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Outcomes of COVID-19 in Patients With Cancer: Report From the National COVID Cohort Collaborative (N3C)

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abstract

PURPOSE Variation in risk of adverse clinical outcomes in patients with cancer and COVID-19 has been reported from relatively small cohorts. The NCATS' National COVID Cohort Collaborative (N3C) is a centralized data resource representing the largest multicenter cohort of COVID-19 cases and controls nationwide. We aimed to construct and characterize the cancer cohort within N3C and identify risk factors for all-cause mortality from COVID-19.

METHODS We used 4,382,085 patients from 50 US medical centers to construct a cohort of patients with cancer. We restricted analyses to adults ≥ 18 years old with a COVID-19–positive or COVID-19–negative diagnosis between January 1, 2020, and March 25, 2021. We followed N3C selection of an index encounter per patient for analyses. All analyses were performed in the N3C Data Enclave Palantir platform.

RESULTS A total of 398,579 adult patients with cancer were identified from the N3C cohort; 63,413 (15.9%) were COVID-19–positive. Most common represented cancers were skin (13.8%), breast (13.7%), prostate (10.6%), hematologic (10.5%), and GI cancers (10%). COVID-19 positivity was significantly associated with increased risk of all-cause mortality (hazard ratio, 1.20; 95% CI, 1.15 to 1.24). Among COVID-19–positive patients, age ≥ 65 years, male gender, Southern or Western US residence, an adjusted Charlson Comorbidity Index score ≥ 4, hematologic malignancy, multitumor sites, and recent cytotoxic therapy were associated with increased risk of all-cause mortality. Patients who received recent immunotherapies or targeted therapies did not have higher risk of overall mortality.

CONCLUSION Using N3C, we assembled the largest nationally representative cohort of patients with cancer and COVID-19 to date. We identified demographic and clinical factors associated with increased all-cause mortality in patients with cancer. Full characterization of the cohort will provide further insights into the effects of COVID-19 on cancer outcomes and the ability to continue specific cancer treatments.

J Clin Oncol 39:2232-2246. © 2021 by American Society of Clinical Oncology

INTRODUCTION

COVID-19 rapidly emerged as a global pandemic affecting access and quality of care, as well as health outcomes.[1,2] Patients with cancer were among vulnerable populations shown to be at increased risk of severe disease and death from COVID-19, which has been attributed to the manifestation of cancer itself, interaction with cancer therapies, and the hindrance of cancer care delivery by the pandemic.[3-6] Compared with patients without cancer, patients with cancer had higher mortality rates despite receipt of more frequent antiviral and immune-related therapies.[7]

The impact of COVID-19 on cancer outcomes and care delivery has been developing over time, with one of the earliest reports demonstrating more than five-fold increase in the likelihood of severe COVID-19 and death among patients with cancer.[8] However, early studies might have suffered from small sample sizes and potential significant confounders.[8-13] Subsequent studies reported increased risk of severe infection and death among patients with cancer but provided a more nuanced picture regarding COVID-19 severity, risk of death, and the impact of the cancer type and cancer therapy. For example, an analysis of the Lean European Open Survey on SARS-CoV-2 Infected Patients registry found minimal change in COVID-19 risk among patients with and without cancer after adjusting for age, sex, and comorbidity.[14] Studies that have specifically assessed the impact of cancer-related

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on May 7, 2021 and published at ascopubs.org/journal/jco on June 4, 2021: DOI https://doi.org/10.1200/JCO.21.01074

CONTEXT

Key Objective

Patients with cancer are among vulnerable populations at increased risk of severe outcomes and death from COVID-19. We used the National COVID Cohort Collaborative (N3C) to build a cohort of patients with cancer with and without COVID-19 and examined risk factors for overall mortality from COVID-19.

Knowledge Generated

Older age, male gender, increasing comorbidities, hematologic malignancy, and recent cytotoxic therapy were associated with higher mortality in COVID-19 patients with cancer. COVID-19–positive patients who received recent immunotherapies or targeted therapies did not have significantly higher risks of overall mortality from COVID-19.

Relevance

The N3C is a large-scale national Real-World Data resource that can be leveraged by clinicians and researchers to examine effects of COVID-19 on outcomes in patients with cancer. Further characterization of the curated cancer cohort will provide additional guidance on resource and clinical management of patients by cancer type.

therapy have demonstrated mixed results. The most recent report from the COVID-19 and Cancer Consortium (CCC-19) found a 28% increased risk of COVID-19 severity and 61% increased risk of 30-day mortality with cytotoxic agents; among specific therapies, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, platinum-etoposide, and DNA methyltransferase inhibitors were associated with increased 30-day all-cause mortality.[15] Conversely, studies like the UK Coronavirus Cancer Monitoring Project and the Gustave Roussy cohort did not find an increased risk of death with immunotherapies, targeted therapies, and hormone therapies after adjusting for age, sex, and comorbidities.[16,17] The inconsistencies in the findings could be due to relatively limited cohort sizes, geographical locations, or lack of a COVID-19–negative cancer control.

