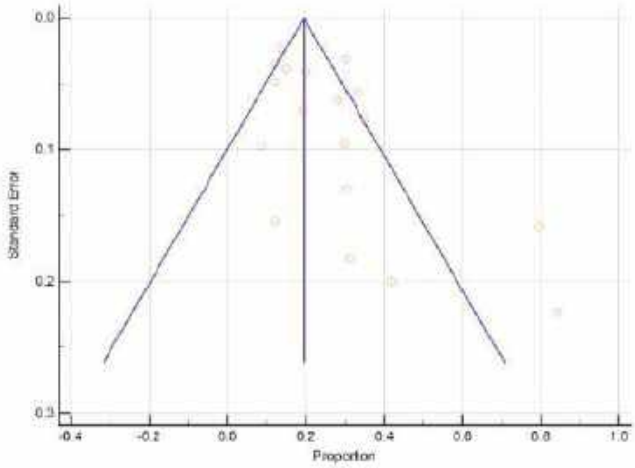

Figure 9. Case-fatality rate in both cancer groups proportional study funnel plot

Our analysis on critical care events, study by Li *et al.* seemed to differ from the rest. This finding might be caused by the COVID-19 diagnosis was based on PCR and/or blood test for anti-SARS-CoV-2 IgG/IgM[11] in Li's study, whereas other studies

included in this systematic review and meta-analysis only used PCR for diagnostic testing, moreover it's a retrospective study which had relatively few subjects yet with enormous number of controls.[11]

Patients with a hematological malignancy seem at risk for more severe disease courses, though this needs to be confirmed by larger multi-center studies. Based on their data,postponing of chemotherapy or necessary surgery for cancer patients during the SARS-CoV-2 pandemic seems less required than initially presumed, especially in areas not overwhelmed by Covid-19 patients. [16]

From our review, several studies from China, Europe, and North America reported an increased death risk in cancer patients with COVID-19 infection who received chemotherapy, immunotherapy, and ICI treatment[4,5,8,14,19]. A meta-analysis in US reported that active cytotoxic chemotherapy was associated with a higher risk of adverse COVID-19 outcomes[20], while Stroppa et al. revealed a better prognosis of COVID-19-infected lung cancer patients treated with immunotherapy[13]. Similarly, Fillmore et al. reported a lower risk of infection was correlated with ICI treatment[13]. A meta-analysis by Yekedüz et al. revealed that cancer treatment did not associate with COVID-19 severity and mortality risk within the last 30 days before COVID-19 diagnosis[21].

A COVID-19 and Cancer Cossortium Cohort Study in US revealed that high-dose corticosteroid plus any other therapy and hydroxychloroquine combined with other drugs or given alone were associated with higher 30-day all-cause mortality risk in cancer patients with COVID-19 infection. While remdesivir has shown as a potential treatment as decreased 30-day all-cause mortality risk[18].

Conclusion

Hematological malignancy, elder age (75 y.o.) and number of comorbidities are predictor factors for bad prognosis in COVID-19 infection. Therapy protocol for cancer patients with COVID-19 infection and COVID-19 therapy in cancer patients are still debatable. We encourage the evaluation of these treatments in prospective RCTs, addressing disparities, and promoting studies evaluating potential anti-COVID-19 therapies.

Limitations

There were missing data points from some studies. Given to these limitations, we encourage for conducting multicenter registries (web/ online-based) to obtain all the datas from every individual case of cancer patients with COVID-19 infection.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'Comparison of Clinical Outcome in Hematological Cancer Compared to Primary Solid Cancer Patients With COVID-19 Infection: a Systematic Review and Meta-Analysis, https://doi.org/10.6084/m9.figshare.17122541

Table 4. Studies summary

Author	Country	Type of Study	Age (Median)	Type of Cancer		Case-fatality Rate	
				Hematological Cancer (%)	Primary Solid Cancer (%)	Hematological Cancer (%)	Primary Solid Cancer (%)
Antrim 2020[22]	US	Retrospective Study	60,5	11	36	3	2
Kuderer 2020[23]	US, Canada, Spain	Retrospective Study	66	204	728	24	76
Dai 2020[8]	China	Retrospective Study	64	9	96	3	6
deMelo 2020[9]	Brazil	Retrospective Study	67,5	34	138	8	52
Ferrari 2021[10]	Brazil	Retrospective Study	61	31	167	5	33
Fillmore 2020[19]	US	Prospective Study	65	176	1483	30	200
Jazieh 2020[24]	Saudi Arab	Retrospective Study	66	9	10	9	7
Lennard 2020[5]	UK	Prospective Study	70	224	801	81	229
Li 2020[11]	China	Prospective Study	63	9	50	2	16
Rivera 2020[18]	US	Retrospective Study	67	470	1781	N/A	N/A
Rüthrich 2020[25]	Germany	Retrospective Study	N/A	124	256	31	156
Shoumariyeh 2020[16]	Germany	Retrospective Study	73	10	29	[illegible]	23
Wang 2020[26]	US	Retrospective Study	41,5	170	640	N/A	N/A
Yang 2020[4]	China	Retrospective Study	63	22	183	9	31
Robilotti 2020[14]	China, Italy	Retrospective Study	64	102	321	N/A	N/A
de Joode 2020[27]	Dutch	Prospective Study	70	111	208	43	62
Meng 2020[12]	China	Retrospective Study	64,5	16	92	8	24
Elkrief 2020[17]	Canada	Retrospective Study	73	66	179	N/A	N/A
Tremblay 2020[15]	US	Prospective Study	69	14	10	N/A	N/A
Stroppa 2020[13]	Italy	Retrospective Study	67	2	22	2	7

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49	platcovid.com Internet	8 words — < 1%
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51	www.wjgnet.com Internet	8 words — < 1%
52	Mariana Chavez-MacGregor, Xiudong Lei, Hui Zhao, Paul Scheet, Sharon H. Giordano. "Evaluation of COVID-19 Mortality and Adverse Outcomes in US Patients With or Without Cancer", JAMA Oncology, 2021 Crossref	7 words — < 1%
53	P. Grivas, A.R. Khaki, T.M. Wise-Draper, B. French et al. "Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium", Annals of Oncology, 2021 Crossref	7 words — < 1%
54	Chao Liu, Kehan Song, Qinyong Hu, Chen Hu, Jinbo Yue, Qibin Song. " Having gastroesophageal cancer is associated with increased risk of severe - 19 - related events in patients with digestive tract cancer: a multicenter, retrospective, cohort study ", International Journal of Cancer, 2020 Crossref	6 words — < 1%
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Clinical outcome of COVID-19 Patient with Solid and Hematological Cancer: a Meta-Analysis and Systematic Review

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Background Previous research has consistently shown the significant difference in outcome between cancerous and non-cancerous COVID-19-infected patients. However, no studies compared the clinical manifestation of COVID-19 in hematologic cancers patients and solid cancers patients. Therefore, we analyze the outcome of COVID-19 patients with hematological cancer and primary solid cancer worldwide through a meta-analysis and systematic review.

Methods This meta-analysis and systematic review included articles published between 2019 – January 2021 that satisfied the Pubmed and Google Scholars PICOS criteria. The outcome measured was death rate or case-fatality rate, critical care events, the death rate in patients with COVID-19 and cancer with multiple comorbidities, and elderly.

Results Critical care events and mortality were higher in the hematological than primary solid cancer group (RR=1.22 & 1.65). Conversely, mortality was lower in patients with two or fewer comorbidities (RR=0.57) and patients under the 75 y.o. group (RR=0.53).

Conclusion Hematologic malignancy, age, and the number of comorbidities are predictor factors for bad prognosis in COVID-19 infection.

Keywords COVID-19, cancer, outcome, oncology

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is viral pneumonia caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2).[1] It is shown that 2.1% of patients with confirmed COVID-19 were reported also to have cancer. A meta-analysis revealed that the mortality rate in cancer with COVID- patients 19 was 21.1%. As many as 45.4% of cancer patients with COVID-19 go through severe or critical symptoms.[2] Cancer patients are a uniquely susceptible population because most of these patients may be in a suboptimal physical condition while also requiring cytotoxic drugs that can

reduce immunity. In addition to the problem of COVID-19, these patients' cancer treatment may also withhold during this pandemic.[3]

Most observational studies have exposed that COVID-19 patients with cancer tended to fare worse.[4,5] Previous research revealed that patients with hematologic cancers (HC) experienced more severe COVID-19 symptoms and higher CFR (Case Fatality Rate) side to those with solid cancers (SC).[6] more severe manifestation and higher CFR are found in hematologic cancer patients compared to solid cancer

Previous research suggested that the presence of hematological malignancies may reduce COVID-19 severity progression due to an attenuated inflammatory response.[7,8] Other studies have reported that solid tumors were a worse prognosis predictor.[10,11] The variation between studies and the lack of publications have encouraged us to analyze if the patient with hematologic cancer and the solid tumor would fare differently in the setting of COVID-19 infection.

MATERIAL AND METHODS

General information and literature search strategy

PRISMA (*Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol*) method guideline was used to select studies involved. The data was collected from *PubMed, Medline,* and *Google Scholar.*

Eligibility Criteria

This review includes clinical studies (Clinical trial, retrospective, or prospective) of all cancer patients who had COVID-19 infection based on polymerase chain reaction (PCR) test. The article's year of publication is from 2019 to 2020. For inclusion, the published articles must have had documentation of COVID-19 infection in both solid cancer and hematological cancer patients. Proceeding, commentaries, and editorials without a peer-review process were excluded.

