Relations of Current and Past Cancer with Severe Outcomes among 104,590 Hospitalized COVID-19 Patients: The COVID EHR Cohort at the University of Wisconsin

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ABSTRACT

Background: There is mixed evidence about the relations of current versus past cancer with severe COVID-19 outcomes and how they vary by patient and cancer characteristics.

Methods: Electronic health record data of 104,590 adult hospitalized patients with COVID-19 were obtained from 21 United States health systems from February 2020 through September 2021. In-hospital mortality and ICU admission were predicted from current and past cancer diagnoses. Moderation by patient characteristics, vaccination status, cancer type, and year of the pandemic was examined.

Results: 6.8% of the patients had current ($n = 7{,}141$) and 6.5% had past ($n = 6{,}749$) cancer diagnoses. Current cancer predicted both severe outcomes but past cancer did not; adjusted odds ratios (aOR) for mortality were 1.58 [95% confidence interval (CI), 1.46–1.70] and 1.04 (95% CI, 0.96–1.13), respectively. Mortality rates

decreased over the pandemic but the incremental risk of current cancer persisted, with the increment being larger among younger vs. older patients. Prior COVID-19 vaccination reduced mortality generally and among those with current cancer (aOR, 0.69; 95% CI, 0.53–0.90).

Conclusions: Current cancer, especially among younger patients, posed a substantially increased risk for death and ICU admission among patients with COVID-19; prior COVID-19 vaccination mitigated the risk associated with current cancer. Past history of cancer was not associated with higher risks for severe COVID-19 outcomes for most cancer types.

Impact: This study clarifies the characteristics that modify the risk associated with cancer on severe COVID-19 outcomes across the first 20 months of the COVID-19 pandemic.

See related commentary by Egan et al., p. 3

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Introduction

The American Association for Cancer Research recently issued a report summarizing the accumulated evidence on the impact of COVID-19 on patients with cancer (1). Some two years since the World Health Organization declared the COVID-19 outbreak a pandemic, research has firmly established that individuals with cancer, especially those with hematologic cancer, are more susceptible to SARS-CoV-2 infection and have a higher probability of severe disease, including mortality, from COVID-19 (1). Patients with cancer may be particularly vulnerable to severe COVID-19 disease because they are often immunocompromised and, compared with the general population, tend to be older and have coexisting medical conditions. Questions remain regarding which patients with cancer are especially likely to develop severe COVID-19 and whether the association of COVID-19 and cancer has remained consistent across the span of the pandemic.

Since early in the pandemic consortia have been assembled to examine data from patients with cancer infected with COVID-19 (2). Such studies that are solely comprised of dually affected patients with both COVID-19 and cancer have tended to find that older age is associated with increased mortality (3, 4). However, studies, including patients with COVID-19, both with and without cancer, have shown that cancer is *less* strongly associated with mortality in older patients (5, 6). These findings encourage further analysis of the relation between age and the severity of COVID-19 outcomes in populations of patients with and without cancer.

Studies have also demonstrated that men dually affected with COVID-19 and cancer have increased mortality compared with dually affected women (2–4). This is consistent with the findings that men typically have greater mortality than women from COVID-19 (7), from cancer (8), and overall (7, 9). To our knowledge, there are no studies that have compared the mortality rates of men with cancer to men without cancer (10), which would provide information about whether there is an incremental effect of cancer on mortality in men with COVID-19.

Most of the studies of cancer and COVID-19 have focused on the approximately 1.9 million patients with a current cancer diagnosis in the United States (11). However, individuals with a history of cancer (16.9 million in 2019; ref. 12) exceed current patients with cancer by nearly 10-fold. The size of the population and the importance of cancer survivorship argues for inclusion of such patients in analyses of COVID-19 outcomes. Advances in early detection and treatment of cancer suggest that the numbers of cancer survivors will continue to grow (11). It is vital to determine the risk of severe COVID-19 outcomes among this large and growing population. This population tends to have more severe outcomes from influenza (13) but little is known about their risk for severe COVID-19 outcomes (4, 14–16). Two studies based on cancer registries in Italy (15) and Belgium (16) reached opposite conclusions. Among individuals in an Italian cancer registry study infected with SARS-CoV-2, the 447 individuals with a history of cancer were more likely to die than the 4,094 without a history of cancer (15). In contrast, a Belgian cancer registry study

observed no excess deaths occurring from January 2020 through June 2020 among those with a history of cancer compared with the general population of Belgium (16).

The primary aim of this retrospective cohort study is to examine the relations of current and past cancer with mortality and ICU admission among 104,590 patients hospitalized with COVID-19 from February 1, 2020 to September 30, 2021. A secondary aim is to determine whether the magnitude of these relations vary by patient characteristics (sex, age, race, ethnicity, and smoking status), vaccination status, cancer type, and year of the pandemic.