To address the lack of a national clinical patient registry that could be used to study COVID-19 at scale, the National COVID Cohort Collaborative (N3C) was developed as a centralized repository of electronic health record (EHR) data representing the largest multicenter cohort of COVID-19 cases and controls nationwide.[18,19] As of March 25, 2021, 1,077,445 confirmed COVID-19 cases and 3,304,640 controls from 50 contributing sites were available in the N3C platform. Our cohort study involved 398,579 patients with cancer who had any encounter with the health system including the emergency department, outpatient, telehealth, home visits, or inpatient hospitalization, and among whom, 63,413 tested positive for COVID-19. In this report, we aimed to characterize the cohort of patients with cancer within N3C and to identify risk factors associated with all-cause mortality within our cohort.

METHODS

Study Cohort

The N3C clinical cohort was built using broad inclusion criteria to include COVID-19 cases and non-COVID-19 controls of both outpatients and inpatients from contributing sites. At each site, all patients with COVID-19 with any clinical encounter after January 1, 2020, were included in the overall N3C clinical cohort. All patients without COVID-19 were initially included from contributing sites and starting December 2020 were randomly selected from the corresponding site using a 2:1 ratio to match the overall prevalence of age, sex, and race of COVID-19 cases. Historical patient data dating back to January 1, 2018, were included to document existing health conditions within the same health system for both cases and controls. Institutions with multiple source data models (eg, PCORNet, Accruals to Clinical Trials, TriNetX, and Observational Medical Outcomes Partnership [OMOP]) have provided data to the consortium. All data were harmonized, mapped, and deposited into an OMOP common data model (CDM)[20] (V5.3.1) following thorough data quality and harmonization checks by the N3C core teams.[19]

To construct a retrospective cohort of patients with cancer for this study within the larger N3C cohort, we used the Observational Health Data Sciences and Informatics ATLAS tool to search and navigate vocabularies and to build cohort definitions. Our study cohort was built using the Malignant Neoplastic Disease standard concept (SNOMED Code: 363346000). Within this cohort, 4,528 SNOMED Neoplasm Concepts were mapped to N3C Enclave Concepts; benign concepts listed in Appendix Table A1 (online only) were excluded.

To define COVID-19 status, we followed the N3C phenotyping guidelines to define COVID-19 positivity on the basis of a COVID-19–positive polymerase chain reaction or antigen test, or an International Classification of Diseases (ICD)-10-CM diagnostic code for COVID-19 during the same single index encounter.[19] We also used N3C guidelines to identify a single index encounter that represented the critical COVID-19–related visit for each laboratory-confirmed positive patient, hereafter referred to

as the index encounter (Appendix 1, online only). We limited our analytic cohort to patients with COVID-19 who had their earliest COVID-19 diagnosis within 21 days before the start of the index encounter and up to 5 days after the start of the index encounter. We restricted the cancer cohort to adult patients ≥ 18 years old with a past or existing primary cancer diagnosis and an index encounter between January 1, 2020, and March 25, 2021 (Fig 1). Finally, because of Health Information Portability and Accountability Act limitations, all age groups > 89 years have been set to 90 years for our analysis.

Indicator Variables

The N3C clinical data set is a collection of limited data sets (ie, containing real dates and geographic location) with potential prognostic variables. In our analysis, we included data for age, sex, race and ethnicity, geographical location of patient residence, smoking status, and COVID-19 treatment received. In addition, we used available data to calculate indicator variables on Charlson Comorbidity Index (CCI)[21] adjusted for a cancer diagnosis, primary cancer diagnosis, and cancer therapies.

Primary Diagnosis

Primary cancer diagnosis and associated diagnostics features are challenging to determine from the CDMs because of the lack of contextual clinical features (eg, pathology). Additionally, limited historical data availability within the N3C Enclave (starting at January 1, 2018) precludes a conclusive determination of a first cancer diagnosis. Using a diagnosis mapping to ICD-10 process (Appendix Fig A1, online only), we were able to map 363,856 patients' diagnosis to one (or more) ICD-10 topography code(s). In 9,924 patients, either the SNOMED-reported cancer type could not be mapped to a single ICD-10 anatomical site or they had an ICD-10 code of C76 or C80 (code C76 corresponds to malignant neoplasm of other and ill-defined sites, and C80 corresponds to malignant neoplasm without specification of site). As such, we were not able to map those patients to a single primary diagnosis and were categorized as having unknown or undefined primary, respectively, in the analyses. As depicted in Appendix Figure A2 (online only), we employed a multistep process to identify a primary diagnosis for patients with a mapped diagnosis. Initially, we extracted the single-cancer ICD-10 topography-reported patients. Second, we searched the keyword primary in cancer type and corresponding ICD-10 topography if it is mapped to a single topography. Third, we extracted secondary-only diagnosis on the basis of ICD-10 topography and finally, identified unique occurrence of an ICD-10 topography within the index encounter. This process resulted in a total of 321,337 patients with a primary diagnosis. We were unable to conclusively associate 52,443 patients with a single primary diagnosis because of reporting of more than one cancer site for these patients and insufficient data to differentiate a primary versus subsequent malignancy vs metastasis.

Cancer Therapies

Exposure to systemic, nontopical cancer therapies were assessed for each person in our cohort using a string search for each cancer therapy in the drug concept name and manually reviewed for correctness. Although steroids are an integral portion of cancer therapy, steroids were excluded from our categorization as a sole indication of cancer therapy exposure. Each cancer therapy was categorized as cytotoxic, targeted, immunotherapy, or endocrine therapy on the basis of the drug's mechanism of action (Appendix Table A2, online only). The most recent cancer therapy received within 30 days of the index encounter was included in the analyses.