Search Strategy and Database Source

We systematically searched databases to selectively identify eligible articles using PubMed and Google Scholar for articles published from December 2019 to June 2020 using keywords our search strategy below (Table 1). We also researched references listed in relevant articles to identify additional primary studies and minimize bias.

Table 1. Search strategy

1	(COVID-19)
2	((COVID19) OR (coronavirus disease-19) OR (COVID-19 pandemic) OR (2019-SarSCoV infection) OR (coronavirus disease 2019) OR (COVID-19 virus disease)
3	#1 OR #2
4	(Cancer)
5	((Neoplasm) OR (Neoplasm, Malignant) OR (Malignant Neoplasms) OR (Malignant Neoplasm) OR (Neoplasms, Malignant) OR (Cancers) OR (Malignancy) OR (Malignancies) OR (Tumor) OR (Tumors) OR (Cancer))
6	#4 OR #5
7	#3 AND #6
8	((Outcome) OR (Outcomes) OR (Clinical Outcome) OR (Clinical Outcomes) OR (COVID-19-related Outcome) OR (coronavirus disease-19-related outcome) OR (COVID-19-related Outcomes) OR (Coronavirus Disease-19-related Outcomes))
9	#7 AND #8

Study Selection

All articles from the search strategy were screened further for eligibility. The titles and abstracts were independently screened and reviewed by three authors (FP, AR, RM). The article's technical uncertainties resolved through discussion between all authors (FP, AR, RM, JH, RI, IB, MJ).

Data Collection & Study Quality Assessment

The data collected were demographic details (e.g., age, race, comorbidities), type of cancer (primary solid tumors and hematological malignancy), patient's anti-cancer therapies (described as surgery, chemotherapy, radiotherapy of immunotherapy), clinical outcomes (developing into severe events, hospitalization rates, ICU admission rates, 30-days mortality rate and case-fatality rate). Three authors (FP, AR, RM) extracted the data, jointly reconciled, and discussed technical uncertainties. The authors then appraise the studies using the Newcastle-Ottawa scale (NOS) for cohort studies (Table 3). From all included studies, there are 15 retrospective studies and five prospective studies (Table 4). Further studies assessment was based on the following criteria: 1) published in English, 2) Prospective or prospective study on cancer patients with COVD-19 infection; 3) Sufficient data as mentioned in PICO table (Table 2) from COVID-19 patients with hematological and primary solid cancer.

Table 2. PICO

Patient	Patients with COVID-19 infection
Intervention	Hematological Cancer Patients
Comparison/ Control	Primary Solid Cancer Patients
Outcome	Death Rate or Case-fatality Rate in COVID-19 Patients with Cancer, Critical Care Events Rate in COVID-19 Patients with Cancer, Death Rate in COVID-19 Patients with Cancer and Multiple Comorbidities, Death Rate in Elderly COVID-19 Patients with Cancer

Table 3. The Newcastle-Ottawa scale for quality assessment of included studies

Author	Selection	Comparability	Exposure/outcome	Total
Antrim 2020	★★	★★	★	★★★★★
Kuderer 2020	★★	★★★	★★★	★★★★★★★★
Dai 2020	★★	★★	★★	★★★★★★
deMelo 2020	★★	★	★★★	★★★★★★
Ferrari 2021	★	★★	★	★★★★
Fillmore 2020	★★	★★	★★	★★★★★★
Jazieh 2020	★★	★★	★	★★★★★
Lennard 2020	★★	★★	★	★★★★★
Li 2020	★★	★★	★★	★★★★★★
Rivera 2020	★	★	★	★★★
Rüthrich 2020	★★	★★★	★★	★★★★★★★★
Shoumariyeh 2020	★★	★★	★★	★★★★★★
Wang 2020	★★	★	★★	★★★★★
Yang 2020	★★	★★	★★	★★★★★★
Robilotti 2020	★	★	★	★★★
de Joode 2020	★	★★	★★	★★★★★
Meng 2020	★★	★★★	★★	★★★★★★★
Elkrief 2020	★★	★	★	★★★★
Tremblay 2020	★★	★	★	★★★★
Stroppa 2020	★★	★★	★★	★★★★★★

Statistical Analysis

The statistical analysis was done using Statistical Package for the Social Sciences (SPSS) 25, MedCalc Statistical Software version 19.3, and RevMan version 5.4.

RESULTS

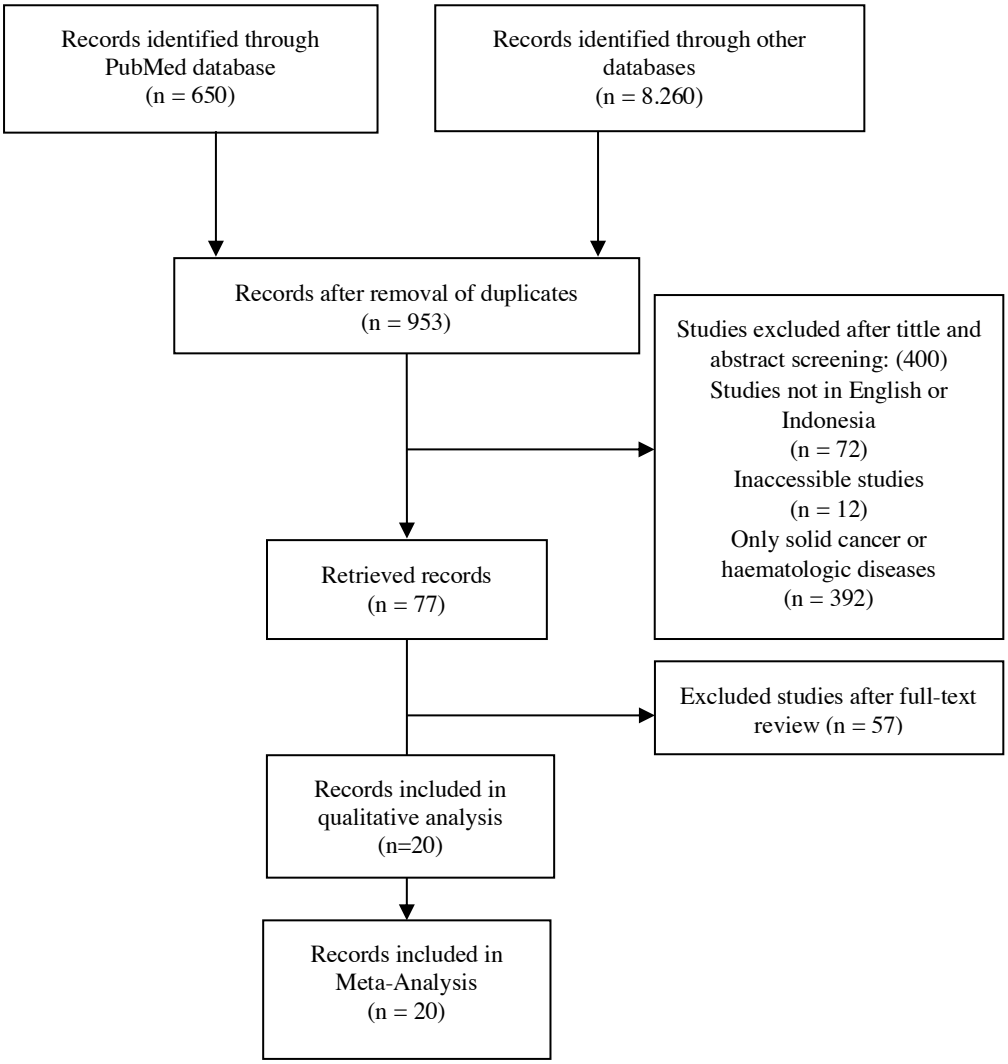

Figure 1 PRISMA flowchart on search, screening, eligibility, and literature inclusion cascade

SYSTEMATIC REVIEW

COVID-19 Severity and Mortality in Cancer Patient

In 2020, DeMelo et al. reported that age, advanced malignancy stage, number of metastases were associated with clinical fragility and higher risk of death in Covid-19 patients[10].

A previous study explained that Covid-19 symptoms in cancer patients ranged from mild symptoms (55% of cases), which required outpatient management only (fever, cough, fatigue, myalgia, etc.) to moderate to severe symptoms (45% of cases). From these patients, 42% were admitted to the ICU.[10] According to a study, a complication such as secondary infection and acute respiratory distress syndrome occurred in a majority of cancer patients (63%).[4] Another study in 2020 found that

patients with malignancy prone to have COVID-19 with severe manifestation (54% vs. 35%; P=0.003). The study mentioned that severe COVID-19 symptoms upon admission are a significant risk of in-hospital death (HR=28.2).[11] Two other studies reported similar findings which support that cancer is associated with worse outcome.[12,13,14]

Regarding type of cancer, Dai and colleagues reported hematologic cancer and lung cancer group have the highest and second highest severity and death rates compared to other cancer groups. The patients with hematological malignancy have reduced immunity and are more prone to infection, which can exacerbate COVID-19 infection[8]. Previous studies showed that leukemia, lymphoma, and myeloma as hematological cancer groups could increase death rate, ICU admission, critical manifestation, and invasive mechanical ventilation requirement.[8]

A study from the UK reported that patients with hematological cancer have a greater risk of higher COVID-19 clinical manifestation, which needed more intensive supportive intervention and a greater risk of death than non-cancer patients. Tremblay and colleagues explained that the hematologic malignancies group of patients might be vulnerable to COVID-19. The preliminary study also suggests that hematological cancer patients have higher mortality than the general population. Robilotti reported that only one patient was on active treatment due to rapid deterioration of COVID-19 manifestation.