Materials and Methods

Study design

The COVID EHR Cohort at the University of Wisconsin (CEC-UW) is a retrospective cohort study supported by the National Cancer Institute (ClinicalTrials.gov NCT04506528). Health systems affiliated with the NCI Cancer Center Cessation Initiative (17) and other health systems were invited to contribute data; 21 health systems from around the United States agreed to participate (Supplementary Fig. S1). These systems performed periodic data extractions (initially monthly and later quarterly) using customized extraction code, which local IT professionals altered to accommodate system-specific EHR features. EHR data were transferred to a central coordinating site at the University of Wisconsin for harmonization and merging. Each data extraction captured data on new patients meeting inclusion criteria and follow-up data on existing cohort members. COVID-19 cases were patients meeting at least one of four criteria: (i) an ICD-10-CM diagnosis of COVID-19 (U07.1), (ii) a COVID-19 PCR test positive result, (iii) a COVID-19 antibody test positive result, (iv) a COVID-19 antigen test positive result. Participating health systems provided selected data elements from the EHR of all patients with COVID-19 encountered during the study period (February 1, 2020 to September 30, 2021). Harmonization, merging, and data analysis occurred September 30, 2021 through March 24, 2022. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study population

The current analyses use data extracted from February 1, 2020 to September 30, 2021 and include individuals at least 18 years of age who had at least one pre-COVID-19 diagnosis contact with the healthcare system. The analysis sample comprised those who were: (i) hospitalized for at least 24 hours due to a COVID-19 infection or (ii) if hospitalized for a COVID-19 infection for less than 24 hours, died or were transferred to the ICU during the hospitalization. Hospitalization for COVID-19 was determined by a positive PCR test within a 14-day window, spanning seven days pre-admission to seven days post-admission and/or by an ICD-10-CM diagnosis of COVID-19 at any point during the index hospitalization. This analysis sample comprised 104,590 hospitalized adult patients.

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Outcomes

Outcomes for hospitalized patients were assessed either during or at the termination of a patient's hospitalization for COVID-19, which occurred at either discharge or death. Only data from a patient's initial COVID-19 hospitalization (index admission) were used in analyses. Patients with an unresolved hospitalization at the time of the most recent data extraction were not included in analyses. Outcomes occurring post-discharge and care or outcomes occurring at nonparticipating health systems were not captured. The primary outcomes were in-hospital mortality and ICU admission.

Non-outcome variables

Patients were characterized with regard to sex, age, race, ethnicity, insurance status, body mass index (BMI; Supplementary Text S1), smoking status, and weighted Elixhauser comorbidity index (ref. 18; excluding cancer) with a 5-year look back (i.e., a 5-year retrospective period in the patient's medical record; Supplementary Text S2). These were used as model covariates in adjusted multivariable models (covariate categorizations are given in **Table 1**). Patients whose hospitalization occurred on or after December 11, 2020, when the FDA issued the first vaccine emergency use authorization (19) were characterized with regard to vaccination status (Supplementary Text S3).

Exposures

The primary exposures were any ICD-10 cancer diagnosis recorded during the index COVID-19 hospitalization (current cancer) and past history of any ICD-10 cancer diagnosis in the patient's EHR (documented at any time before the COVID-19 diagnosis). Patients with current cancer, regardless of their past cancer history, were categorized in the "current cancer" group. Current cancer was based on being assigned an ICD-10 diagnosis of cancer on admission, at discharge, or during the index hospitalization. Patients categorized as having "past cancer" had to have a cancer diagnosis before the index hospitalization but no cancer diagnosis during that hospitalization. Past cancer was based on a thorough look-back of the entire electronic health record of each patient for ICD-10 diagnoses of cancer made on admission, at discharge, or during a particular medical encounter (usually a hospitalization).

Current and past cancer diagnoses were broken down by cancer type: Solid tumor without metastasis, hematologic, and metastatic. More specific cancer types were also examined given sufficient numbers of cases (>500): That is, lymphomas, leukemias, lung/bronchus, digestive system (including colon, rectum, and pancreas), breast, and prostate cancer.

Statistical analysis

The overall prevalence of any current and past cancer diagnosis and the prevalence by patient level characteristics were estimated. Separate models were fit for the two COVID-19 outcomes (mortality and ICU admission) with the exposure of interest being cancer diagnosis [current, past (no current), with neither current nor past cancer history as the reference category]. Multilevel generalized linear models with a logit link were used to account for patients clustered within the 21 health systems. Unadjusted models were fit with the three-level cancer diagnosis variable predicting each of the two COVID-19 outcomes. Adjusted models were fit that included the following covariates: sex, age, race, ethnicity, insurance status, BMI, smoking status, and comorbidity index. Additional models were fit to test whether the relations between cancer diagnosis and the two COVID-19 outcomes were moderated by sex, age group, race, ethnicity, smoking status, vaccination status, or year of the pandemic (February 1, 2020, through December 31, 2020 vs. January 1, 2020, through September 31, 2021), before and after covariate adjustment. Each moderator and outcome combination was tested via an interaction term between the three-level cancer diagnosis and each moderator as a predictor of each outcome. There were limited missing data for the primary outcome and exposure measures; patients with missing values on most covariates were included in the statistical models (**Table 1**). Analyses were conducted with SPSS, version 27 (20). Statistical significance was defined as $P < 0.0125$, (i.e., 0.05/4) to account for the inclusion of two exposures and two main outcomes.

Data availability

The existing Data Transfer and Use Agreements negotiated with each of the participating health systems preclude the University of Wisconsin from sharing these data with any entity at this time. Information Management Services, Inc. (IMS), under contract from the National Cancer Institute (NCI) is responsible for housing the final CEC-UW data. A small number of health systems have put limits on the extent of data sharing. Data from most health systems will eventually be made available to approved researchers, who are to be determined by NCI and/or IMS.

