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# Mortality in hospitalized patients with cancer and coronavirus disease 2019: A systematic review and meta-analysis of cohort studies.

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Original Article

# Mortality in Hospitalized Patients With Cancer and Coronavirus Disease 2019: A Systematic Review and Meta-Analysis of Cohort Studies

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**BACKGROUND:** Heterogeneous evidence exists on the effect of coronavirus disease 2019 (COVID-19) on the clinical outcomes of patients with cancer. **METHODS:** A systematic review was performed using the Medline, Embase, and CENTRAL databases and the World Health Organization Novel Coronavirus website to identify studies that reported mortality and characteristics of patients with cancer who were diagnosed with COVID-19. The primary study outcome was mortality, defined as all-cause mortality or in-hospital mortality within 30 days of initial COVID-19 diagnosis. The pooled proportion of mortality was estimated using a random-effects model, and study-level moderators of heterogeneity were assessed through subgroup analysis and metaregression. **RESULTS:** Among 2922 patients from 13 primarily inpatient studies of individuals with COVID-19 and cancer, the pooled 30-day mortality rate was 30% (95% CI, 25%-35%). The overall pooled 30-day mortality rate among 624 patients from 5 studies that included a mixture of inpatient and outpatient populations was 15% (95% CI, 9%-22%). Among the hospitalized studies, the heterogeneity ($I^2$ statistic) of the meta-analysis remained high ($I^2$, 82%). Cancer subtype (hematologic vs solid), older age, male sex, and recent active cancer therapy each partially explained the heterogeneity of mortality reporting. In multivariable metaregression, male sex, along with an interaction between the median patient age and recent active cancer therapy, explained most of the between-study heterogeneity ($R^2$, 96%). **CONCLUSIONS:** Pooled mortality estimates for hospitalized patients with cancer and COVID-19 remain high at 30%, with significant heterogeneity across studies. Dedicated community-based studies are needed in the future to help assess overall COVID-19 mortality among the broader population of patients with cancer. ***Cancer* 2021;127:1459-1468**. © *2020 American Cancer Society*.

**KEYWORDS:** cancer, coronavirus disease 2019 (COVID-19), malignancy, mortality, novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

## INTRODUCTION

Since the first outbreak in Wuhan, China, in late December 2019, the coronavirus disease 2019 (COVID-19) pandemic has been declared by the World Health Organization as a global public health emergency.[1] As of August 24, 2020, there are over 23 million cases of COVID-19 and more than 812,999 deaths worldwide.[2] Although, the burden of COVID-19 is uniformly distributed among individuals of all age groups, reports suggest a higher incidence among older adults, men, and those with underlying comorbidities, including cancer.[3]

Data on the risks of COVID-19 among patients with cancer continue to evolve. Early reports from Wuhan, China suggested that patients with cancer have a higher burden of COVID-19 and a greater risk of severe illness and mortality.[4,5] Since then, several systematic reviews have attempted to assess the impact of cancer on COVID-19 severity and mortality.[6-8] However, these studies have been limited by their inclusion criteria, small subgroups of the population, and case duplications.[9] Subsequently, these often lacked the details regarding cancer or cancer treatment and short-term mortality data.

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Recently, a few large, multinational cohort studies dedicated to COVID-19 and cancer have been published,[10] including the COVID-19 and Cancer Consortium (CCC-19)[11] from the United States and Canada and the UK Coronavirus Cancer Monitoring Project (UKCCMP)[12] from the United Kingdom. These cohorts continue to evaluate both short-term and long-term outcomes associated with COVID-19 based on key demographic and clinical characteristics of patients with cancer. As we gather more information on the relation and effects of COVID-19 on cancer, our objective was to assess the overall mortality in this population through a meta-analysis of published data on COVID-19 and cancer. We also assessed the drivers of heterogeneity in mortality estimates across published studies.

## MATERIALS METHODS

### *Search Strategy*

We performed a search of peer-reviewed literature in the English language, conference abstracts, and trial registrations from the Medline (Ovid), Embase (Elsevier), and CENTRAL (Cochrane Library) databases; the World Health Organization Novel Coronavirus website[13]; and major international oncology meetings from 2019 to 2020 (last date of search, June 8, 2020) with the help of a health sciences librarian (L.O.). We developed the search strategy initially on Medline and then translated it to other databases (for the full search syntax and details, see Supporting Table 1). We prespecified the searches to studies written in or translated into English. The search and analysis strategy were registered on the PROSPERO international prospective register of systematic reviews (Center for Reviews and Dissemination, University or York) before data extraction (registration number CRD42020189350).[14] Covidence was used for removal of duplication, storing, and managing citations across all databases.[15] We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct our literature search and reporting.[16]

### *Study Selection*

Two authors (A.D. and R.G.) independently screened all titles and abstracts after initial de-duplication. The inclusion criteria included studies reporting on adults aged >18 years who had an existing diagnosis of cancer and were subsequently diagnosed with COVID-19 infection by either: 1) polymerase chain reaction (PCR) or quantitative real-time PCR, or 2) clinical diagnosis based on presentation. We excluded studies with <10 patients diagnosed with both cancer and COVID-19, or without specific outcomes information on cancer patients, or nonoriginal studies (review articles, viewpoints, editorials, or commentaries). Then, 2 authors (A.D. and R.G.) independently performed full-text reviews to determine final study inclusion for data extraction. Specifically, studies were excluded if they had an incorrect study design, did not include a cancer-specific population, did not contain cancer-specific outcomes, were duplicate publications from larger studies (ie, a single-center study published separately from a multicenter study that included the same center), or had <10 patients in the study (see Supporting Table 2). All discrepancies were resolved by consensus and were further adjudicated by a third author (A.L.).