In contrast, a study showed that patients with and without cancer had similar COVID-19 severity. In the said study, hematological and solid tumors groups showed non-significant trends for immediate manifestation of severe events (hematological group cohort = 30% vs. solid group cohort = 61.4%).[16]

A study from Canada investigated 252 cancer patients with COVID-19 and showed that 28% of adult patients had a high mortality rate, whereas none of the patients in the pediatric cohort had a significant illness. In hospital-acquired patients with COVID-19, overall survival (OS) was shorter than those with community-acquired infection.[17]

Anti-cancer Treatment-Related Outcome

Different cancer treatment includes surgical, radiotherapy and COVID-19-specific medication which has been done within 60 days before COVID-19 infection

did not affect the death risk.[10] Another also failed to demonstrate an increased risk of worse severity nor outcome in relation to the therapy received by COVID-19 infected cancer patients.[10]

Two studies reported an increased death rate in patients who received immunotherapy[5,8,19] and surgery[8] and chemotherapy[19]. Robilloti demonstrated that lung cancer patients treated with Immune Checkpoint Inhibitor (ICI) correlated with worse COVID-19 infection outcomes.[14] On the other hand, patients with lung cancer who had COVID-19 had better outcomes despite getting immunotherapy.[13]

COVID-19 treatment-related Outcome

Rivera et al. (2020) analyzed the treatments of COVID-19 in patients with cancer. High-dose corticosteroids combined with other therapies were correlated to higher mortality than positive and negative controls. Hydroxychloroquine combined with other drugs also demonstrated similar results, in which when combined, the risk o all-cause mortality every 30-day was increased when compared with the positive control (OR=2.15). On the other hand, remdesivir showed potential benefit as lower 30-day all-cause mortality compared to positive group (OR=0.41)[19].

METAANALYSIS

Table 4. Studies summary

Author	Country	Type of Study	Age (Median)	Type of Cancer	
				Hematological Cancer (%)	Primary Solid Cancer (%)
Antrim 2020[23]	US	Retrospective Study	60,5	11	36
Kuderer 2020[24]	US, Canada, Spain	Retrospective Study	66	204	728
Dai 2020[8]	China	Retrospective Study	64	9	96
deMelo 2020[10]	Brazil	Retrospective Study	67,5	34	138
Ferrari 2021[11]	Brazil	Retrospective Study	61	31	167
Fillmore 2020[20]	US	Prospective Study	65	176	1483
Jazieh 2020[25]	Saudi Arab	Retrospective Study	66	9	10
Lennard 2020[5]	UK	Prospective Study	70	224	801
Li 2020[12]	China	Prospective Study	63	9	50
Rivera 2020[19]	US	Retrospective Study	67	470	1781
Rüthrich 2020[26]	Germany	Retrospective Study	N/A	124	256
Shoumariyeh 2020[15]	Germany	Retrospective Study	73	10	29
Wang 2020[27]	US	Retrospective Study	41,5	170	640
Yang 2020[4]	China	Retrospective Study	63	22	183
Robilotti 2020[17]	China, Italy	Retrospective Study	64	102	321
de Joode 2020[28]	Dutch	Prospective Study	70	111	208
Meng 2020[13]	China	Retrospective Study	64,5	16	92
Elkrief 2020[16]	Canada	Retrospective Study	73	66	179
Tremblay 2020[18]	US	Prospective Study	69	14	10
Stroppa 2020[14]	Italy	Retrospective Study	67	2	22

Case-Fatality Rate

Fourteen studies included detailed case fatality rate of hematological cancer and primary solid cancer groups s case-fatality rate. Overall, the case-fatality rate in the hematological cancer group was 1.22 folds higher than the primary solid cancer group (263/976 vs. 852/4373; RR 1.22; CI 95% [1.08-1.37]; P<0.001) (Figure 2).

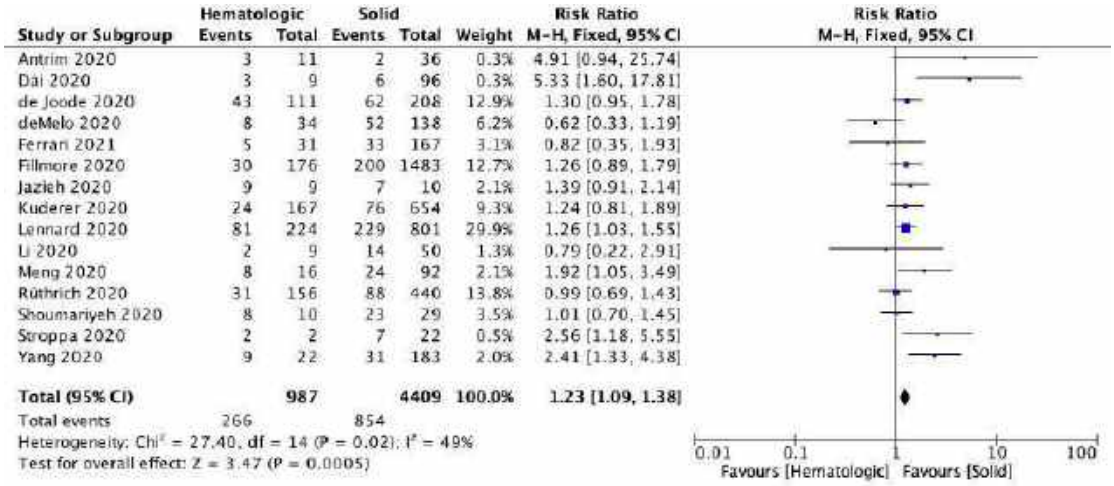

Figure 2. Case-fatality rate in hematological vs primary solid cancer patients forest plot

We performed two sub-analyses on case-fatality rate; which are correlation between case-fatality rate with comorbidities and age. Two studies provided data on the patients' comorbidites (two or less comorbidities and more than two comorbidities group). Overall, the case-fatality rate in patients with two or fewer comorbidities group was 0.57 folds lower than patients with more than two comorbidities group (97/694 vs. 65/327; RR 0.57; CI 95% [0.42-0.76]; P<0.001) (Figure 3). We also calculated the pooled proportion of case-fatality rate in the cardiovascular disease group (42.5%) (Figure 4), hypertension (36.8%) (Figure 5), and diabetes mellitus (36,8%) (Figure 6), as those three were deemed the most prevalent comorbidities.

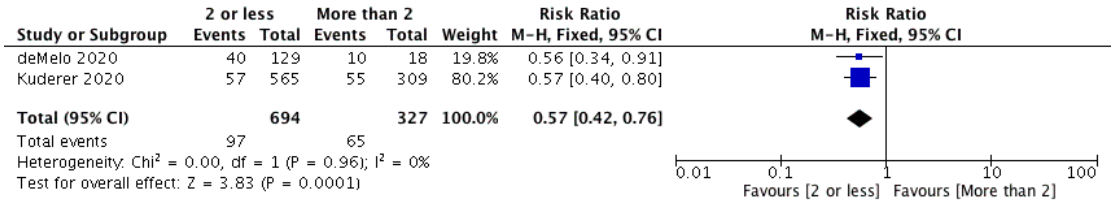

Figure 3. Case-fatality rate with multiple comorbidities in both cancer groups forest plot