Results

Prevalence of cancer and characteristics of the inpatient sample

Of the 104,590 adult inpatients with COVID-19, 7,141 (6.8%) had a current diagnosis of cancer, and 6,749 (6.5%) had a pre-existing (without current) diagnosis of cancer in their EHR (**Table 1**). Having a current or past cancer diagnosis was more common among inpatients who were older than 65 years of age, White, underweight, current or former smokers, affected with many comorbid conditions, and recipients of Medicare. A current cancer diagnosis was more common among men and those residing in the Western United States (**Table 1**).

Current and past cancer and severe outcomes of COVID-19

COVID-19 in patients with a current cancer diagnosis were significantly more likely to die [14.6% v 9.2%, adjusted odds ratio (aOR), 1.58; 95% confidence interval (CI), 1.46–1.70] and be admitted to the ICU (24.7% vs. 19.9%; aOR, 1.24; 95% CI, 1.17–1.32) than were those without any current or past cancer history (**Table 2**). In contrast, COVID-19 in patients with a past cancer diagnosis were not more likely to die (12.3% vs. 9.2%; aOR, 1.04; 95% CI, 0.96–1.13) or be admitted to the ICU (22.0% vs. 19.9%; aOR, 0.98; 95% CI, 0.92–1.05) than those without a history of cancer (**Table 2**).

Cancer type and severe outcomes of COVID-19

Of the seven types of cancer examined (leukemia, multiple myeloma, lymphoma, prostate, breast, lung/bronchus, and digestive), all except cancer of the prostate were statistically significantly associated with higher aORs of in-hospital mortality compared with those with no current or past cancer history. Stronger adjusted associations were noted for metastatic and hematologic cancers relative to non-metastatic solid tumor cancers (**Fig. 1A**). With regard to past cancer, hematologic cancer was unique in being related to greater aORs of mortality relative to nondiagnosed patients and, in addition, hematologic cancer was associated with greater aORs of mortality than was the comparison condition of non-metastatic solid tumor cancer (**Fig. 1B**). Unadjusted estimates are presented in Supplementary Figs. S2A and S2B.

Table 1. Demographic characteristics of the CEC-UW COVID-19 inpatients ages 18+ overall and by cancer diagnosis.[a,b]

Characteristic	All inpatients N = 104,590 (100%)	Cancer diagnosis			Cramer's V[d]
		None N = 90,700 (86.7%)	Past[c] N = 6,749 (6.5%)	Current N = 7,141 (6.8%)	
Sex					0.029
Female	52,701 (50.4)	46,090 (87.5)	3,400 (6.5)	3,211 (6.1)	
Male	51,887 (49.6)	44,608 (86.0)	3,349 (6.5)	3,930 (7.6)	
Other	2 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	
Age					0.114
18–29	6,360 (6.1)	6,146 (96.6)	64 (1.0)	150 (2.4)	
30–39	8,520 (8.2)	8,159 (95.7)	150 (1.8)	219 (2.6)	
40–49	10,602 (10.1)	9,803 (92.5)	330 (3.1)	469 (4.4)	
50–64	29,032 (27.8)	25,563 (88.1)	1,492 (5.1)	1,977 (6.8)	
65–74	21,795 (20.8)	17,959 (82.4)	1,886 (8.7)	1,950 (8.9)	
75–84	17,428 (16.7)	13,986 (80.3)	1,808 (10.4)	1,634 (9.4)	
85+	10,845 (10.4)	9,084 (83.8)	1,019 (9.4)	742 (6.8)	
Race					0.055
American Indian or Alaska Native	389 (0.4)	339 (87.1)	20 (5.1)	30 (7.7)	
Asian	3,047 (2.9)	2,732 (89.7)	132 (4.3)	183 (6.0)	
Black or African American	25,073 (24.0)	21,891 (87.3)	1,717 (6.8)	1,465 (5.8)	
Native Hawaiian or Pacific Islander	484 (0.5)	435 (89.9)	21 (4.3)	28 (5.8)	
White	59,362 (56.8)	50,406 (84.9)	4,261 (7.2)	4,695 (7.9)	
Other or Not Specified	14,116 (13.5)	12,996 (92.1)	528 (3.7)	592 (4.2)	
More than one	366 (0.3)	323 (88.3)	21 (5.7)	22 (6.0)	
Missing	1,753 (1.7)	1,578 (90.0)	49 (2.8)	126 (7.2)	
Ethnicity					0.050
Hispanic or Latino	16,661 (15.9)	15,286 (91.7)	619 (3.7)	756 (4.5)	
Not Hispanic or Latino	84,827 (81.1)	75,592 (85.6)	6,005 (7.1)	6,230 (7.3)	
Missing	3,102 (3.0)	2,822 (91.0)	125 (4.0)	155 (5.0)	
Body Mass Index					0.063
Underweight (<18.5)	3,042 (2.9)	2,462 (80.9)	251 (8.3)	329 (10.8)	
Healthy Weight (18.5 to <25)	23,483 (22.7)	19,419 (82.7)	1,807 (7.7)	2,257 (9.6)	
Overweight (25 to <30)	29,940 (28.9)	25,848 (86.3)	1,957 (6.5)	2,135 (7.1)	
Obese (30 to <40)	35,095 (33.9)	31,044 (88.5)	2,125 (6.1)	1,926 (5.5)	
Severely Obese (40 or higher)	11,997 (11.6)	10,955 (91.3)	584 (4.9)	458 (6.4)	
Smoking status					
Never smoker	57,454 (54.9)	51,106 (89.0)	3,038 (5.3)	3,310 (5.8)	0.079
Current/former smoker	40,865 (39.1)	33,647 (82.3)	3,602 (8.8)	3,616 (8.8)	
Missing	6,271 (6.0)	5,947 (94.8)	109 (1.7)	215 (3.4)	
Weighted Elixhauser Comorbidity Index[e]					
≤0	59,324 (56.7)	54,809 (92.4)	1,845 (3.1)	2,670 (4.5)	0.149
1–10	24,297 (23.2)	20,170 (83.0)	2,067 (8.5)	2,060 (8.5)	
11–56	20,969 (20.0)	15,721 (75.0)	2,837 (13.5)	2,411 (11.5)	
Region					
Northeast	42,882 (41.0)	37,904 (88.4)	2,357 (5.5)	2,621 (6.1)	0.040
Midwest	28,739 (27.5)	24,441 (85.0)	2,286 (8.0)	2,012 (7.0)	
South	27,857 (26.6)	24,139 (86.7)	1,753 (6.3)	1,965 (7.1)	
West	5,098 (4.9)	4,204 (82.5)	353 (6.9)	541 (10.6)	
Missing	14 (0.0)	12 (0.0)	0 (0.0)	2 (0.0)	
Insurance Status					
Medicare	55,427 (53.1)	45,728 (82.5)	5,111 (9.2)	4,588 (8.3)	0.099
Medicaid	12,177 (11.6)	11,150 (91.6)	477 (3.9)	550 (4.5)	
Commercial	27,921 (26.7)	25,445 (91.1)	906 (3.2)	1,570 (5.6)	
Uninsured	1,967 (1.9)	1,842 (93.6)	54 (2.7)	71 (3.6)	
Other	7,098 (6.8)	6,535 (92.1)	201 (2.8)	362 (5.1)	