### *Data Extraction*

Three authors (A.D., R.G., and S.A.) independently extracted all eligible studies. Important fields extracted included study characteristics, setting (inpatient vs inpatient and outpatient), patient demographics and comorbidities, cancer types (solid vs hematologic as well as individual cancer types), cancer-relevant details (including ongoing treatment vs not and the presence of existing comorbidities), COVID-19–relevant details, and outcomes of interest. All-cause mortality was our primary outcome and was defined as death from any cause within 30 days of initial COVID-19 diagnosis or in-hospital mortality if adequate follow-up had been achieved. For studies that only reported mortality during the study period with inadequate follow-up, we contacted the corresponding authors for updated data (see Supporting Table 3); if these data were not available or we did not receive a reply, the lack of follow-up information was marked as a bias under *missing information* on the quality-assessment form. Finally, we requested individual patient-level data from each study, and, if provided or available, we integrated the updated data or publication into the final data analysis. All discrepancies in data extraction were adjudicated by a fourth author (A.L.).

### *Quality Assessment*

We used a modified version of the Risk of Bias in Nonrandomized Studies-of Interventions (ROBINS-I) risk-assessment tool from the Cochrane Method group.[17,18] Because most studies were retrospective case series and cohort studies without specific exposure or intervention, we focused quality assessment on 5

domains: bias in selection, bias because of missing data, bias in measurement of outcomes, bias in selection of reported results, and confounding if risk factors were assessed. A study was considered to have high overall bias if 2 of the 5 domains were considered to be high-risk. Finally, publication bias was examined by using funnel plots of study effect size relative to the standard error as a visual aid for assessing systematic heterogeneity or bias.

### *Statistical Analysis*

The primary goal of the current study was to estimate the overall mortality among patients with cancer and COVID-19 infection and to assess drivers of heterogeneity between studies. For the main meta-analysis, we included studies that were conducted predominantly among hospitalized patients who had cancer and COVID-19 to avoid an admixture of different populations (ie, nonhospitalized patients who were inherently less sick and less likely to die).

We calculated the pooled proportion of mortality for hospitalized patients across studies using a random-effects model. An aggregate participant meta-analysis of proportion was conducted using the *metaprop* and *meta* packages from Stata version 16.1 (StataCorp).[19] Specifically, CIs of studies were estimated using the Clopper-Pearson exact binomial method.[20] Effect size was estimated using the DerSimonian and Laird random-effects models after Freeman-Tukey double arcsine transformation of proportion to stabilize the variances in the pooled proportion.[21,22] Forest plots were generated to visualize pooled point estimates and CIs. Heterogeneity (between-study variance) was quantified using the $I^2$ statistic, in which a higher percentage suggests higher heterogeneity.[23] A subgroup analysis was performed for binary study characteristics (eg, solid vs hematologic cancer type) after pooling the results from each subgroup. Metaregression with a random-effects model was performed for continuous study characteristics (eg, age, percentage male, percentage receiving active treatment) to identify additional moderating factors that could explain the effect size inconsistencies. The $R^2$ percentage (variance explained by the model with included covariates/total variance without covariates) was used determined the best fit of the derived models.

## RESULTS

### *Systematic Review*

In total, we identified 3033 studies from 5 data sources (Medline, n = 759; Embase, n = 1267; CENTRAL, n = 24; the World Health Organization website, n = 978; and national oncology meeting abstracts, n = 5) (Fig. 1). After de-duplication, 1764 studies underwent title and abstract screening, and 80 full-text articles were assessed for eligibility. Eighteen studies were included in the final qualitative review. The excluded references and the reasons for exclusion are provided in Supporting Table 2.

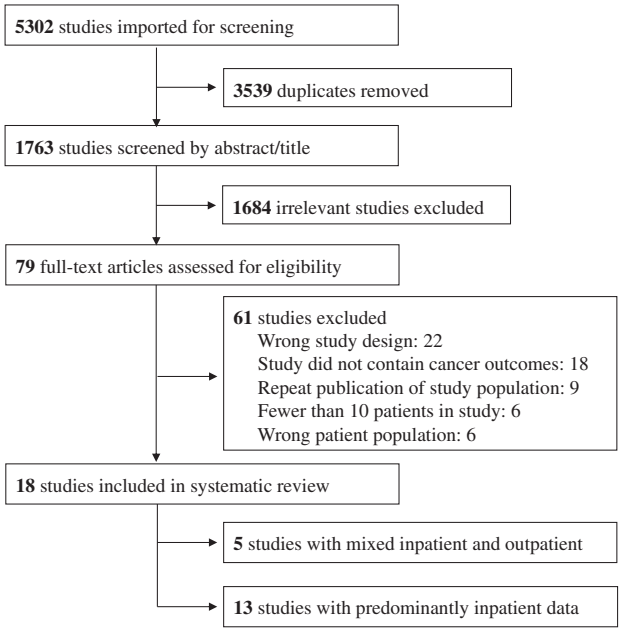



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses study inclusion and exclusion are illustrated.