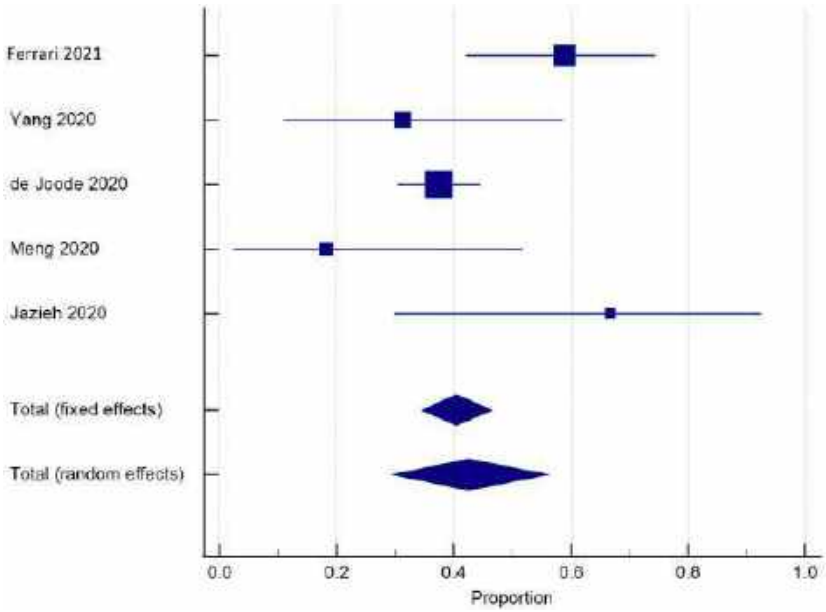

Figure 4. Death event in patients with cardiovascular comorbid

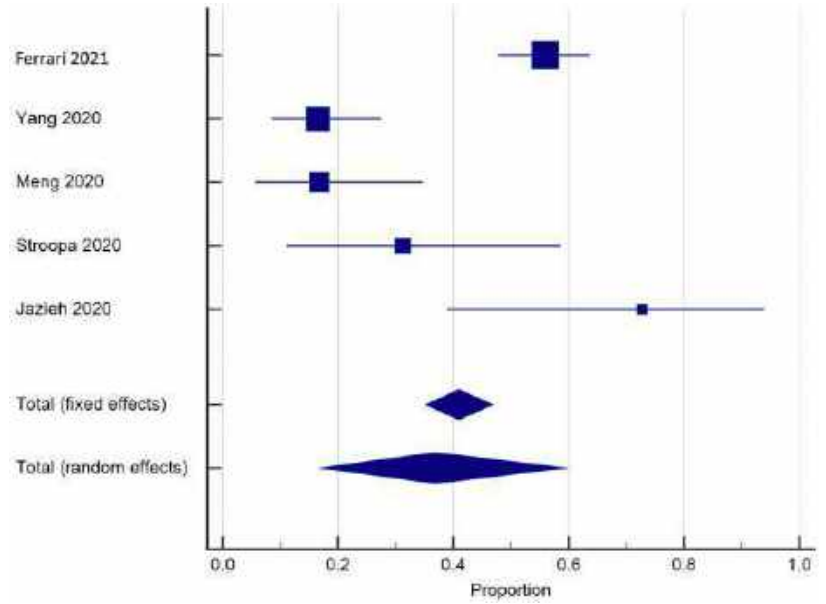

Figure 5. Death event in patients with hypertension

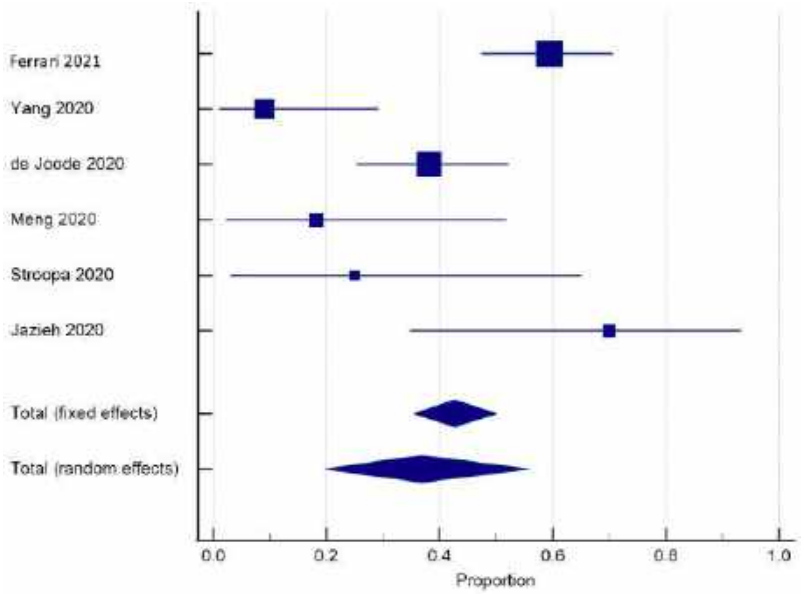

Figure 6. Death event in patients with diabetes mellitus

Six studies included detailed data of elderly patients (under 75 y.o. and 75 y.o. or older) in both cancer groups. Overall, the rate of death in patients under 75 y.o. group was 0.53 folds lower than patients under 75 y.o. group (250/1350 vs. 154/465; RR 0.53; CI 95% [0.36-0.80]; P=0.002) (Figure 7).

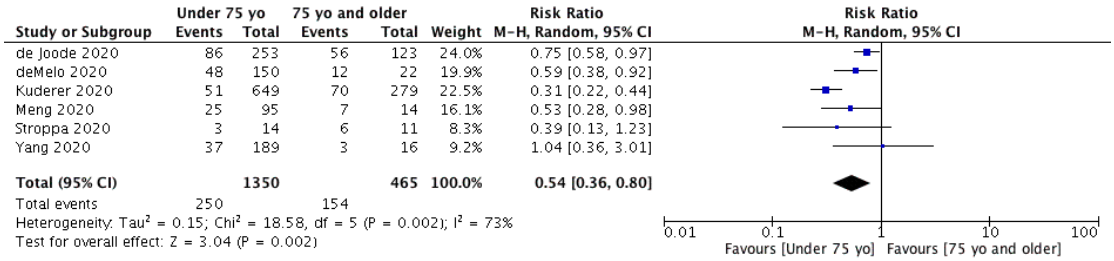

Figure 7. Case-fatality rate in elderly patients in both cancer groups forest plot

Critical Care Events Rate

Five studies included detailed data of patients who developed into critical events in hematological and primary solid cancer groups separately. Overall, the rate of critical care events in the hematological cancer group was 1.65 folds higher than the primary solid cancer group (140/371 vs. 585/2312; RR 1.65; CI 95% [1.22-2.23]; P=0.001) (Figure 8).

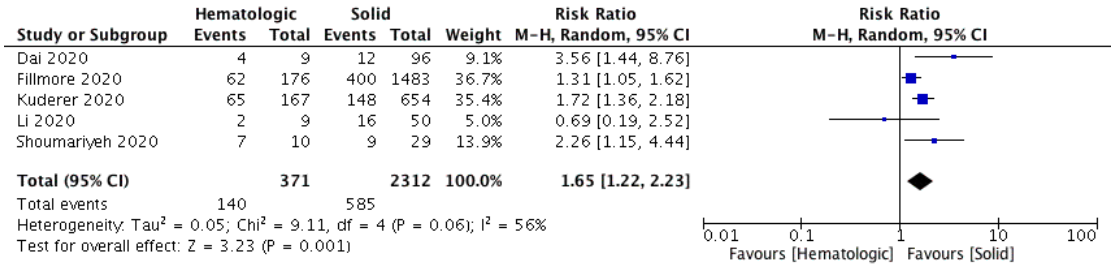

Figure 8. Critical care events rate in hematological cancer vs primary solid cancer patients forest plot

DISCUSSION

To our best knowledge, the severity of COVID-19 can be worsened by cancer. The risk of death may also increase due to cancer. Patient with hematologic malignancy has immunocompromised state which may induce co-infection and thus aggravate COVID-19 clinical presentation.[4,5,8–14,17]. Our meta-analysis shows that the rate of mortality and critical care events were higher in the hematologic group than in primary solid cancer. At the same time, the case-fatality is higher in patients who had more than 2 comorbidites and patients aged 75 or older. Thus our analysis showed a tendency toward publication bias for case-fatality rate (P=0.03) (Figure 9) likely to the presence of small sample size studies.

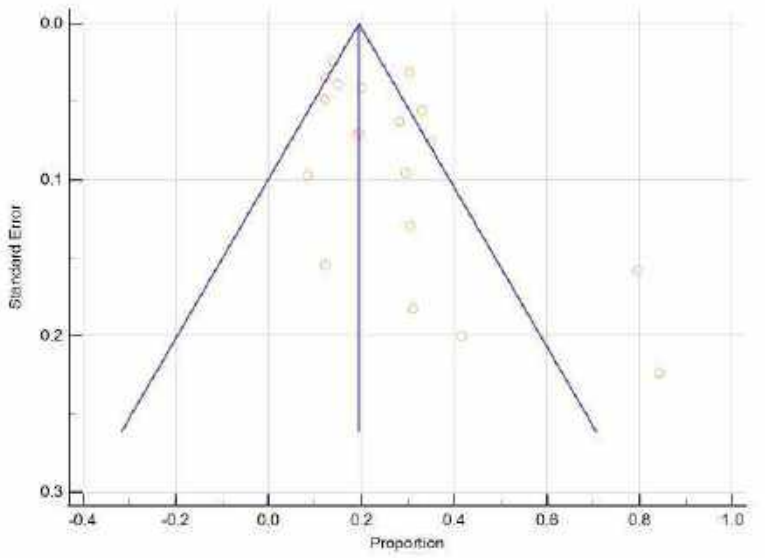

Figure 9. Case-fatality rate in both cancer groups proportional study funnel plot

Our analysis on critical care events, study by Li *et al.* seemed to differ from the rest. The COVID-19 diagnosis might cause this finding was based on both PCR with blood anti-SARS-CoV-2 IgG/IgM test[12] in Li's study, whereas other studies included

in meta-analysis only used PCR for diagnostic testing. Moreover, it's a retrospective study with relatively few subjects yet with an enormous number of controls.[12]

The hematological cancer group had more severe COVID-19 manifestation. However, this finding required further verification through multi-center studies. Based on the previous study also showed that delaying surgery or chemotherapy for patients with cancer during the COVID-19 pandemic is not required, especially in areas with fewer Covid-19 patients.[16]

From our review, several studies from China, Europe, and North America reported that cancer patients with COVID-19 infection who received chemotherapy, immunotherapy, and ICI treatment had higher death risk[4,5,8,17,20]. A meta-analysis in US reported that active cytotoxic chemotherapy was associated with a high risk of adverse outcomes from COVID-19 [21]. At the same time, Stroppa et al. revealed a better prognosis of COVID-19-infected lung cancer patients treated with immunotherapy[14]. Similarly, Fillmore et al. reported a lower risk of infection was correlated with ICI treatment[14]. A meta-analysis by Yekedüz et al. revealed that cancer treatment did not associate with severity and mortality risk of COVID-19 within the last 30 days before diagnosis[22].