Outcomes

The primary outcome of interest was all-cause mortality during the index encounter. Secondary outcomes included indicators of clinical severity requiring hospitalization: use of mechanical ventilation and extracorporeal membrane oxygenation.

Statistical Analysis

We calculated frequencies of potential prognostic factors comparing COVID-19 cases with controls using chi-square tests. We calculated frequency of death from any cause in the entire cohort and death and clinical severity indicators in hospitalized patients. Survival probabilities for the study cohort from 3 days, 10 days, and up to 90 days, as well as their 95% CIs, were estimated using the Kaplan-Meier estimator for censored data. We also estimated the survival probability for the major cancer types in the COVID-19–positive patients. Kaplan-Meier curves were used to visualize the corresponding survival probability, and the log-rank test to test statistical differences in survival probability between COVID-19–positive and COVID-19–negative patients. Multivariable analyses were performed using Cox Proportional Hazard models to estimate hazard ratios (HRs) for association of potential risk factors with all-cause mortality within 1 year comparing COVID-19–positive and COVID-19–negative patients adjusting for age group, sex, race and ethnicity, smoking status, geographical location of patient residence, adjusted CCI index, primary cancer types, and cancer treatment at 30 days. All tests were 2-sided using a 5% significance threshold. We also fit a separate model including only COVID-19–positive patients adding COVID-19 treatments including azithromycin, hydroxychloroquine, remdesivir, systemic steroids, and antibiotics to the model.

Per N3C policy, exact counts that are 20 or less were not reported to protect the privacy of individuals. All analyses were performed in the N3C Data Enclave on the Palantir platform.

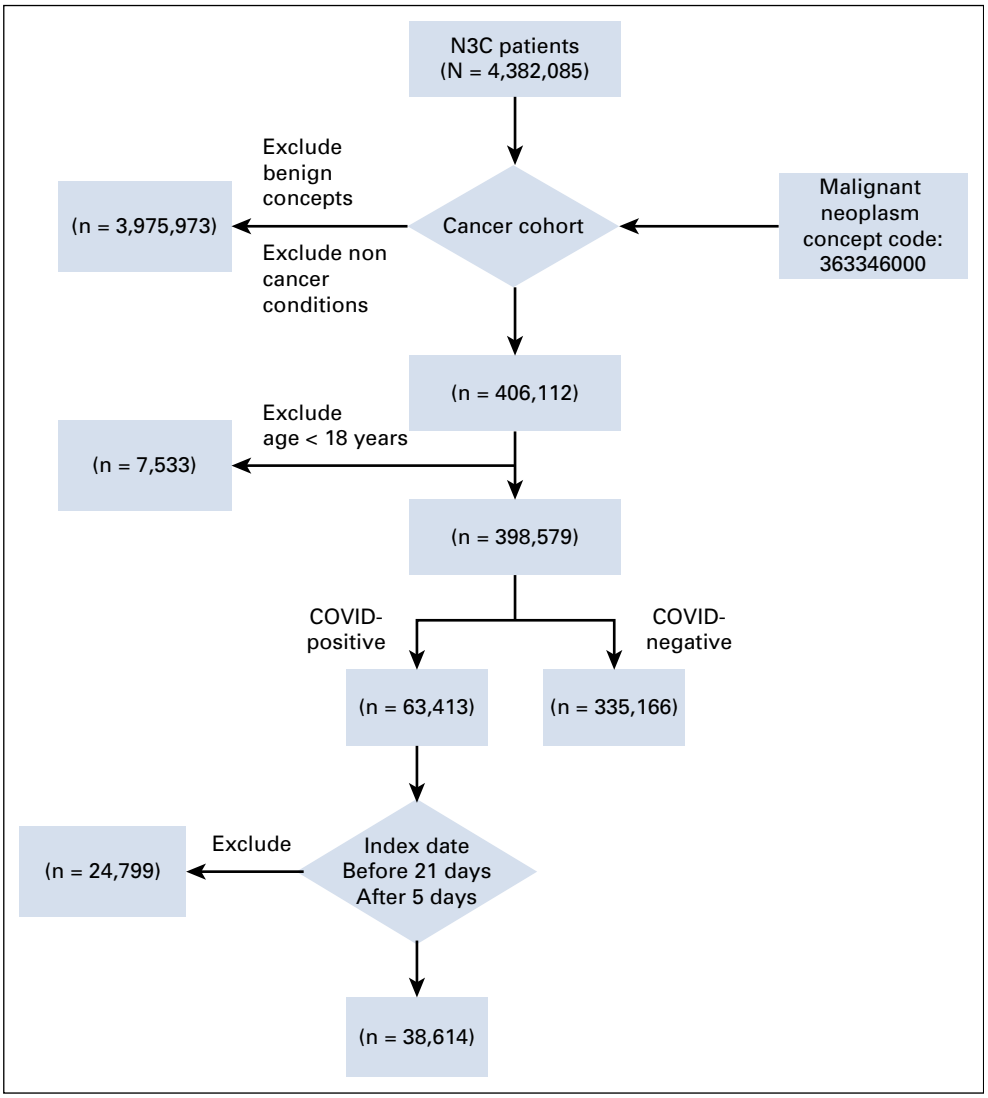

FIG 1. Flow diagram for study cohort. N3C, National COVID Cohort Collaborative.