Details of the 18 included studies are provided in Table 1.[11,12,24-40] Two studies reported by Kuderer et al[11] and Rivera et al[28] both provided data from the COVID-19 and Cancer Consortium (CCC19); therefore, they were considered as 1 study for inclusion. Furthermore, because the latter publication provided detailed patient-level data as a supplement, we used those specifically relevant to patients with moderate-to-severe COVID-19 illness as a surrogate for hospitalized patients in the current review. Overall, there was significant heterogeneity in the inclusion criteria and variability in study follow-up periods. Five studies included both hospitalized patients and outpatients diagnosed with COVID-19 or failed to specify a particular study setting. Thirteen studies (including the CCC19 patient-level subgroup update and the Thoracic Cancers International COVID-19 Collaboration [TERAVOLT] hospitalized cohort[33]) predominantly recruited patients admitted to the hospital and formed the core group for the final meta-analysis.

**TABLE 1.** Systematic Review of Cohort Studies in Patients With Coronavirus Disease 2019 (COVID-19) and Cancer

| Reference | Country: Timing | No. of Patients | Median Age, y | No. of Men (%) | Study Setting: No. (%) | | Cancer Type No. (%) | | Active Therapy | | Mortality | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Outpatient | Inpatient | Solid | Heme | Therapy No. (%) | Duration | Deaths, No. (%) | Follow-Up |
| Predominantly hospitalized patients | | | | | | | | | | | | |
| Aries 2020[24] | UK: 3/11 to 5/11 | 35 | 69 | 23 (66) | 0 (0) | 35 (100) | 0 (0) | 35 (100) | 24 (69) | 1 mo | 14 (40) | 14 d |
| Cook 2020[25] | UK: NA to 5/18 | 75 | 73 | 45 (60) | 3 (4) | 72 (96) | 0 (0) | 75 (100) | 75 (100) | 1 mo | 41 (55) | Study period |
| Dai 2020[26] | China: 1/1 to 2/24 | 105 | 64 | 57 (54) | 0 (0) | 105 (100) | 96 (91) | 9 (9) | 48 (46) | 1 mo | 12 (11) | Study period |
| Fattizzo 2020[27] | Italy: 3/10 to 4/24 | 16 | 77 | 10 (63) | 3 (19) | 13 (81) | 0 (0) | 16 (100) | 2 (13) | NA | 6 (38)[a] | 30 d[a] |
| Kuderer 2020,[11] Rivera 2020[28]: CCC19[b] | USA: 3/17 to 6/26 | 1149 | 71 | 612 (53) | 0 (0) | 1149 (100) | 931 (81)[c] | 218 (19)[c] | 455 (40)[c] | 1 mo | 304 (26) | 30 d |
| Lee 2020[12]: UKCCMP | UK: 3/18 to 4/26 | 800 | 69 | 449 (56) | 96 (12) | 704 (88) | 631 (79) | 169 (21) | 518 (65) | 1 mo | 226 (28) | Hospital discharge |
| Martin-Moro 2020[29] | Spain: 3/9 to 4/17 | 34 | 73 | 19 (56) | 0 (0) | 34 (100) | 0 (0) | 34 (100) | 19 (56) | 6 mo | 11 (32)[a] | 30 d[a] |
| Mehta 2020[30] | USA: 3/18 to 4/8 | 218 | 69 | 127 (58) | 0 (0) | 218 (100) | 164 (75) | 54 (25) | 96 (44) | 1 mo | 61 (28) | Study period |
| Rogado 2020[31] | Spain: 2/1 to 4/7 | 45 | 71 | 30 (67) | 7 (16) | 38 (84) | 45 (100) | 0 (0) | 32 (71) | NA | 19 (42) | Study period |
| Stroppa[32] | Italy: 2/21 to 3/18 | 25 | 72 | 20 (80) | 0 (0) | 25 (100) | 23 (92) | 2 (8) | 12 (48) | NA | 9 (36)[a] | 30 d[a] |
| Garassino 2020[33]: TERAVOLT[d] | Europe: 3/26 to 4/12 | 152 | 68.5 | 110 (72) | 0 (0) | 152 (100) | 152 (100) | 0 (0) | 106 (70) | 1 mo | 60 (39) | Study period |
| Yang 2020[34] | China: 1/13 to 3/18 | 205 | 63 | 96 (47) | 0 (0) | 205 (100) | 183 (89) | 22 (11) | 54 (26) | 1 mo | 40 (20) | Hospital discharge |
| Yarza 2020[35] | Spain: 3/9 to 4/19 | 63 | 66 | 34 (54) | 0 (0) | 63 (100) | 63 (100) | 0 (0) | 61 (97) | 1 mo | 16 (25) | Study period |
| Mixture of outpatient and hospitalized patients or not specified | | | | | | | | | | | | |
| Vuagnat 2020[36] | France: 3/13 to 4/25 | 59 | 58 | 0 (0) | 31 (53) | 28 (47) | 59 (100) | 0 (0) | 52 (88) | 1 mo | 4 (7) | Study period |
| Luo 2020[37] | USA: 3/12 to 4/13 | 69 | 69 | 33 (48) | 27 (39) | 42 (61) | 69 (100) | 0 (0) | NA | NA | 16 (23) | Study period |
| Kabarriti 2020[38] | USA: 3/14 to 4/15 | 107 | 70 | 53 (50) | NA | NA | 103 (96) | 4 (4) | NA | NA | 24 (22) | Study period |
| Assaad 2020[39] | France: 3/1 to 4/25 | 55 | Mean, 64 | 26 (47) | NA | NA | 35 (64) | 20 (36) | 29 (53) | 1 mo | 8 (15) | 30 d |
| Miyashita 2020[40] | USA: 3/1 to 4/6 | 334 | NA | NA | NA | NA | NA | NA | NA | NA | 37 (11) | Study period |