A COVID-19 and Cancer Consortium Cohort Study in US revealed that corticosteroids in high dose administration combined with any other therapies and hydroxychloroquine combined with other drugs or given alone were associated with higher 30-day all-cause mortality risk in cancer patients with COVID-19 infection. While remdesivir has shown as a potential treatment, the all-cause mortality rate in 30 days decreases [19].

Conclusion

Hematological malignancy, elder age (75 y.o.) and the number of comorbidities are predictors for worse prognosis in COVID-19 infection. Therapy protocol for cancer patients with COVID-19 infection and COVID-19 therapy is still debatable. Future research needs to evaluate these treatments in prospective RCTs, address disparities, and promote studies evaluating potential anti-COVID-19 therapies.

Limitations

There were missing data points from some studies. Given these limitations, we encourage conducting multi-center registries (web/ online-based) to obtain all the data from every individual case of cancer patients with COVID-19 infection.

Data availability

Underlying data

All involved data are publicly accessible thus no additional data source required.

Reporting guidelines

Figshare: PRISMA checklist for 'Comparison of Clinical Outcome in Hematological Cancer Compared to Primary Solid Cancer Patients With COVID-19 Infection: a Systematic Review and Meta-Analysis, https://doi.org/10.6084/m9.figshare.17122541

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Clinical outcomes of COVID-19 patients with solid and hematological cancer: a meta-analysis and systematic review

Joni Wahyuhadi[1*], Fadhillah Putri Rusdi[1], I G. M. Aswin R. Ranuh[1], Rizki Meizikri[1], Irwan Barlian Immadoel Haq[1], Rahadian Indarto Susilo[1], Makhyan Jibril Al Farabi[2]
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Abstract

Background: Previous research has consistently shown the significant difference in outcome between cancerous and non-cancerous patients with coronavirus disease 2019 (COVID-19). However, no studies have compared the clinical manifestation of COVID-19 in hematologic cancers patients and solid cancers patients. Therefore, we analyzed the outcome of COVID-19 patients with hematological cancer and primary solid cancer worldwide through a meta-analysis and systematic review.

Methods: This meta-analysis and systematic review included 20 articles with total of published between 2019 – January 2021 from Pubmed and Google Scholar which fit our inclusion criteria. Newcastle Ottawa Score was used to assess the quality and bias of included studies. The outcome measured were case-fatality rate and critical care events for COVID-19 patient with cancer and comorbidities.

Results: Critical care events and mortality were higher in the hematological than primary solid cancer group (RR (Relative Risk)=1.22 & 1.65; p <0.001). Conversely, mortality was lower in patients with two or fewer comorbidities (RR=0.57; p<0.001) and patients under the 75 year old group (RR=0.53; p< 0.05).

Conclusions: Hematologic malignancy, age, and the number of comorbidities are predictor factors for worse prognosis in COVID-19 infection.

Keywords COVID-19, cancer, outcome, oncology

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It is shown that 2.1% of patients with confirmed COVID-19 were reported also to have cancer.[2] A meta-analysis revealed that the mortality rate for COVID-19 patients with cancer was 21.1%. As many as 45.4% of cancer patients with COVID-19 have severe or critical symptoms.[2]

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Cancer patients are a uniquely susceptible population because most of these patients may be in a suboptimal physical condition while also requiring cytotoxic drugs that can reduce immunity. In addition to the symptoms of COVID-19, these patients' cancer treatment may also be delayed during the pandemic.[3]

Most observational studies have exposed that COVID-19 patients with cancer tended to have worse prognosis compared to non cancerous COVID-19 patients.[4,5] Previous research revealed that patients with hematologic cancers (HC) experienced more severe COVID-19 symptoms and higher CFR (case fatality rate) side to those with solid cancers (SC).[6] More severe manifestation and higher CFR are found in hematologic cancer patients compared to solid cancer patients.

Previous research suggested that the presence of haematological malignancies may reduce COVID-19 severity progression due to an attenuated inflammatory response.[7,8] Other studies have reported that solid tumors were a worse prognosis predictor.[10,11] The variation between studies and the lack of publications have encouraged us to analyze if patients with hematologic cancer and those with solid tumors would fare differently in the setting of COVID-19 infection.

METHODS

Study design

The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol) guidelines were used to guide this study.

Eligibility criteria

This review included clinical studies (clinical trial, retrospective, or prospective) of all cancer patients who had COVID-19 infection based on polymerase chain reaction (PCR) test. The article's year of publication was from 2019 to 2021 with English language. For inclusion, the published articles must have had documentation of COVID-19 infection in both solid cancer and hematological cancer patients. Proceeding, commentaries, and editorials without a peer-review process were excluded.

Search strategy and database source

We systematically searched databases to identify eligible articles using PubMed and Google Scholar for articles published from December 2019 to January 2021 using

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keywords our search strategy below (Table 1). We also researched references lists of relevant articles to identify additional primary studies and minimize bias.

Table 1. Search strategy for All Database

1	(COVID-19)
2	((COVID19) OR (coronavirus disease-19) OR (COVID-19 pandemic) OR (2019-SarSCoV infection) OR (coronavirus disease 2019) OR (COVID-19 virus disease)
3	#1 OR #2
4	(Cancer)
5	((Neoplasm) OR (Neoplasm, Malignant) OR (Malignant Neoplasms) OR (Malignant Neoplasm) OR (Neoplasms, Malignant) OR (Cancers) OR (Malignancy) OR (Malignancies) OR (Tumor) OR (Tumors) OR (Cancer))
6	#4 OR #5
7	#3 AND #6
8	((Outcome) OR (Outcomes) OR (Clinical Outcome) OR (Clinical Outcomes) OR (COVID-19-related Outcome) OR (coronavirus disease-19-related outcome) OR (COVID-19-related Outcomes) OR (Coronavirus Disease-19-related Outcomes))
9	#7 AND #8

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Study selection

All articles from the search strategy were screened further for eligibility. The titles and abstracts were independently screened and reviewed by three authors (FP, AR, RM). The workflow of the study selection can be seen on Figure 1. The article's technical uncertainties were resolved through discussion between all authors (FP, AR, RM, JH, RI, IB, MJ). Study assessment was based on the following criteria: 1) published in English, 2) prospective or prospective study on cancer patients with COVD-19 infection; 3) sufficient data relating to PICO (participants/interventions/comparisons/outcomes) criteria (Table 2) from COVID-19 patients with hematological and primary solid cancer.

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Data collection & study quality assessment

The data collected were demographic details (e.g., age, race, comorbidities), type of cancer (primary solid tumors and hematological malignancy), patient's anti-cancer therapies (described as surgery, chemotherapy, radiotherapy of immunotherapy), clinical outcomes (developing severe events, hospitalization rates, intensive care unit (ICU) admission rates, 30-days mortality rate and case-fatality rate). Three authors (FP, AR, RM) extracted the data, jointly reconciled, and discussed technical uncertainties. The authors then appraise the studies using the Newcastle-Ottawa scale (NOS) for cohort studies (Table 3).[2]

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Table 2. PICO (participants/interventions/comparisons/outcomes) criteria. COVID-19=coronavirus disease 2019.

Patient	Patients with COVID-19 infection
Intervention	Hematological Cancer Patients
Comparison/ Control	Primary Solid Cancer Patients
Outcome	Death Rate or Case-fatality Rate in COVID-19 Patients with Cancer, Critical Care Events Rate in COVID-19 Patients with Cancer, Death Rate in COVID-19 Patients with Cancer and Multiple Comorbidities, Death Rate in Elderly COVID-19 Patients with Cancer

Table 3. The Newcastle-Ottawa scale for quality assessment of included studies

Author	Selection	Comparability	Exposure/outcome	Total
Antrim 2020	★★	★★	★	★★★★★
Kuderer 2020	★★	★★★	★★★	★★★★★★★★
Dai 2020	★★	★★	★★	★★★★★★
deMelo 2020	★★	★	★★★	★★★★★★
Ferrari 2021	★	★★	★	★★★★
Fillmore 2020	★★	★★	★★	★★★★★★
Jazieh 2020	★★	★★	★	★★★★★
Lennard 2020	★★	★★	★	★★★★★
Li 2020	★★	★★	★★	★★★★★★
Rivera 2020	★	★	★	★★★
Rüthrich 2020	★★	★★★	★★	★★★★★★★★
Shoumariyeh 2020	★★	★★	★★	★★★★★★
Wang 2020	★★	★	★★	★★★★★
Yang 2020	★★	★★	★★	★★★★★★
Robilotti 2020	★	★	★	★★★
de Joode 2020	★	★★	★★	★★★★★
Meng 2020	★★	★★★	★★	★★★★★★★
Elkrief 2020	★★	★	★	★★★★
Tremblay 2020	★★	★	★	★★★★
Stroppa 2020	★★	★★	★★	★★★★★★

Statistical analysis

The statistical analysis, including Cochran–Mantel–Haenszel test (CMH), Risk Ratio, Heterogenicity test, and funnel plotting were done using Statistical Package for the Social Sciences (SPSS) 25, MedCalc Statistical Software version 19.3, and RevMan version 5.4.