The Role of the Institutional Review Board

All authors who performed analyses and had access to N3C data in the Enclave obtained individual institutional review board approvals from their respective institutions for this project and were also approved to use a limited data set by the N3C Data Use Request Committee.

RESULTS

As of March 25, 2021, our N3C-derived cohort consists of 373,780 adults (≥ 18 years old) with a history of cancer (mean age 65 years, 51% female, 68% non-Hispanic White, and 39% with four or more comorbidities). The median observation time over the study period between January 1, 2018, and March 25, 2021, was 2.85 years (interquartile range: 1.2 years). Within the analytic cohort, 38,614 patients were COVID-19–positive and 335,166 patients were negative (Fig 1). COVID-19–positive and COVID-19–negative subgroups did not have significantly different proportions by sex, whereas more non-Hispanic White individuals were COVID-19–negative (69% *v* 62%; $P < .001$). COVID-19–negative individuals were more likely to have a higher CCI compared with COVID-19–positive patients (CCI ≥ 4 was observed in 41% *v* 28%, respectively; $P < .001$). Top four cancer subtypes were more prevalent in the COVID-19–positive patients compared with COVID-19–negative patients. Recent cancer-related therapies for both COVID-19–positive and COVID-19–negative patients were low (overall approximately 1% on any specific therapy) (Table 1).

Among the 373,780 patients in the analytic cohort, the index encounter was a hospitalization visit in 204,503 patients (19,515 COVID-19–positive and 184,988 COVID-19–negative). The average length of stay in the hospital was 6.5 days (standard deviation 10.3 days). Among COVID-19–positive hospitalized patients, 14.8% of patients died and 8.2% required invasive ventilation during their index

TABLE 1. Study Cohort Demographic, Clinical, and Tumor Characteristics

Baseline Characteristic	Total (N = 373,780), No. (%)	COVID-19–Positive (n = 38,614), No. (%)	COVID-19–Negative (n = 335,166), No. (%)	P[a]
Age, years[b]				< .001
Mean (SD)	65.25 (14.59)	64.81 (14.96)	65.30 (14.54)	
Median (range)	67 (18 to > 90)	66 (18 to > 90)	67 (18 to > 90)	
18-29	7,320 (1.96)	840 (2.18)	6,480 (1.93)	
30-49	44,286 (11.85)	4,906 (12.71)	39,380 (11.75)	
50-64	112,675 (30.14)	11,921 (30.87)	100,754 (30.06)	
65+	209,499 (56.05)	20,947 (54.25)	188,552 (56.26)	
Sex				.433
Female	189,392 (50.67)	19,503 (approximately 50)	169,889 (50.69)	
Male	184,025 (49.23)	19,095 (approximately 49)	164,930 (49.21)	
Missing or unknown	363 (0.10)	< 20	347 (0.10)	
Race and ethnicity				< .001
Hispanic	8,860 (2.37)	1,413 (3.66)	7,447 (2.22)	
Non-Hispanic Black	41,873 (11.20)	5,066 (13.12)	36,807 (10.98)	
Non-Hispanic White	253,653 (67.86)	23,785 (61.60)	229,868 (68.58)	
Other or unknown	69,394 (18.57)	8,350 (21.62)	61,044 (18.21)	
Geographical location[c]				< .001
US Northeast	38,493 (10.30)	4,330 (11.21)	34,163 (10.19)	
US Midwest	123,639 (33.08)	12,941 (33.51)	110,698 (33.03)	
US South	109,769 (29.37)	10,918 (28.27)	98,851 (29.49)	
US West	26,055 (6.97)	2,084 (53.97)	23,971 (7.15)	
Unknown	75,824 (20.29)	8,341 (21.60)	67,483 (20.13)	
Smoking status				< .001
Nonsmoker	309,090 (82.69)	33,266 (86.15)	275,824 (82.29)	
Current or former smoker	64,690 (17.31)	5,348 (13.85)	59,342 (17.71)	
Adjusted CCI[d]				< .001
0	101,213 (27.08)	15,648 (40.52)	85,565 (25.53)	
1	61,401 (16.43)	6,122 (15.85)	55,279 (16.49)	
2	37,697 (10.09)	3,510 (9.09)	34,187 (10.20)	
3	26,192 (7.01)	2,406 (6.23)	23,786 (7.10)	
≥ 4	147,277 (39.40)	10,928 (28.30)	136,349 (40.68)	
Type of primary malignancy[e]				< .001
Skin cancers	51,778 (13.85)	5,743 (14.87)	46,035 (13.73)	
Breast cancer	51,018 (13.65)	5,482 (14.20)	45,536 (13.59)	
Prostate cancer	39,472 (10.56)	4,738 (12.27)	34,734 (10.36)	
Hematologic cancers	39,345 (10.53)	4,749 (12.30)	34,596 (10.32)	
GI cancers	37,543 (10.04)	3,413 (8.84)	34,130 (10.18)	
Multisite	52,443 (14.03)	4,225 (10.94)	48,218 (14.39)	
Type of cancer therapy (yes)[f]				.001
Cytotoxic	5,193 (1.39)	333 (0.86)	4,860 (1.45)	
Targeted	3,895 (1.04)	324 (0.84)	3,571 (1.06)	
Immunotherapy	1,753 (0.46)	147 (0.38)	1,606 (0.48)	
Endocrine	3,225 (0.86)	259 (0.67)	2,966 (0.84)	