Abbreviations: CCC19, COVID-19 and Cancer Consortium; Heme, hematologic; NA, not available/not reported from the study; TERAVOLT, Thoracic Cancers International COVID-19 Collaboration; UKCCMP, UK Coronavirus Cancer Monitoring Project.

[a]These numbers were obtained directly from the study's corresponding author after 30 days of follow-up.

[b]The study by Rivera et al was an updated publication from the same data set (CCC19) used in the study by Kuderer et al. The key difference was that Rivera and colleagues included more patients and provided publicly available, patient-level data (provided by the study's corresponding author), including the initial COVID-19 severity variable, which allowed for further stratification into hospitalized versus outpatient subgroups. For consistency in study setting, the hospitalized subgroup (moderate-to-severe COVID-19) from Rivera et al was included as a substitute for the study by Kuderer and colleagues. All characteristics in this table are derived from available columns provided for this subgroup.

[c]These numbers were not explicitly provided in the moderate-to-severe subgroup and were estimated from the overall population.

[d]The TERAVOLT study reported hospitalized and nonhospitalized cohort characteristics separately in the article. The data presented here were restricted to the hospitalized cohort. In that study, 52 patients died in hospital, 8 died in the intensive care unit, 3 died at home, and 3 had an unknown location of death. Because the cohort was restricted to inpatients only, only inpatient and intensive care unit deaths (52 + 8 = 60) are reported.

These studies were largely conducted and had representative population from the United States (5 studies), the United Kingdom (3 studies), Spain (3 studies), France (2 studies), Italy (2 studies), China (2 studies), and multiple European sites (1 study). The sample sizes of these studies ranged from 25 to 1149 patients. The median age of patients in all studies ranged from 58 to 77 years. Four studies reported on patients with hematologic malignancies only,[24,25,27,29] whereas others had an admixture of both solid and hematologic malignancies. Among these studies, there was wide variation in the percentage of patients receiving active cancer treatment (usually defined as cancer treatment received in the past 1 month), ranging from 26% to 100%. Although all-cause mortality was 1 of the major outcomes described consistently, the follow-up period and outcome reporting varied among different studies. Some studies defined 14-day or 30-day mortality, whereas others defined mortality during the study period or at hospital discharge. Given the difference in the mortality definitions and patient characteristics, there was wide variation among the mortality rates from 7% to 42%.

Although many studies attempted to assess the association between patient characteristics and mortality, most had a very high risk of bias because of confounding or missing data. Among the 4 studies that included a sample size >200 and had a relatively low risk of bias, commonly reported risk factors on univariable analysis included older age (3 studies), male sex (3 studies), higher number of comorbidity, including hypertension or cardiovascular disease (3 studies), COVID-19 severity score or intensive care unit admission (3 studies), and active or advanced cancer (2 studies) (see Supporting Table 4). Multivariable models from each study were created with different assumptions and parameters and thus could not be directly compared. Nonetheless, there were conflicting data on whether or not recent anticancer therapy (specifically chemotherapy) was harmful.[12,34]

### *Quality Assessment*

Overall, 10 of the 18 studies were found to have low overall bias (Fig. 2).[11,12,24-40] Bias because of missing data was 1 of the major flaws for some studies that lacked appropriate follow-up intervals[27,32] and uniform reporting of mortality period.[31,39] To decrease this bias, we contacted the corresponding authors of all the included studies and requested further clarification and updated mortality reports, if available. A few studies were also found to have bias in the selection of participants by selecting patients only from a specific subgroup, such as those with