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RESULTS

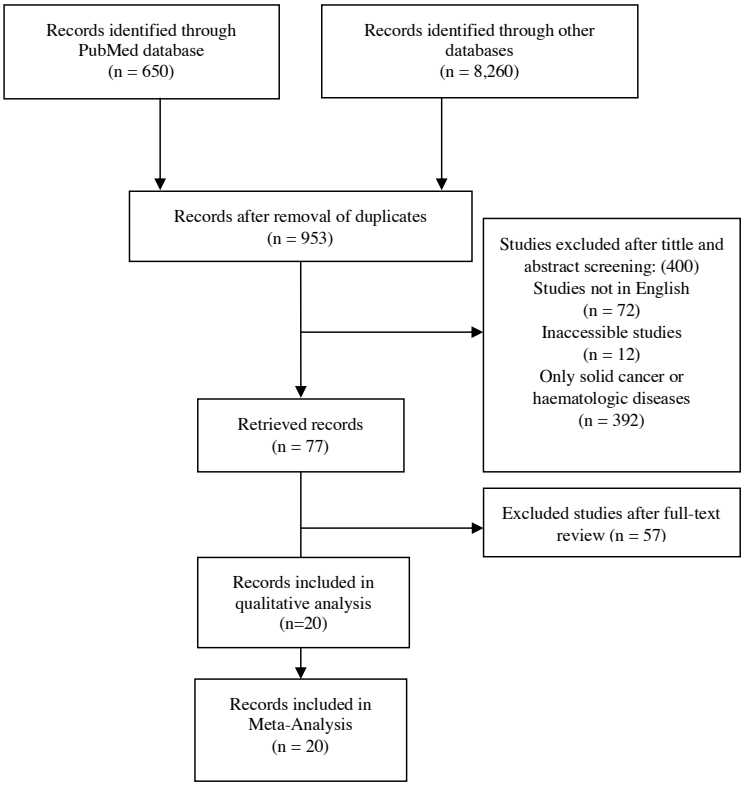

Figure 1 PRISMA flowchart on search, screening, eligibility, and literature inclusion cascade

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SYSTEMATIC REVIEW

COVID-19 severity and mortality in cancer patients

In 2020, DeMelo et al. reported that age, advanced malignancy stage, and number of metastases were associated with clinical fragility and higher risk of death in COVID-19 patients[10].

A previous study explained that COVID-19 symptoms in cancer patients ranged from mild symptoms (55% of cases), which required outpatient management only (fever, cough, fatigue, myalgia, etc.) to moderate to severe symptoms (45% of cases).

From these patients, 42% were admitted to the ICU.[10] According to a study, a complication such as secondary infection and acute respiratory distress syndrome occurred in a majority of cancer patients (63%).[4] Another study in 2020 found that patients with malignancy were prone to having COVID-19 with severe manifestation (54% vs. 35%; P=0.003). The study mentioned that severe COVID-19 symptoms upon admission are a significant risk of in-hospital death (Hazard Ratio=28.2).[11] Two other studies reported similar findings which support that cancer is associated with worse outcome.[12,13]

Regarding type of cancer, Dai and colleagues reported the hematologic cancer and lung cancer group had the highest and second highest severity and death rates compared to other cancer groups. The patients with hematological malignancy have reduced immunity and are more prone to infection, which can exacerbate COVID-19 infection[8]. Previous studies showed that leukemia, lymphoma, and myeloma as hematological cancer groups could increase death rate, ICU admission, critical manifestation, and invasive mechanical ventilation requirement.[8]

Previous study showed that patients with and without cancer had similar COVID-19 severity. In the said study, the hematological and solid tumors groups showed non-significant trends for immediate manifestation of severe events (hematological group cohort = 30% vs. solid group cohort = 61.4%).[16] However, another study from Canada investigated 252 cancer patients with COVID-19 and showed that 28% of adult patients had a high mortality rate, whereas none of the patients in the pediatric cohort had a significant illness. In hospital-acquired patients with COVID-19, overall survival (OS) was shorter than those with community-acquired infection.[17] Similarly, study from the UK reported that patients with hematological cancer have a greater risk of severe COVID-19 clinical manifestation, which needs more intensive supportive interventions and poses a greater risk of death than non-cancer patients.[5] Tremblay and colleagues explained that the hematologic malignancies group of patients might be vulnerable to COVID-19. The preliminary study also suggests that hematological cancer patients have higher mortality than the general population.[18]

Anti-cancer treatment-related outcome

Different cancer treatments including surgical, radiotherapy and COVID-19-specific medication done within 60 days before COVID-19 infection did not affect the death risk.[10] Two studies reported an increased death rate in patients who received

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immunotherapy, surgery and chemotherapy [8,19]. Robilloti demonstrated that lung cancer patients treated with immune checkpoint inhibitors (ICI) correlated with worse COVID-19 infection outcomes.[17] On the other hand, patients with lung cancer who had COVID-19 had better outcomes despite having immunotherapy.[13]

COVID-19 treatment-related outcome

Rivera et al. analyzed the treatments of COVID-19 in patients with cancer. High-dose corticosteroids combined with other therapies were correlated to higher mortality than positive and negative controls. Hydroxychloroquine combined with other drugs also demonstrated similar results, in which when combined, the risk of all-cause mortality every 30-day was increased when compared with the positive control (OR=2.15). On the other hand, remdesivir showed potential benefit as lower 30-day all-cause mortality compared to positive group (OR=0.41)[19].

METAANALYSIS

Table 4. Studies summary

Author	Country	Type of Study	Age (Median years)	Type of Cancer		Case-fatality Rate	
				Hematological Cancer (%)	Primary Solid Cancer (%)	Hematological Cancer (%)	Primary Solid Cancer (%)
Antrim 2020[23]	US	Retrospective Study	60.5	11	36	3	2
Kuderer 2020[24]	US, Canada, Spain	Retrospective Study	66	204	728	24	76
Dai 2020[8]	China	Retrospective Study	64	9	96	3	6
deMelo 2020[10]	Brazil	Retrospective Study	67.5	34	138	8	52
Ferrari 2021[11]	Brazil	Retrospective Study	61	31	167	5	33
Fillmore 2020[20]	US	Prospective Study	65	176	1483	30	200
Jazieh 2020[25]	Saudi Arab	Retrospective Study	66	9	10	9	7
Lennard 2020[5]	UK	Prospective Study	70	224	801	81	229
Li 2020[12]	China	Prospective Study	63	9	50	2	16
Rivera 2020[19]	US	Retrospective Study	67	470	1781	N/A	N/A
Rüthrich 2020[26]	Germany	Retrospective Study	N/A	124	256	31	156
Shoumariyeh 2020[15]	Germany	Retrospective Study	73	10	29	8	23
Wang 2020[27]	US	Retrospective Study	41.5	170	640	N/A	N/A
Yang 2020[4]	China	Retrospective Study	63	22	183	9	31
Robilotti 2020[17]	China, Italy	Retrospective Study	64	102	321	N/A	N/A
de Joode 2020[28]	Dutch	Prospective Study	70	111	208	43	62
Meng 2020[13]	China	Retrospective Study	64.5	16	92	8	24
Elkrief 2020[16]	Canada	Retrospective Study	73	66	179	N/A	N/A
Tremblay 2020[18]	US	Prospective Study	69	14	10	N/A	N/A
Stroppa 2020[14]	Italy	Retrospective Study	67	2	22	2	7

Case-fatality rate

In total, 14 studies included detailed case fatality rates of hematological cancer and primary solid cancer groups. Overall, the case-fatality rate in the hematological cancer group was 1.22 fold higher than the primary solid cancer group (263/976 vs. 852/4373; RR 1.22; CI 95% [1.08-1.37]; P<0.001) (Figure 2).

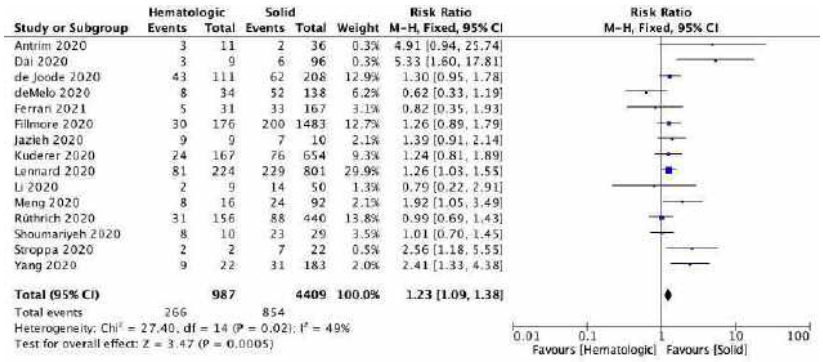

Figure 2. Case-fatality rate in hematological vs primary solid cancer patients forest plot. CI=confidence interval, df=degrees of freedom, M-H=Mantel Haenszel Method

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We performed two sub-analyses on case-fatality rate, to determine the correlation with comorbidities and age. Two studies provided data on the patients' comorbidites (two or less comorbidities and more than two comorbidities group).[10,24] Overall, the case-fatality rate in patients with two or fewer comorbidities group was 0.57 fold lower than patients with more than two comorbidities group (97/694 vs. 65/327; RR 0.57; CI 95% [0.42-0.76]; P<0.001) (Figure 3). We also calculated the pooled proportion of case-fatality rate in the cardiovascular disease group (42.5%) (Figure 4), hypertension (36.8%) (Figure 5), and diabetes mellitus (36,8%) (Figure 6), as those three were deemed the most prevalent comorbidities.