Note: CEC-UW, COVID EHR Cohort at the University of Wisconsin; all Cramer's V values are significant at $P < 0.001$.
[a]The denominator for the percentages for the "all inpatients" column is the total sample size (104,590), the denominators for the three cancer groups are the total number of inpatients in each demographic characteristic category. For example, the 87.5% in the "female" row and "none" column is 46,090/52,701 and indicates that 87.5% of the females in the sample did not have a current or past cancer diagnosis.
[b]See Text S2 in the Supplementary Materials for more information about the Weighted Elixhauser Comorbidity Score.
[c]No current.
[d]Cramer's V is a measure of association between nominal variables (Harald, C. 1946. Mathematical Methods of Statistics. Princeton: Princeton University Press).
[e]Excluding cancer groupings.

Table 2. Associations of current and past cancer diagnosis with hospital outcomes in CEC-UW–hospitalized patients 18 years or older.

Cancer History	Outcome Mortality, *N* (%)	Unadjusted			Adjusted[b]		
		OR	95% CI	*P*	OR	95% CI	*P*
No Current or Past (Ref)	8,384 (9.2)	1.00	—	—	1.00	—	—
Current	1,040 (14.6)	1.91	1.78–2.06	<0.001	1.58	1.46–1.70	<0.001
Past[a] (No Current)	829 (12.3)	1.44	1.34–1.56	<0.001	1.04	0.96–1.13	0.36
	ICU Admission, *N* (%)	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
No Current or Past (Ref)	18,063 (19.9)	1.00	—	—	1.00	—	—
Current	1,763 (24.7)	1.31	1.24–1.39	<0.001	1.24	1.17–1.32	<0.001
Past[a] (No Current)	1,482 (22.0)	1.05	0.99–1.12	0.124	0.98	0.92–1.05	0.579

Note: CEC-UW, COVID EHR Cohort at the University of Wisconsin; OR, odds ratio; CI, 95% confidence interval; ICU, admission to intensive care unit.
[a]6,749 of 104,590 inpatients (6.5%) had a history of past (with no current) cancer in their electronic health record, of these 1,705 (25.3%) occurred in the past year, 5,169 (76.6%) occurred in the past five years, and 1,580 (23.4%) occurred more than five years before their index COVID-19 hospitalization.
[b]Adjusted for sex, age, race, ethnicity, BMI, smoking status, insurance status, and past 5-year comorbidity score. Covariate categorizations are given in **Table 1**.