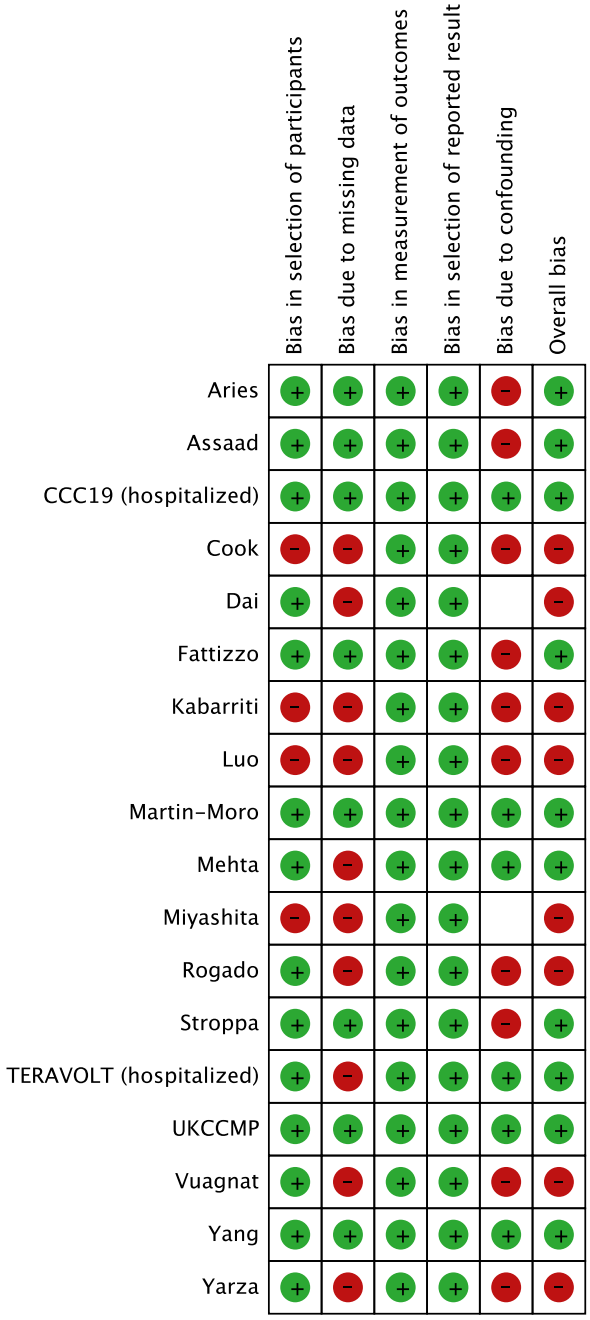



**Figure 2.** This chart illustrates a risk-of-bias assessment of studies that were included in the systematic review. Green circles with plus signs indicate a risk of bias; red circles with minus signs, indicate low risk of bias. CCC19 indicates Coronavirus Disease 2019 (COVID-19) and Cancer Consortium (Kuderer et al[11] and Rivera et al[28]); TERAVOLT, Thoracic Cancers International COVID-19 Collaboration (Garassino et al[33]); UKCCMP, UK Coronavirus Cancer Monitoring Project (Lee et al[12]). Names on the left are lead author names from the remaining studies that were included in the systematic review.[24-27,29-32,34-40]

hematologic malignancies,[29] undergoing radiation treatment,[38] receiving immunotherapy,[37] using *International*