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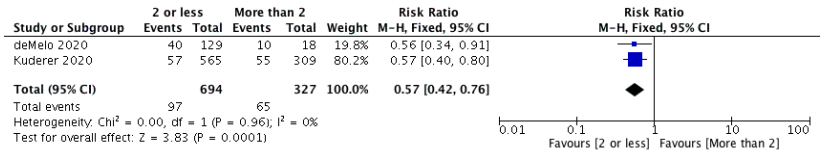

Figure 3. Case-fatality rate with multiple comorbidities in both cancer groups forest plot

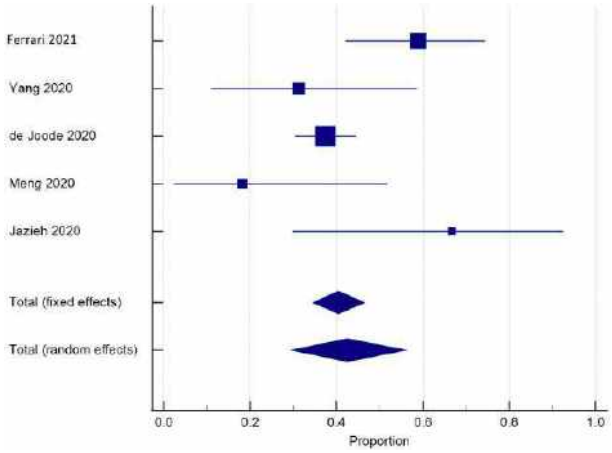

Figure 4. Case Fatality Rate in patients with cardiovascular comorbid

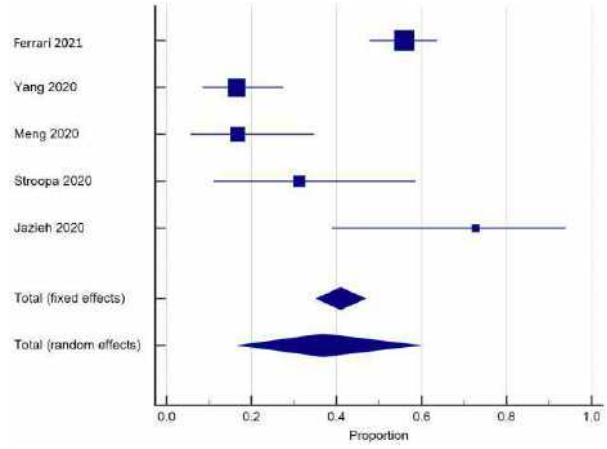

Figure 5. Case Fatality Rate in patients with hypertension

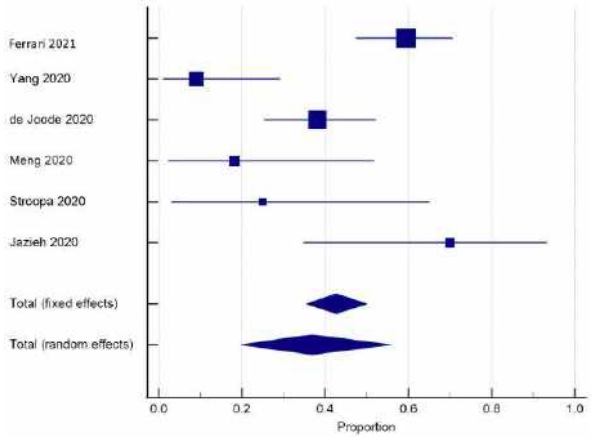

Figure 6. Death event in patients with diabetes mellitus

In total, six studies included detailed data of elderly patients (under 75 y.o. and 75 y.o. or older) in both cancer groups. Overall, the rate of death in patients under 75 y.o. group was 0.53 fold lower than patients under 75 y.o. group (250/1350 vs. 154/465; RR 0.53; CI 95% [0.36-0.80]; P=0.002) (Figure 7).

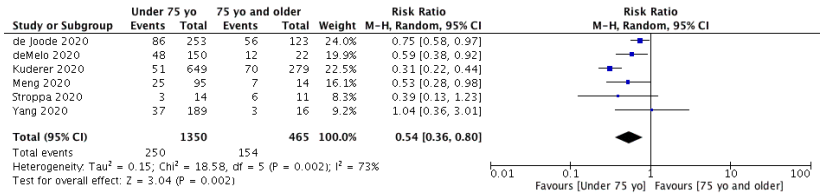

Figure 7. Case-fatality rate in elderly patients in both cancer groups forest plot

Critical care events rate

Overall, five studies included detailed data of patients who developed critical events in the hematological and primary solid cancer groups separately. Overall, the rate of critical care events in the hematological cancer group was 1.65 fold higher than the primary solid cancer group (140/371 vs. 585/2312; RR 1.65; CI 95% [1.22-2.23]; P=0.001) (Figure 8).

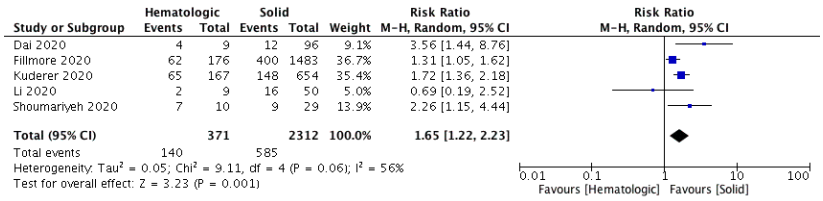

Figure 8. Critical care events rate in hematological cancer vs primary solid cancer patients forest plot

DISCUSSION

To our best knowledge, the severity of COVID-19 can be worsened by cancer. The risk of death may also increase due to cancer. Patients with hematologic malignancy have an immunocompromised state which may induce co-infection and thus aggravate COVID-19 clinical presentation.[4,5,8–14,17]. Our meta-analysis shows that the rate of mortality and critical care events were higher in the hematologic group than in the primary solid cancer group. At the same time, the case-fatality is higher in patients who had more than two comorbidities and patients aged 75 or older. Thus, our analysis showed a tendency toward publication bias for case-fatality rate (P=0.03) (Figure 9) likely to the presence of small sample size studies.

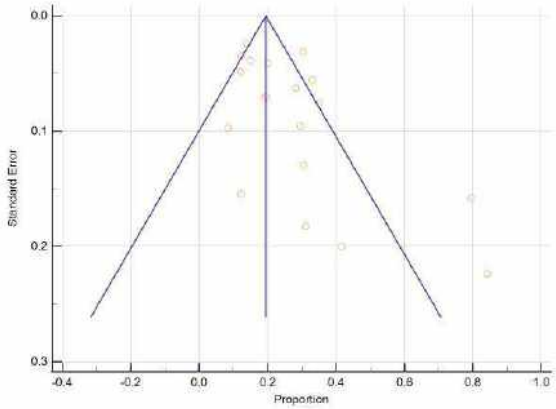

Figure 9. Case-fatality rate in both cancer groups proportional study funnel plot

Our analysis on critical care events seemed to differ from the rest of the study. The COVID-19 diagnosis test might cause this as both PCR and anti-SARS-CoV-2 IgG/IgM antibody tests[12] were used in Li's study, whereas other studies included in the

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Commented [MJ36R35]: Okay

meta-analysis only used PCR for diagnostic testing. Moreover, This was etrospective study with relatively few subjects yet with an enormous number of controls.[12]

The hematological cancer group had more severe COVID-19 manifestation.[12] However, this finding requires further verification through multi-center studies. Based on a previous study, delaying surgery or chemotherapy for patients with cancer during the COVID-19 pandemic is not required, especially in areas with fewer COVID-19 patients.[16]

Commented [TF37]: Please clarify which previous study. Or change wording to "Based on a previous study"

Commented [MJ38R37]: okay

From our review, several studies from China, Europe, and North America reported that cancer patients with COVID-19 infection who received chemotherapy, immunotherapy, and ICI treatment had a higher death risk[4,5,8,17,20]. A meta-analysis in the US reported that active cytotoxic chemotherapy was associated with a high risk of adverse outcomes from COVID-19 [21]. At the same time, Stroppa et al. revealed a better prognosis of COVID-19-infected lung cancer patients treated with immunotherapy[14]. Similarly, Fillmore et al. reported a lower risk of infection was correlated with ICI treatment[14]. A meta-analysis by Yekedüz et al. revealed that cancer treatment was not associated with severity and mortality risk of COVID-19 within the last 30 days before diagnosis[22].

A COVID-19 and Cancer Consortium Cohort Study in US revealed that corticosteroids in high dose administration combined with any other therapies, and hydroxychloroquine combined with other drugs or given alone were associated with higher 30-day all-cause mortality risk in cancer patients with COVID-19 infection. While remdesivir has shown to be a potential treatment, the all-cause mortality rate in 30 days decreases [19].

Commented [TF39]: Comma here OK? To separate corticosteroids and hydroxychloroquine.

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Conclusion

Hematological malignancy, elder age (75 years) and the number of comorbidities are predictors for worse prognosis in COVID-19 infection. The therapy protocol for cancer patients with COVID-19 infection and COVID-19 therapy is still debatable. Future research needs to evaluate these treatments in prospective randomized controlled trials (RCTs), address disparities, and promote studies evaluating potential anti-COVID-19 therapies.