Differences in the relations between cancer and severe outcomes of COVID-19 by vaccination status, pandemic year, and age group

Tests of differential relations between cancer and severe COVID-19 outcomes for seven potential moderators (sex, age group, race, ethnicity, smoking status, vaccination status, and pandemic year) are presented in Supplementary Table S1A and S1B. Of particular interest was whether the outcomes differed by vaccination status, year of the pandemic, and age group. A prior history of vaccination was associated with significantly decreased odds (Supplementary Table S2) and rates (**Fig. 2A** and **B**) of death and ICU admission for patients both with and without cancer. For example, in models stratified by cancer status the aORs of the association between vaccination status and mortality were 0.53 (95% CI, 0.46–0.61) among inpatients with no cancer history, 0.45

(95% CI, 0.32–0.63) among those with past cancer, and 0.69 (95% CI, 0.53–0.90) among those with current cancer. These decreased risks for patients with a prior history of vaccination did not vary as a function of cancer history [i.e., current, past (but not current), and no cancer history; *p*s > 0.08, Supplementary Table S1A and S1B].

There were also no statistically significant differences in the relations of cancer with severe COVID-19 outcomes as a function of the year of the pandemic (*p*s > 0.38, Supplementary Table S1A–S1B). Supplementary Table S3 and **Fig. 2C** and **D** show that the levels of mortality and ICU admission decreased similarly in 2020 and 2021 for patients with and without cancer.

The relations of cancer with severe COVID-19 outcomes did not significantly vary as a function of sex, race, ethnicity, or smoking status (Supplementary Table S1A and S1B). In contrast, age group did yield
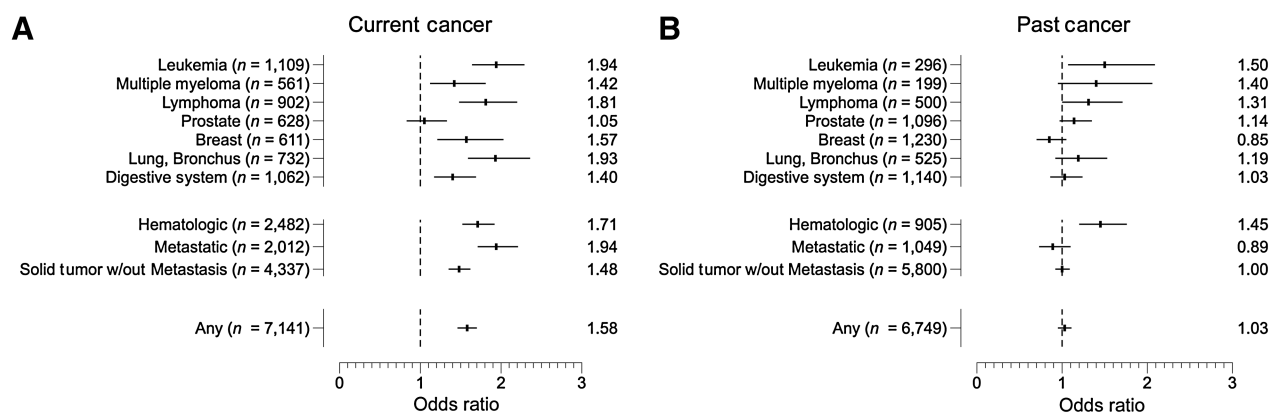
Figure 1.
Adjusted odds ratios (and 95% confidence intervals) of the associations (relative to no cancer, current or past) of specific current cancers (top **A**), current cancer types (middle **A**), specific past cancers (top **B**), and past cancer types (middle **B**) with in-hospital mortality among 104,590 CEC-UW cohort inpatients with COVID-19. Odds ratio point estimates are presented alongside the right of each panel. Note: There was a significantly greater odds of mortality associated with current hematologic (OR, 1.18; 95% CI, 1.02, 1.37) and