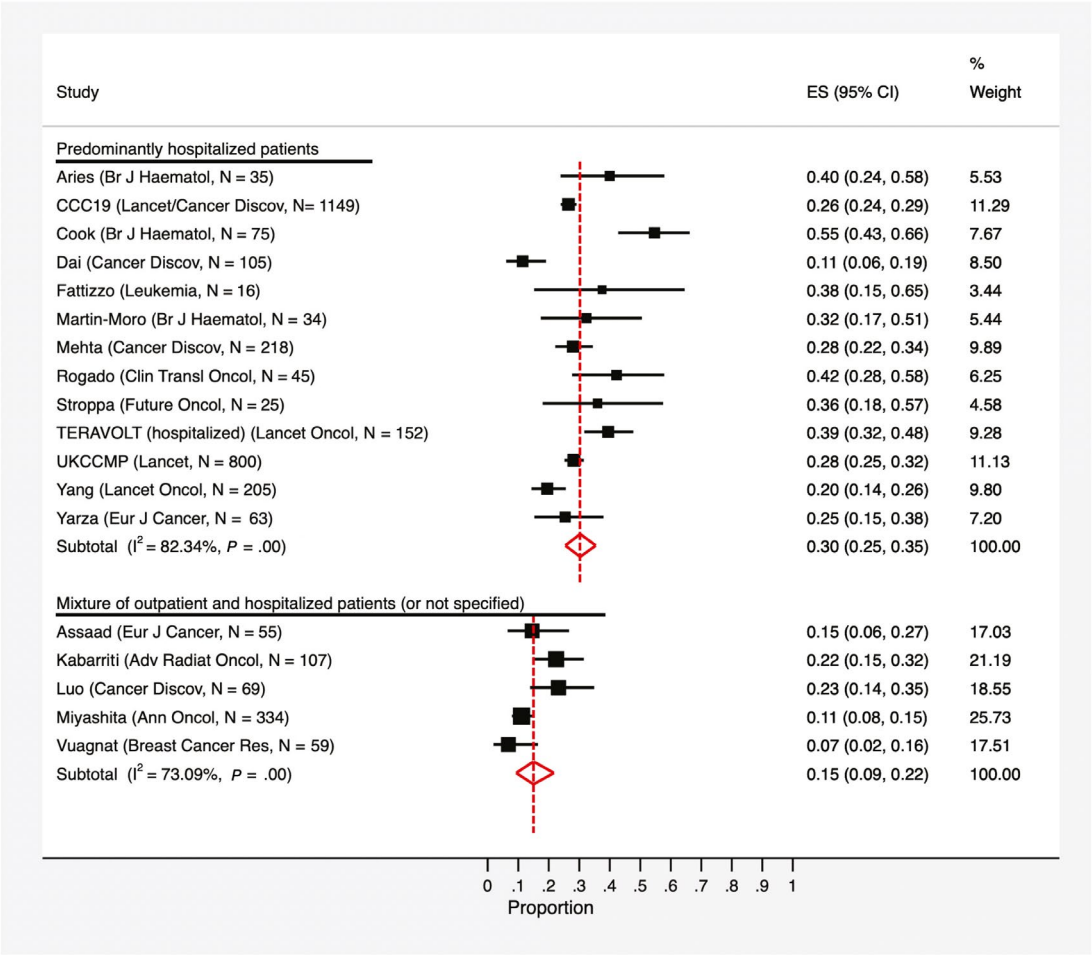



**Figure 3.** A meta-analysis of overall mortality among patients with cancer and coronavirus disease 2019 (COVID-19) (all studies) is illustrated. CCC19 indicates COVID-19 and Cancer Consortium (Kuderer et al[11] and Rivera et al[27]); ES, effect size; TERAVOLT, Thoracic Cancers International COVID-19 Collaboration (Garassino et al[33]); UKCCMP, UK Coronavirus Cancer Monitoring Project (Lee et al[12]). Names on the left are lead author names from the remaining studies that were included in the meta-analysis.[24-27,29-32,34-40]

*Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10) codes only,[40] or missing selection criteria.[25] Most studies had a high bias because of confounding for predictors of mortality given small sample sizes and lack of multiplicity or multivariable adjustment.[24,25,27,31,32,35,36,39] There was asymmetry in the scatter of small studies for hospitalized patients, demonstrating publication bias with under-reporting for smaller studies with decreased mortality (see Supporting Fig. 1).

### *Meta-Analysis*

The 13 studies that included predominantly hospitalized patients formed the core of the meta-analysis (Fig. 3).[11,12,24-40] Among the 2922 patients who had COVID-19 and cancer, the pooled 30-day mortality rate was 30% (95% CI, 25%-35%; $I^2$, 82%). This estimate was significantly different from the 5 studies comprising 624 patients with a mixture of inpatient and outpatient population; those studies had an estimated 30-day mortality rate of 15% (95% CI, 9%-22%; $I^2$, 73%). Because of the extreme differences in patient selection and outcomes, a pooled overall estimate was not performed, and further analysis was only dedicated to the inpatient group.

Among the hospitalized patients, heterogeneity remained high ($I^2$, 82%). We first examined cancer type (solid vs hematologic) as a prespecified moderator. For this analysis, we separated the 2 studies that reported cancer type-specific mortalities into the appropriate subgroups.[12,30] In total, 2539 patients from 9 studies formed the solid tumor subgroup (range, 81%-100%); in contrast, 383 patients from 6 studies formed the hematologic