Limitations

There were missing data points from some studies. Given these limitations, we encourage conducting multi-center registries (web/ online-based) to obtain all the data from every individual case of cancer patients with COVID-19 infection. The review section may also influenced of the authors' personal viewpoints, gaps in literature searching practices that may lead to the omission of relevant research, errors in the translation of data from the primary literature to summarization in the review.

Commented [TF41]: Please Discuss any limitations of the review processes used.

Commented [MJ42R41]: done

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required. *Reporting guidelines*

Figshare: PRISMA checklist for 'Comparison of Clinical Outcome in Hematological Cancer Compared to Primary Solid Cancer Patients With COVID-19 Infection: a Systematic Review and Meta-Analysis, https://doi.org/10.6084/m9.figshare.17122541

Competing interests

No competing interests were disclosed

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If there are any outstanding queries on your reviewer suggestions, then we will be in touch with you shortly.

Best regards,

Manahil
The Editorial Team, F1000Research

Joni Wahyuhadi <joniwahyuhadi.rsudsoetomo@gmail.com> 21 Januari 2022 10.34
Kepada: production@f1000research.com

Dear Editorial Team

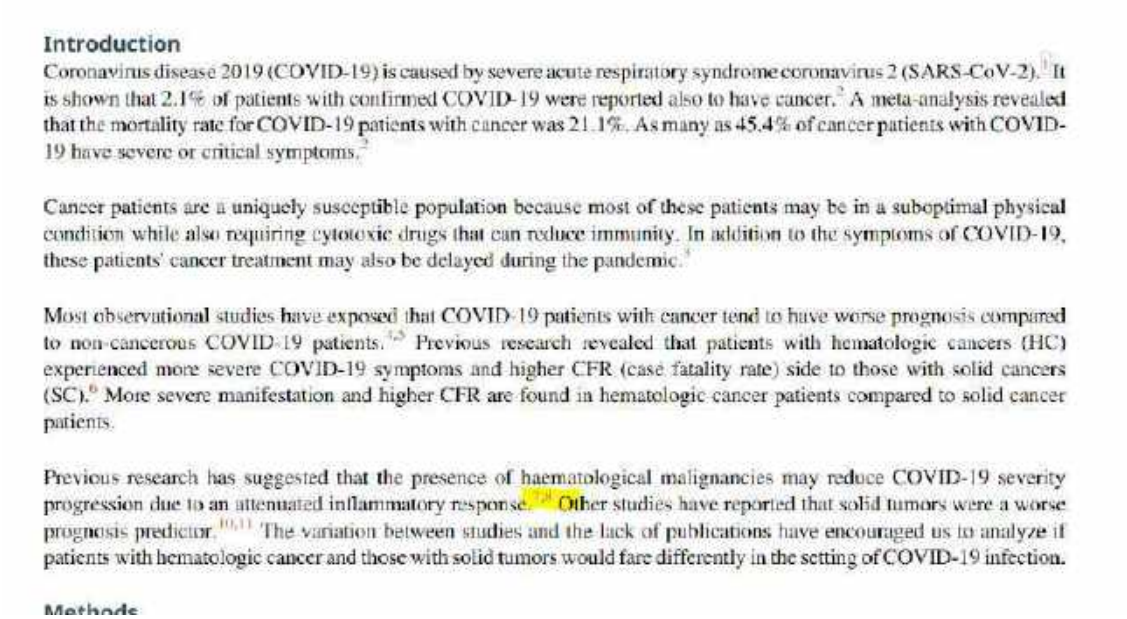
Thank you very much for your email

I apologize for missing reference 9, it should be located in this sentence

Please add this no 9 references at this sentence

Other than that, I think it will be okay

Best Regards
Joni



Introduction

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Cancer patients are a uniquely susceptible population because most of these patients may be in a suboptimal physical condition while also requiring cytotoxic drugs that can reduce immunity. In addition to the symptoms of COVID-19, these patients' cancer treatment may also be delayed during the pandemic.[3]

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Methods

[Kutipan teks disembunyikan]

Joni Wahyuhadi <joniwahyuhadi.rsudsoetomo@gmail.com> 6 Februari 2022 10.00
Kepada: production@f1000research.com

Dear Editorial team?
May i know when the article will be published?

Is there anything else that i need to do?

Best regards

Joni
[Kutipan teks disembunyikan]

F1000.Production.Research <production.research@f1000.com> 7 Februari 2022 19.12
Kepada: Joni Wahyuhadi <joniwahyuhadi.rsudsoetomo@gmail.com>

Dear Joni,

Thanks for the email. Looking at your article, it looks like you need to suggest some potential peer reviewers to invite to review the article. We cannot publish unless our peer review team are able to approve a set of 5 suitable reviewers suggested by yourselves. You can read more about how to suggest reviewers here: https://f1000research.com/for-authors/tips-for-finding-referees.

Many thanks,

Jess

Jess Fenn

Production Editor

E jessica.fenn@f1000.com

F1000

240 Blackfriars Rd
London SE1 8BF

www.f1000.com

From: Joni Wahyuhadi <joniwahyuhadi.rsudsoetomo@gmail.com>
Sent: 06 February 2022 03:00
To: F1000Research.Production <production@F1000Research.com>
Subject: Re: Article 76143 - Query

Dear Editorial team?

May i know when the article will be published?

Is there anything else that i need to do?

Best regards

Joni

Pada tanggal Jum, 21 Jan 2022 pukul 10.34 Joni Wahyuhadi <joniwahyuhadi.rsudsoetomo@gmail.com> menulis:

> Dear Editorial Team
>
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>
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>
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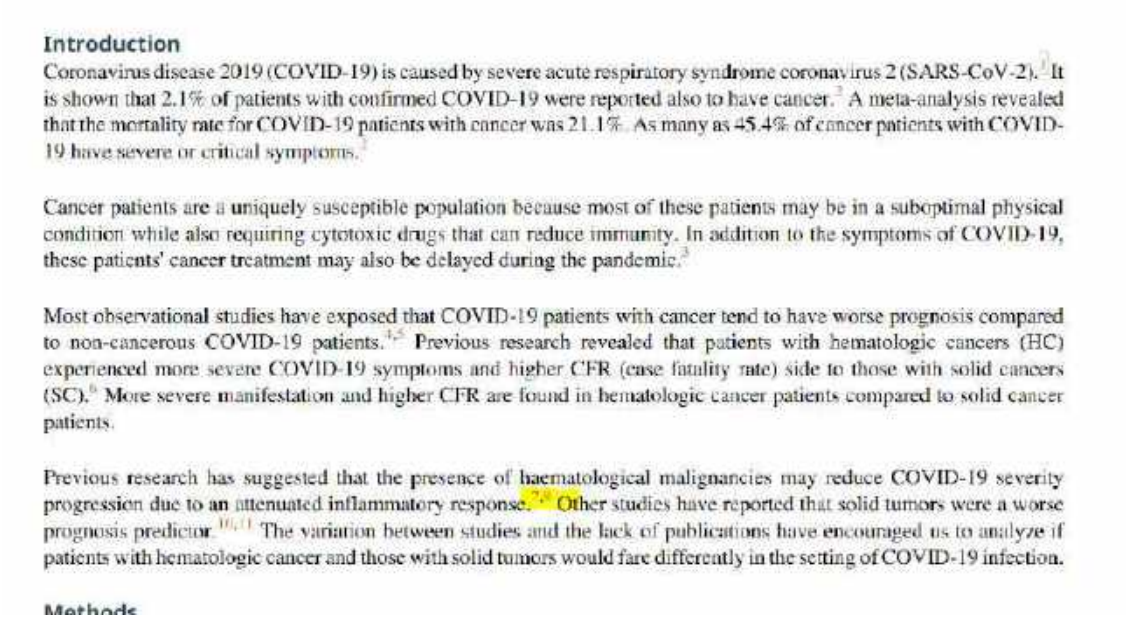

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Methods

Pada tanggal Rab, 19 Jan 2022 pukul 19.53 <production@f1000research.com> menulis:

> Dear Joni
>
> Clinical outcomes of COVID-19 patients with solid and hematological cancer: a meta-analysis and systematic review
> Wahyuhadi J, Rusdi FP, Ranuh IGMAR, Meizikri R, Haq IBI, Susilo RI and Al Farabi MJ
>
> Please click here to download the PDF proof of your F1000Research article.
>
> **Note: Reference 9 is not cited in text, and references are not in sequential order, please check.**
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> - All links within the article are working, and correct
>
> Please note that connecting an ORCID account to F1000Research requires the account holder to sign in to both F1000Research and ORCID, **therefore it isn't possible for us to add ORCID badges for your co-authors on their behalf.** When the article is published, they will receive an email encouraging them to connect their ORCID account to F1000Research. If they do this, their ORCID badge will be displayed next to their name.
>
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The Editorial Team, F1000Research

Joni Wahyuhadi <joniwahyuhadi.rsudsoetomo@gmail.com> 12 Februari 2022 12.38
Kepada: "F1000.Production.Research" <production.research@f1000.com>

Dear F1000 Team

Thank you very much for your response

I have added the reviewer

Hopefully this will be sufficient

Best Regards
Joni
[Kutipan teks disembunyikan]

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