metastatic (OR, 1.44; 95% CI, 1.21–1.70) cancers relative to current solid non-metastatic cancer (middle **A**), and a significantly greater odds of mortality associated with past hematologic (OR, 1.38; 95% CI, 1.22–1.58) relative to past solid non-metastatic cancer (middle **B**). Ns represent the number of patients with the specific cancer or cancer group within the specified time frame (current or past). Cancer types were created by combining any positive diagnosis in either of the three categories of hematologic, metastatic, and solid tumors without metastasis together into a single binary composite. Hematologic cancer was composed of 13 specific cancers (ICD-10-CM codes C81-C88, C90-C95), metastatic cancer was composed of four specific cancers (ICD-10-CM codes C77-C80), and solid tumor without metastasis was composed of 67 specific cancers (ICD-10 codes C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C75). The sum of the cancer types exceed the number of patients with any cancer because some patients had more than one type of cancer. Odds ratios were adjusted for sex, age, race, ethnicity, BMI, smoking status, insurance status, and past 5-year comorbidity score. See Supplementray Fig. S2 for unadjusted estimates. CEC-UW, COVID EHR Cohort at the University of Wisconsin.
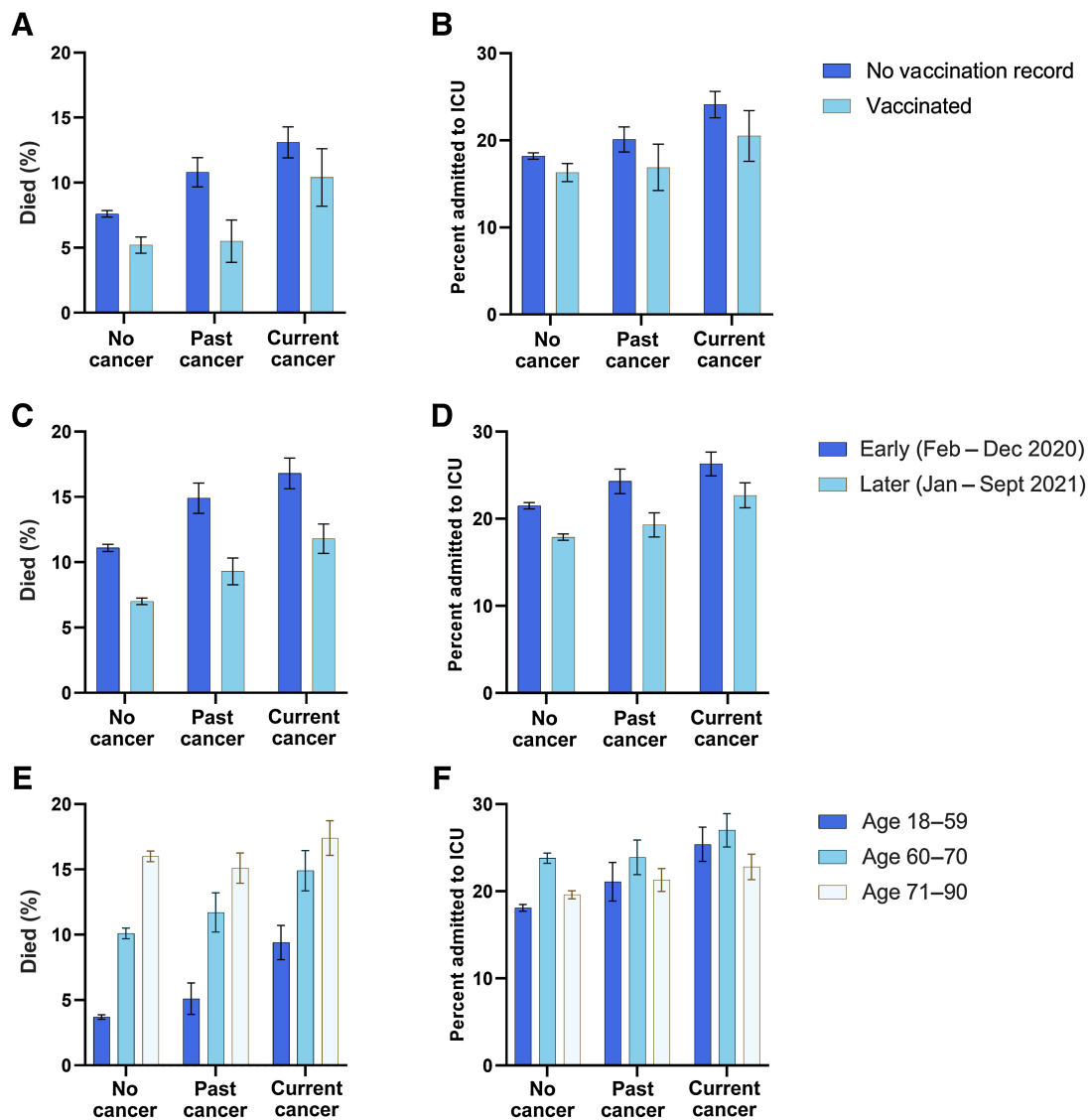
Figure 2.
Percentage (and 95% confidence intervals) of severe outcomes among CEC-UW cohort inpatients with COVID-19 with no (current or past) cancer, past cancer, and current cancer by vaccination status (**A** and **B**), pandemic year (**C** and **D**), and age group (**E** and **F**). Note: Vaccination status analyses were conducted among 54,983 CEC-UW cohort inpatients with COVID-19 who were hospitalized on or after December 11, 2020 when the first SARS-CoV-2 vaccines became available. "Vaccinated" was defined as receipt of at least one vaccine dose before the index hospital admission date, 67.3% had received at least two doses of Pfizer or Moderna or one dose of Janssen. The sample sizes for earlier and later in the pandemic were 57,649 and 46,941, respectively. The sample size for the age group analyses was 104,590. See Supplementary Text S4 for the rationale for the use of these three age groups in lieu of the seven shown in **Table 1**. The age of individuals greater than 90 years of age were recoded as 90. CEC-UW, COVID EHR Cohort at the University of Wisconsin.