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TABLE 1. Study Cohort Demographic, Clinical, and Tumor Characteristics (continued)

Baseline Characteristic	Total (N = 373,780), No. (%)	COVID-19–Positive (n = 38,614), No. (%)	COVID-19–Negative (n = 335,166), No. (%)	P[a]
COVID-19 treatment (yes)				
Systemic antibiotics		4,032 (15.75)		
Systemic steroids		3,514 (13.73)		
Azithromycin		1,197 (4.68)		
Remdesivir		1,047 (4.09)		
Dexamethasone		1,029 (4.02)		
Hydroxychloroquine		364 (1.42)		

Abbreviations: CCI, Charlson Comorbidity Index; SD, standard deviation.
[a]Calculated using chi-square tests to compare COVID-19 cases with controls.
[b]Age ≥ 90 years are reported as the exact age of 90 years and grouped in the 65+ age group.
[c]US census tract regions defined using reported zip code of patient residence.
[d]CCI adjusted for the cancer diagnosis.
[e]Top prevalent cancer types are reported.
[f]Cancer therapy received within 30 days from the index date.

hospitalization compared with 12.5% and 5.2%, respectively, in COVID-19–negative patients (Table 2). Only 0.14% of COVID-19–positive hospitalized patients required extracorporeal membrane oxygenation.

Among COVID-19–positive patients, survival probabilities were 84% at 10 days, 55% at 30 days, and 35% at 90 days, compared with 82%, 64%, and 50% in COVID-19–negative patients, respectively. Overall, there was no statistically significant difference in survival probabilities using log-rank test ($P = .07$). At 90 days survival, COVID-19–positive breast cancer showed better survival than other cancer types (51%; 95% CI, 44 to 61), whereas patients with multisite cancers showed lowest survival (26%; 95% CI, 18 to 39) (Figs 2 and 3; Table 3). Survival curves for the top cancer types by age group are shown in Appendix Figure A3 (online only).

COVID-19 positivity was significantly associated with increased risk of all-cause mortality (HR, 1.14; 95% CI, 1.1 to 1.2; $P < .001$) after adjusting for all other potential risk factors (Fig 4A). Among COVID-19–positive patients, older age more than 65 years (HR, 1.9; 95% CI, 1.3 to 3.1), male gender (HR, 1.11; 95% CI, 1.02 to 1.20), Southern and Western US regions (HR, 1.3; 95% CI, 1.1 to 1.6 and HR, 1.7; 95% CI, 1.3 to 2.2, respectively), higher number of comorbidities (HR, 2.0; 95% CI, 1.8 to 2.3), hematologic malignancies (HR, 1.2; 95% CI, 1.0 to 1.3) and multisite tumors (HR, 1.3; 95% CI, 1.1 to 1.4), and recent cytotoxic therapy (HR, 1.5; 95% CI, 1.1 to 2.1) were associated with increased risk of all-cause mortality (Fig 4B; Appendix Table A3, online only). Recent receipt of immunotherapies and targeted therapies were not associated with increased all-cause mortality. Non-Hispanic Black race (HR, 0.8; 95% CI, 0.7 to 0.9), recent hormonal therapy (HR, 0.5; 95% CI, 0.3 to 0.9), and treatment of COVID-19 with dexamethasone (HR, 0.8; 95% CI, 0.7 to 0.9) were associated with decreased risk of all-cause mortality (Fig 4B). Our analysis of the hematologic malignancy subcohort showed no significant statistical difference among myeloid and lymphoid malignancies in mortality risk (Appendix Table A4, online only).

DISCUSSION

We used the harmonized and integrated N3C clinical cohort, a patient registry that includes data on approximately 4.3 million COVID-19–tested patients with at least one clinical encounter after January 1, 2020 (inpatient or outpatient), at 50 US medical centers, to construct a cohort of patients with cancer. To the best of our knowledge, this is the first collaborative network study on patients with cancer and COVID-19 of this magnitude that demonstrates the feasibility of performing such large-scale observational research on the interaction of COVID-19 infection and cancer management across multiple healthcare sites nationwide.

The survival profile of patients with cancer infected by SARS-CoV-2 demonstrated characteristics related to both COVID-19 and cancer. Older age, male gender, and existing comorbidities are well-established mortality risk factors for COVID-19. The impact of age, sex, and comorbidity on survival remained prominent in our cohort with a pre-existing cancer diagnosis. Although some studies have shown racial disparities in mortality risk from COVID-19 between non-Hispanic Whites and Blacks,[15,22,23] other large studies did not find that race significantly affected rates of hospitalization or all-cause mortality.[24-26] Notably, our analysis showed that non-Hispanic Black and Hispanic patients with cancer had significantly lower risk of mortality. A more nuanced examination of neighborhood level characteristics, social determinants of health, and health literacy may provide better insights into the association of race and mortality risk from COVID-19.[27,28]

TABLE 2. Prevalence of Death and Invasive Ventilation in the Entire and Hospitalized Cohort by Risk Factor