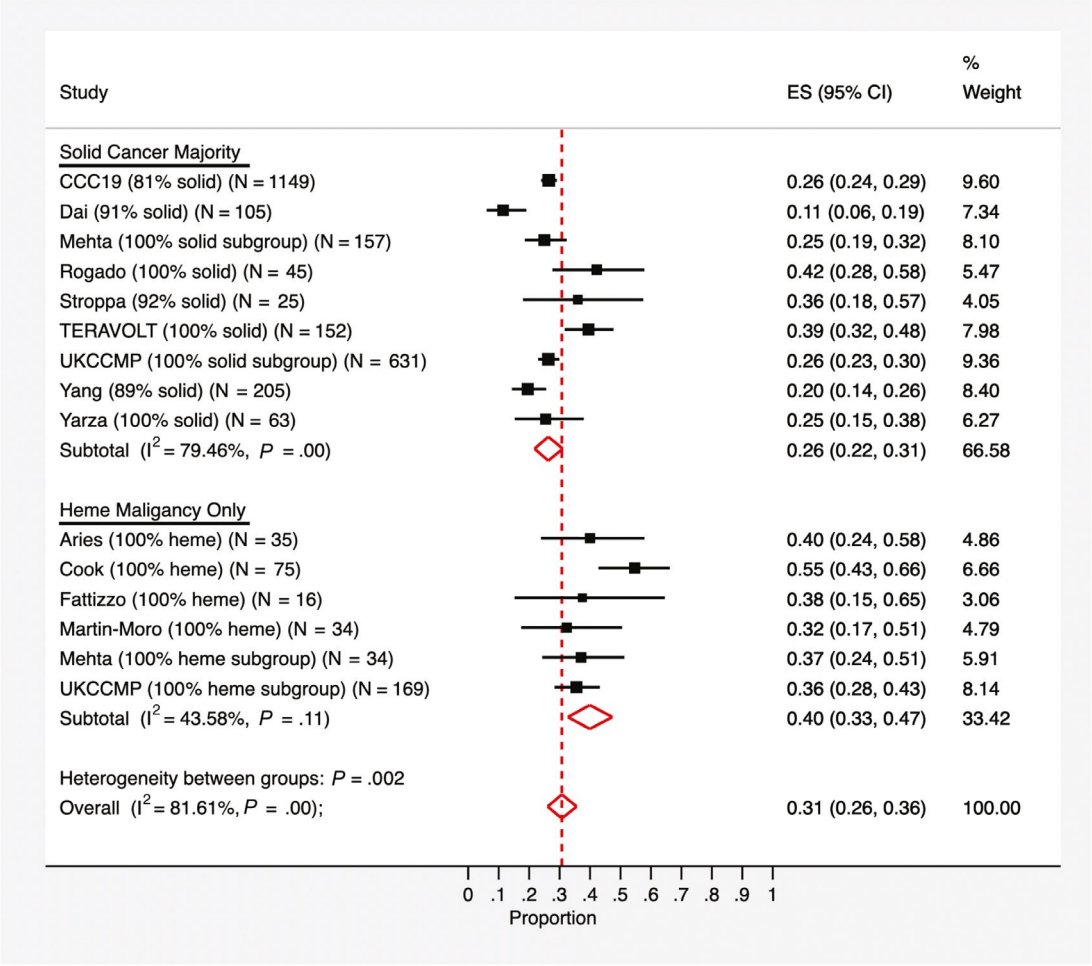
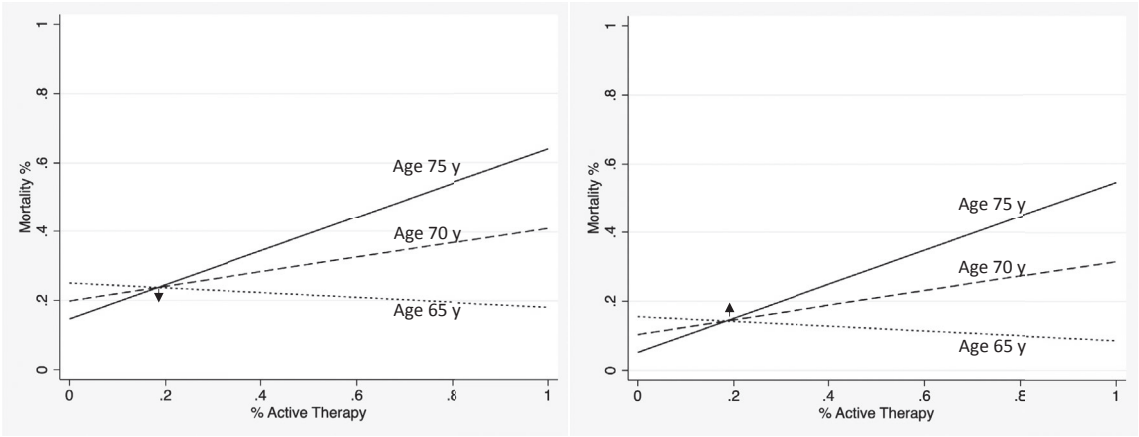



**Figure 4.** A subgroup analysis of overall mortality among hospitalized patients with cancer and coronavirus disease 2019 (COVID-19) (hospitalized only) is illustrated. CCC19 indicates COVID-19 and Cancer Consortium (Kuderer et al[11] and Rivera et al[28]); ES, effect size; TERAVOLT, Thoracic Cancers International COVID-19 Collaboration (Garassino et al[33]); UKCCMP, UK Coronavirus Cancer Monitoring Project (Lee et al[12]). Names on the left are lead author names from the remaining studies that were included in the subgroup analysis.[24-27,29-33,34,35]

malignancy subgroup (100%). The pooled 30-day mortality rate was significantly higher in the hematologic subgroup (40%; 95% CI, 33%-47%) compared with the solid tumor subgroup (26%; 95% CI, 22%-31%) (Fig. 4).[11,12,24-35] Nonetheless, residual heterogeneity remained high, and patients in the hematologic subgroup were older and received more active therapy.

To further explore heterogeneity, we performed metaregression on continuous study characteristics in addition to cancer type, including the number of participants, median age, percentage of men, and percentage receiving recent active anticancer therapy. In univariable metaregression, the size of the study was not associated with the effect size (reported mortality percentage) (see Supporting Fig. 2A). In contrast, increasing age, male sex, and a higher proportion receiving recent active treatment were significantly associated with increasing effect size (see Supporting Fig. 2B-D). In multivariable meta-regression of the studies, the model that included the interaction between age and recent active therapy, along with male sex as a separate covariate, resulted in an optimally fitted model with an $R^2$ of 96%. Specifically, the association between a higher mortality rate and a higher percentage receiving active therapy was observed in studies with an older median age, but not in those with a younger median age, whereas male sex remained an independent predictor of a higher mortality rate (Fig. 5). After accounting for these patient-specific characteristics, cancer type was no longer associated with increased mortality.




| Study-Level Variable | Coefficient | *P* | Summary Statistics |
|---|---|---|---|
| Median age (1-year increase) | -0.010 | .203 | $R^2$ = 96.05%<br>tau2 (current) = 0.000212<br>tau2 (null) = 0.00538<br>$I^2$ residual = 12.45% |
| Active therapy (1% increase) | -3.719 | .002 | |
| Interaction term | 0.056 | .001 | **Interpretation:** older age and male sex are associated with mortality, whereas the effect of active therapy depends on age (significant interaction) |
| Male (1% increase) | 0.473 | .024 | |
| Constant term | 0.638 | .238 | |

**Figure 5.** Multivariable meta-regression for mortality among hospitalized patients with cancer and coronavirus disease 2019 (COVID-19) is illustrated.