statistically significant moderation effects (Supplementary Table S1A and S1B, **Table 3** and **Fig. 2E** and **F**). The magnitude of the relations between current cancer status and mortality and ICU admission was diminished in older versus younger age groups. For example, the aORs of the association between current cancer and mortality were 2.62 (95% CI, 2.20–3.12) among inpatients 18 to 59 years of age, 1.82 (95% CI, 1.59–2.09) among those 60–70 years of age, and 1.26 (95% CI, 1.14–1.40) among those 71 years and older (**Table 3**). This age pattern did not seem to be due to different types of cancer presenting in the younger inpatients; the relative distributions of the specific cancers did not appear to differ across the three age groups (Supplementary Table S4). As expected, the three age groups differed substantially in

other mortality-relevant comorbid conditions in the past five years (Supplementary Table S5).

Sensitivity analyses

Two sensitivity analyses were conducted. First, we ascertained whether including the 20% of inpatients in the sample who did not have a positive PCR test (but did have an ICD-10 COVID-19 diagnosis) may have obscured the findings. Supplementary Table S6 shows that the findings with the full sample were highly similar to the sample that had a positive PCR test. Second, we tested whether the findings for past cancer were altered when omitting data from those patients with recent past cancer (1,705 had an ICD-10 cancer diagnosis in the past

Table 3. Associations of current and past cancer diagnosis with mortality and ICU admission in CEC-UW hospitalized patients in three different age groups.[a]

Age, Cancer History	Outcome Mortality, N (%)	Unadjusted			Adjusted[b]		
		OR	95% CI	P	OR	95% CI	P
18–59 Years							
No Current or Past (Ref)	1,495 (3.7)	1.00	—	—	1.00	—	—
Current	180 (9.4)	2.94	2.49–3.37	< 0.001	2.62	2.20–3.12	< 0.001
Past (No Current)	66 (5.1)	1.45	1.12–1.87	0.005	1.05	0.80–1.36	0.182
60–70 Years							
No Current or Past (Ref)	2,092 (10.1)	1.00	—	—	1.00	—	—
Current	305 (14.9)	1.69	1.48–1.93	<0.001	1.82	1.59–2.09	<0.001
Past (No Current)	207 (11.7)	1.23	1.05–1.43	0.010	1.20	1.02–1.40	0.026
71–90+ Years							
No Current or Past (Ref)	4,797 (16.0)	1.00	—	—	1.00	—	—
Current	555 (17.4)	1.27	1.15–1.40	<0.001	1.26	1.14–1.40	<0.001
Past[a] (No Current)	556 (15.1)	0.98	0.89–1.08	0.68	0.95	0.86–1.05	0.313

Age, Cancer History	Outcome ICU, N (%)	Unadjusted			Adjusted[b]		
		OR	95% CI	P	OR	95% CI	P
18–59 Years							
No Current or Past (Ref)	7,260 (18.1)	1.00	—	—	1.00	—	—
Current	484 (25.4)	1.49	1.34–1.67	<0.001	1.37	1.22–1.53	<0.001
Past (No Current)	274 (21.1)	1.12	0.98–1.29	0.095	0.98	0.85–1.13	0.746
60–70 Years							
No Current or Past (Ref.)	4,919 (23.8)	1.00	—	—	1.00	—	—
Current	551 (27.0)	1.17	1.05–1.30	0 0.004	1.20	1.08–1.34	0.001
Past (No Current)	423 (23.9)	0.93	0.82–1.04	0.191	0.93	0.82–1.04	0.200
71–90+ Years							
No Current or Past (Ref.)	5,884 (19.6)	1.00	—	—	1.00	—	—
Current	728 (22.8)	1.19	1.09–1.31	<0.001	1.16	1.06–1.27	0.002
Past (No Current)	785 (21.3)	1.00	0.92–1.09	0.933	1.00	0.91–1.09	0.936

Note: Tests of interactions for mortality, unadjusted $F (4, 104,581) = 20,784$, $P < 0.001$; adjusted $F (4, 103,523) = 15,589$, $P < 0.001$.
for ICU admission, unadjusted $F (4, 104,580) = 5,028$, $P < 0.001$; adjusted $F (4, 103,522) = 5,282$, $P < 0.001$.
Abbreviations: CEC-UW, COVID EHR Cohort at the University of Wisconsin; OR, odds ratio; ICU, admission to intensive care unit.
[a]See Text S4 for the rationale for the use of these three age groups in lieu of the seven shown in **Table 1**.
[b]Adjusted for sex, continuous age, race, ethnicity, BMI, smoking status, insurance status, and past 5-year comorbidity score; covariate categorizations are given in **Table 1**.

year). Supplementary Table S7 shows that the results were nearly identical to the **Table 2** results that included these patients.

Discussion

This study comprised 104,590 adult COVID-19 patients hospitalized from February 1, 2020 to September 30, 2021, including 7,141 (6.8%) with a current diagnosis of cancer, and 6,749 (6.5%), who had a history of cancer but no current cancer diagnosis (past cancer). Compared with patients without a history of cancer, those with a current cancer diagnosis had a 24% increased odds of requiring intensive care and a 58% increased odds of in-hospital mortality. This robust effect of current cancer on severe outcomes among patients with COVID-19 is consistent with prior research (21, 22).

Access to extensive historical diagnostic data, not available in the largest US COVID-19 EHR cohort (22, 23), allowed for an examination of the relations of a past cancer diagnosis with severe COVID-19 outcomes. A past history of cancer was not significantly associated with severe outcomes in this large COVID-19 sample even though past cancer was associated with heightened levels of medical comorbidities (**Table 1**). The extensive diagnostic data in this EHR study also made it possible to estimate the associations

between past cancer and severe COVID-19 outcomes after taking into account medical comorbidities and other potential confounders. Before adjustment, there was a significant and substantial association between past cancer and mortality (**Table 2** and Supplementary Fig. S2B) that was diminished and no longer statistically significant after adjustment (**Table 2** and **Fig. 1B**). The two previous studies that used data from national cancer registries were only able to adjust for age and sex (15, 16). The present study illustrates the importance of statistically controlling for alternate links between cancer and severe COVID-19 outcomes to better home in on a potential cancer-specific effect.