	Entire Cohort (N = 373,780)		Hospitalized Cohort (n = 204,503)			
	COVID-19–Positive (n = 38,614), No. (%)	COVID-19–Negative (n = 335,166), No. (%)	COVID-19–Positive (n = 19,515), No. (%)	COVID-19–Negative (n = 184,988), No. (%)	COVID-19–Positive (n = 19,515), No. (%)	COVID-19–Negative (n = 184,988), No. (%)
Baseline Characteristic	Deaths[a]		Deaths[a]		Invasive Ventilation[a]	
Age, years						
18-29	26 (0.82)	282 (1.09)	25 (0.86)	265 (1.14)	< 20	198 (2.01)
30-49	144 (4.55)	1,735 (6.69)	136 (4.70)	1,599 (6.89)	104 (approximately 6)	951 (9.93)
50-64	563 (17.79)	6,236 (24.03)	505 (17.45)	5,659 (24.38)	424 (approximately 26)	2,941 (30.71)
65+	2,431 (76.83)	17,695 (68.19)	2,228 (76.99)	15,684 (67.58)	1,062 (approximately 66)	5,486 (57.29)
Sex						
Female	1,272 (approximately 40)	11,172 (43.06)	1,164 (approximately 40)	9,954 (42.89)	611 (approximately 38)	3,793 (approximately 39)
Male	1,888 (approximately 59)	14,731 (56.77)	1,726 (approximately 59)	13,210 (56.92)	994 (approximately 61)	5,781 (approximately 60)
Unknown	< 20	45 (0.17)	< 20	43 (0.19)	< 20	< 20
Race and ethnicity						
Hispanic	90 (2.84)	378 (1.46)	78 (2.70)	326 (1.40)	40 (2.49)	122 (1.27)
Non-Hispanic Black	515 (16.28)	3,411 (13.15)	494 (17.07)	3,176 (13.69)	361 (22.48)	1,401 (14.63)
Non-Hispanic White	1,857 (58.69)	17,541 (67.60)	1,715 (59.26)	15,581 (67.14)	893 (55.60)	6,266 (65.43)
Other or unknown	702 (22.19)	4,618 (17.80)	607 (20.97)	4,124 (17.77)	312 (19.43)	1,787 (18.66)
Geographical location						
US Northeast	388 (12.26)	2,430 (9.36)	370 (12.79)	2,223 (9.58)	97 (6.04)	506 (5.28)
US Midwest	1,035 (32.71)	9,755 (37.59)	954 (32.96)	8,708 (37.52)	603 (37.55)	3,251 (33.95)
US South	1,102 (34.83)	9,019 (34.76)	1,035 (35.76)	8,124 (35.01)	552 (34.37)	3,219 (33.62)
US West	148 (4.68)	1,674 (6.45)	125 (4.32)	1,378 (5.94)	59 (3.67)	481 (5.02)
Unknown	491 (15.52)	3,070 (11.83)	410 (14.17)	2,774 (11.95)	295 (18.37)	2,119 (22.13)
Smoking status						
Nonsmoker	2,648 (83.69)	20,752 (79.98)	2,407 (83.17)	18,409 (79.33)	1,404 (87.42)	7,344 (76.69)
Current or former smoker	516 (16.31)	5,196 (20.02)	487 (16.83)	4,798 (20.67)	202 (12.58)	2,232 (23.31)
Adjusted CCI						
0	512 (16.18)	1,019 (3.93)	436 (15.07)	795 (3.43)	244 (15.19)	344 (3.59)
1	328 (10.37)	1,359 (5.24)	293 (10.12)	1,129 (4.86)	167 (10.40)	613 (6.40)
2	270 (8.53)	1,389 (5.35)	245 (8.47)	1,172 (5.05)	155 (9.65)	689 (7.20)
3	253 (8.00)	1,338 (5.16)	230 (7.95)	1,166 (5.02)	136 (8.47)	779 (8.13)
≥ 4	1,801 (56.92)	20,843 (80.33	1,690 (58.40)	18,945 (81.63)	904 (56.29)	7,151 (74.68)

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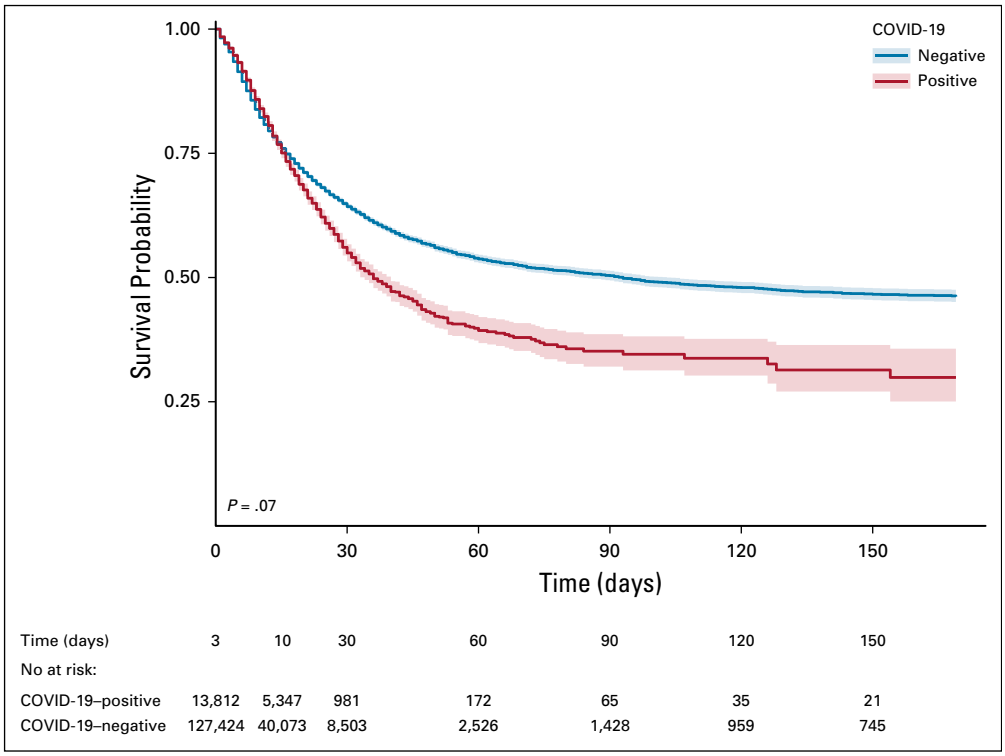
TABLE 2. Prevalence of Death and Invasive Ventilation in the Entire and Hospitalized Cohort by Risk Factor (continued)