## DISCUSSION

In this systematic review and meta-analysis, we observed that overall mortality was 30% among hospitalized patients who had a confirmed cancer diagnosis and COVID-19. Comparing these with the estimates of mortality in the general hospitalized population (range, 21%-22%),[41,42] we noted that hospitalized patients with cancer appear to have a higher risk of death. These findings have important implications for health care providers, patients, and policy makers alike as we continue to fight COVID-19 across the globe. Although much discussion has revolved around how the COVID-19 pandemic has disrupted the spectrum of cancer care, including delaying diagnoses and treatment and halting clinical trials, our findings justify the need for continued caution as we aim to successfully navigate our patients through the pandemic.[43]

The science around factors affecting mortality outcomes among patients with cancer who are diagnosed with COVID-19 continues to evolve. There are ongoing debates about what drives increased mortality in patients with cancer and whether this is related to cancer type, cancer treatment, or underlying patient characteristics. As expected, we noted a high degree of heterogeneity between published studies. Through metaregression, we explored the contribution of each of these characteristics at a study level. Indeed, we found that increasing age, male sex, hematologic malignancy (vs solid tumor), and recent anticancer therapy each contributed to the increased mortality reported in the studies and partially explained some of the heterogeneities. This is not surprising, because age and male sex have been consistently reported as significant predictors of mortality in other noncancer cohorts[44,45] as well as cancer cohorts.[11,12,34] Active cancer treatment is possibly related to increased levels of immunosuppression (intrinsic or iatrogenic) and impaired T-cell responses, potentially leading to an increased risk of poor outcomes with COVID-19.[46] This may also explain the higher mortality among patients with hematologic cancers, because these patients often have impaired immune system mechanisms by virtue of their disease process.[24]

Although it is exploratory, the finding that age may have moderated the association between active cancer therapy and observed mortality (along with male

sex as an independent predictor) at a study level is intriguing. Because of the conflicting reports on whether active cancer therapy heightens COVID-19–related mortality,[12,34] cancer centers have adopted differing practices on withholding cancer treatment for those who test positive for the virus. In our current analysis, this significant interaction was specifically limited to age and anticancer therapy. This remains highly exploratory, because we did not have patient-level data from most studies and we did not have the power to adjust for all other covariates, such as individual tumor types or patient comorbidities. However, we encourage future studies that aim to examine the impact of cancer treatment on COVID-19–related mortality to also report potential interactions with age groups in addition to adjusting for common demographic and comorbidity confounders.

Our current study has certain limitations of importance. The mortality reported here was all-cause mortality because the majority of included studies did not differentiate between cancer-related and COVID-related deaths. At an outcome level, our study is limited by reporting of outcomes across various studies done in different study settings, demographic populations, and health systems. This introduces significant heterogeneity in the pooled estimates, the causes of which were explored by conducting multivariable metaregression. Furthermore, our analysis is limited by the risk of bias from selection, missing data, reporting, and publication in individual studies. We used a modified ROBINS-I quality-assessment tool to quantify and report these biases to enable an accurate interpretation of the existing data. On the basis of our observation from the current review, we would like to offer suggestions for future study designs. First, patients with cancer who are treated as outpatients have much lower mortality than those admitted to the hospital with COVID-19; therefore, the health care recruitment setting should be carefully considered to avoid potential selection bias. Second, all studies should strive to report outcomes after a minimum of 30 days or provide detailed information on the follow-up period to adequately quantify a time-to-event analysis. Finally, publication of smaller cohorts with low mortality estimates are encouraged to mitigate the publication bias observed in this review.

In conclusion, we found that the short-term mortality estimate for patients with cancer and COVID-19 remains high at 30%. Significant between-study heterogeneity appeared to be driven by male sex, median patient age, and receipt of active anticancer therapy. We believe that the pooled analysis estimate of the risk of mortality and predictors of mortality in patients with cancer afflicted with COVID-19 remains an essential piece of evidence needed to help mitigate the challenges of the current pandemic.

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## CONFLICT OF INTEREST DISCLOSURES

Nicole M. Kuderer is a former (founding) member of the COVID-19 and Cancer Consortium (CCC19) Steering Committee. Gary H. Lyman reports institutional research funding from Amgen and personal fees from Invitae, Spectrum, Samsung, Beyond Spring, G1 Therapeutics, and Partners, outside the submitted work. The remaining authors made no disclosures.

## AUTHOR CONTRIBUTIONS

**Aakash Desai** designed the study, performed the systematic review, and wrote the article. **Rohit Gupta** and **Shailesh Advani** performed the systematic review and wrote the manuscript. **Lara Ouellete** assisted with the systematic review syntax search. **Nicole M. Kuderer** provided critical revision of the article. **Gary H. Lyman** designed the study and conducted the statistical analysis. **Ang Li** designed the study, performed the systematic review, conducted the statistical analysis, and wrote the article.

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