This is the only study, to our knowledge, that has systematically compared the incremental risk of current and past cancer on severe outcomes among subpopulations of patients with COVID-19. Data from registries of patients with both cancer and COVID-19 are useful, but they cannot address the incremental risk for adverse outcomes in those with cancer compared with cancer-free patients with COVID-19. Identifying cancer subpopulations at heightened incremental COVID-19 risk may be useful in making decisions about COVID-19 treatment and prevention interventions. The risk patterns associated with current and past cancer appeared to be fairly consistent across sex, age, race, ethnicity, and smoking status

(Supplementary Table S1A and S1B). For example, risk of severe cancer outcomes did not differ substantially across men and women with current or past cancer despite the fact that men in general (regardless of cancer status) are more likely than women to experience adverse COVID-19 outcomes (7).

Subpopulations defined by age showed differential associations between cancer status and adverse COVID-19 outcomes. As observed in some prior research (5, 6), there were much stronger associations between current cancer and adverse outcomes among younger patients compared with older patients, which is a well-known phenomenon in the field of insurance medicine (24). Although older patients were more likely to have current cancer than younger patients (Supplementary Table S4) they were also more likely to be affected by other serious medical conditions, such as heart, liver, or kidney disease, all of which can lead to adverse outcomes somewhat independent of cancer effects (Supplementary Table S5). Thus, in younger patients, cancer may pose a greater relative risk for adverse outcomes than in older patients because other factors are less likely to operate.

Although mortality and ICU admission rates for COVID-19 both decreased over the course of the pandemic, the attributable risk of current cancer on severe outcomes from COVID-19 remained constant; that is, current cancer was associated with a greater risk of serious COVID-19 outcomes (ICU admission and death) across the first two years of the pandemic (2020 and 2021). This is despite the introduction of vaccinations in 2021 (25) and continued improvements in the treatment of COVID-19 (26). Reasons for the stable level of risk posed by cancer status is unclear but it is certainly possible that such improvements exerted fairly equivalent effects across the total population, leaving relative risks fairly undisturbed.

Moreover, vaccination before COVID-19 hospital admission substantially decreased the risk of ICU admission and death, irrespective of cancer status. Both patients with and without cancer appeared to benefit from vaccination. This finding may encourage patients with cancer to secure vaccination as one potential strategy to mitigate their substantially increased risk of severe outcomes from COVID-19 infection (1, 27).

Limitations

There are at least eight limitations of this study. First, the cause of death could not be definitively attributed to COVID-19 per se as some patients could have died during hospitalization from other causes. Second, this sample comprised only hospitalized adult patients during their first hospitalization for COVID-19, so it does not reflect the course of COVID-19 and the relations of risk factors with COVID-19 outcomes in a broader population. Third, hospital admission policies and resource availability (ICU space) might have affected some outcomes (28). Fourth, although the reliability of an ICD-10 diagnosis of any current cancer is good, the reliability of specific cancer types is much less so (29, 30). Fifth, the EHR records of past diagnoses of cancer, as with all EHR-based studies, were limited to the date of EHR implementation of each health system (31).

A sixth limitation of this study is that results across time could not be linked with type of COVID-19 variant. The analyses were conducted over the first two years of the pandemic, suggesting that the data obtained were contemporaneous with high prevalences of alpha and delta variants (32). Seven, we were unable to examine the effects of specific cancer treatments on adverse outcomes among patients with COVID-19. Some recent large EHR cohorts have implicated certain cancer treatments in the severe outcomes experienced by patients with COVID-19 and cancer (21, 22). An eighth limitation is that data on

cancer stage and grade were not available, which typically requires information from unstructured data sources in the EHR (33). The observation that metastatic solid tumors and hematologic cancer were more strongly associated with mortality suggests that stage and grade may be important predictors of COVID-19 outcomes.

Strengths

One strength of this study is that it is comprised of a large cohort of patients with COVID-19 from 21 geographically diverse United States Health Systems. EHR data were extracted and updated across 20 months of the pandemic. The inclusion of patients with COVID-19 with and without cancer enabled us to examine the relative risk associated with cancer in COVID-19 patient subpopulations, a comparison that is not possible in cohorts comprising only patients with both COVID-19 and cancer diagnoses. Diagnoses of current cancer were synchronized with the COVID-19 diagnoses; past cancer diagnoses were based on extensive historical EHR records, many occurring more than 5 years before the index hospitalization. Information on vaccination status allowed for an examination of the level of protection obtained by patients with cancer compared with patients without cancer.

Conclusions

Hospitalized adult patients with current cancer are at increased relative risk for severe COVID-19 disease and death, a pattern manifest across the duration of the pandemic. The magnitude of the incremental risk associated with current cancer varies with age and is greatest among younger patients. Moreover, a history of most types of cancer (versus current cancer) did not place those infected with COVID-19 at higher risk for severe outcomes. Information on risks of severe COVID-19 outcomes in cancer populations may inform clinician and patient decision making regarding COVID-19 treatment and prevention. The finding that prior COVID-19 vaccination was associated with reduced risk of death for all hospitalized patients with COVID-19, including those with current cancer, supports an increased urgency to vaccinate individuals with cancer (1, 27).

Authors' Disclosures

Disclaimer

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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