	Entire Cohort (N = 373,780)		Hospitalized Cohort (n = 204,503)			
	COVID-19–Positive (n = 38,614), No. (%)	COVID-19–Negative (n = 335,166), No. (%)	COVID-19–Positive (n = 19,515), No. (%)	COVID-19–Negative (n = 184,988), No. (%)	COVID-19–Positive (n = 19,515), No. (%)	COVID-19–Negative (n = 184,988), No. (%)
Baseline Characteristic	**Deaths[a]**		**Deaths[a]**		**Invasive Ventilation[a]**	
Type of primary malignancy						
Skin cancers	290 (9.17)	1,435 (5.53)	264 (9.12)	1,206 (5.20)	136 (8.47)	599 (6.26)
Breast cancer	223 (7.05)	1,573 (6.06)	210 (7.26)	1,388 (5.98)	24 (1.49)	549 (5.73)
Prostate cancer	397 (12.55)	1,630 (6.28)	357 (12.34)	1,413 (6.09)	218 (13.57)	691 (7.22)
Hematologic cancers	545 (17.23)	3,372 (13.00)	502 (17.35)	3,140 (13.53)	317 (19.74)	1,388 (14.49)
GI cancers	410 (12.96)	4,252 (16.39)	374 (12.92)	3,834 (16.52)	192 (11.96)	1,351 (14.11)
Multisite	492 (15.55)	6,362 (24.52)	447 (15.45)	5,664 (24.41)	182 (11.33)	1,829 (19.10)
COVID-19 treatment						
Systemic antibiotics	711		710		404	
Systemic steroids	639		638		396	
Azithromycin	232		232		162	
Remdesivir	210		210		123	
Dexamethasone	203		202		139	
Hydroxychloroquine	84		84		37	

Abbreviation: CCI, Charlson Comorbidity Index.

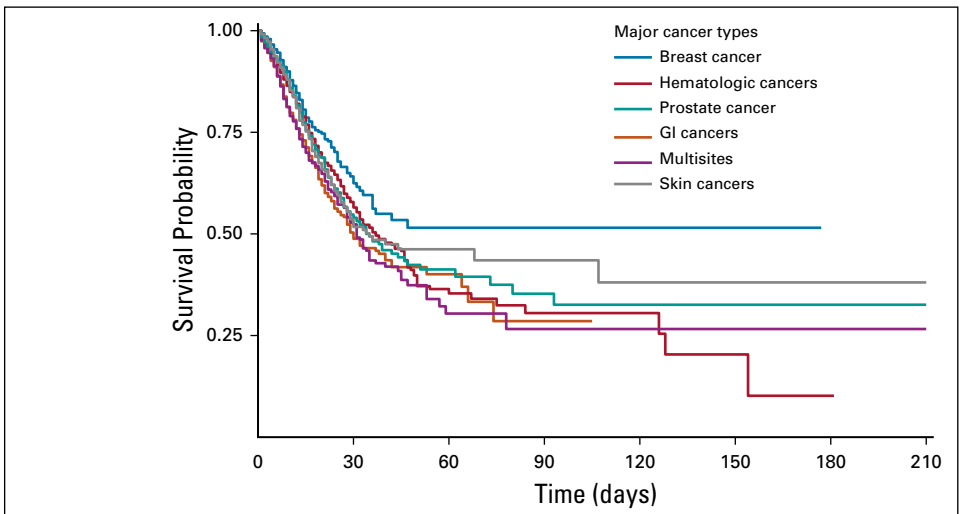
[a]Percentages are calculated from column totals for each indicator variable.



Time (days)	3	10	30	60	90	120	150
No at risk:							
COVID-19–positive	13,812	5,347	981	172	65	35	21
COVID-19–negative	127,424	40,073	8,503	2,526	1,428	959	745

FIG 2. Survival probability curves for COVID-19–positive and COVID-19–negative patients.

Although patients with cancer in our entire cohort who were on active cytotoxic therapies, targeted therapies, and immunotherapies were at increased mortality risk, consistent with previous studies,[16,17,29-31] receipt of recent immunotherapy and targeted cancer therapy did not appear to have a significantly increased effect on the mortality risk in COVID-19–



Time (days)	3	10	30	60	90	120	150	180	210
No at risk:									
Skin cancers	1,469	501	85	22	12	8	7	6	6
Breast cancer	1,472	503	76	14	5	5	5	0	0
Prostate cancer	1,690	713	137	27	16	9	5	5	5
Hematologic cancers	2,171	974	212	34	13	7	3	2	0
GI cancers	1,476	566	98	18	3	0	0	0	0
Multisites	1,804	685	118	18	5	4	4	4	3

FIG 3. Survival probability curve by cancer type for COVID-19–positive patients.

TABLE 3. Survival Probabilities for COVID-19–Positive Patients Over Time

COVID-19 Status	3-Day Survival Probability (95% CI)	10-Day Survival Probability (95% CI)	30-Day Survival Probability (95% CI)	60-Day Survival Probability (95% CI)	90-Day Survival Probability (95% CI)
COVID-19–positive	0.962 (0.959 to 0.964)	0.840 (0.832 to 0.847)	0.549 (0.533 to 0.567)	0.393 (0.368 to 0.420)	0.352 (0.321 to 0.386)
COVID-19–negative	0.954 (0.953 to 0.955)	0.822 (0.819 to 0.824)	0.643 (0.637 to 0.648)	0.537 (0.529 to 0.546)	0.504 (0.494 to 0.513)
Primary Cancer Type	**3-Day Survival Probability (95% CI)**	**10-Day Survival Probability (95% CI)**	**30-Day Survival Probability (95% CI)**	**60-Day Survival Probability (95% CI)**	**90-Day Survival Probability (95% CI)**
Skin cancers	0.973 (0.966 to 0.980)	0.853 (0.830 to 0.877)	0.517 (0.460 to 0.581)	0.462 (0.398 to 0.536)	0.435 (0.360 to 0.526)
Breast cancer	0.980 (0.974 to 0.985)	0.878 (0.856 to 0.901)	0.625 (0.567 to 0.688)	0.515 (0.437 to 0.607)	0.515 (0.437 to 0.607)
Prostate cancer	0.960 (0.953 to 0.968)	0.859 (0.840 to 0.879)	0.540 (0.495 to 0.589)	0.413 (0.353 to 0.482)	0.353 (0.278 to 0.447)
Hematologic cancers	0.956 (0.949 to 0.964)	0.849 (0.832 to 0.867)	0.565 (0.528 to 0.604)	0.354 (0.299 to 0.418)	0.305 (0.241 to 0.387)
GI cancers	0.945 (0.936 to 0.955)	0.798 (0.774 to 0.822)	0.488 (0.439 to 0.543)	0.401 (0.339 to 0.473)	0.285 (0.185 to 0.448)
Multisite	0.946 (0.937 to 0.955)	0.790 (0.768 to 0.813)	0.523 (0.479 to 0.572)	0.304 (0.232 to 0.398)	0.266 (0.183 to 0.387)

positive patients. On the other hand, recent cytotoxic therapy was associated with increased mortality risk,[15] whereas hormonal therapy was associated with decreased mortality risk. In addition, patients with COVID-19 also demonstrated differential prognosis by cancer type, which is largely consistent with prior knowledge before the COVID-19 pandemic, with breast cancers having the best prognosis and hematologic and GI cancers showing poor survival. Despite the observed high mortality rate in our cohort, the cancer therapy exposure detected in the preceding 30 days of the index encounter was lower than expected in our cohort especially when compared with manually extracted registry data (eg, the CCC19 cohort).[15,31] Our cohort consists of patients who are at varying stages in their cancer journey and could be on active treatment, in remission, or receiving end-of-life care. It is also possible that despite being on active cancer therapy, a COVID-19 diagnosis might have delayed or prevented a planned or ongoing cancer treatment.[32,33] We defined our cohort by an index encounter within a specified timeframe, which might have inadvertently decreased the likelihood of capturing recent cancer therapy particularly if a patient has received care for COVID-19 diagnosis at an institution different from where they receive their usual cancer care. The N3C Real-World Data–based cohort was constructed from a wide range of institutions that included patients with and without cancer, as such certain health systems may be better at documenting cancer diagnosis or respective therapy in their data warehouse especially if there is an embedded or linked cancer center within the health system. We attempted to minimize potential therapy misclassification by excluding certain non-cancer–specific therapies such as steroids or certain hormonal therapies and by considering spelling variations of therapy names.

Strengths of this study are derived from the construction of a large-scale patient registry such as N3C.[18] Through concept mapping and standardization, the OMOP CDM in the N3C platform facilitates collaboration and interoperability across heterogeneous EHR databases. As more high-quality extract, transform, and load tools are being developed in the Observational Health Data Sciences and Informatics community,[20,34] the CDM holds promise to decrease barriers to open collaborative cancer research. With data originating from 50 sites via four different data models (ie, Accruals to Clinical Trials, OMOP, PCORNet, and TriNetX), we encountered data quality issues during the aggregation and mapping of the data. Identifying the primary cancer diagnosis from the structured EHR data is a known challenge. The limited historical data within the N3C platform further restricted our ability to identify a single primary diagnosis for all the patients within our study cohort. Some patients might be misclassified with cancer while they were in remission or they merely underwent workups for cancer rule-out. More than half of our study population were hospitalized patients, which may explain the poor long-term survival outcomes observed in our study cohort. The continuing growth of the N3C cohort will, however, provide further insight into the outcomes of hospitalized and nonhospitalized patients with COVID-19 and cancer. We opted to define our cohort using the index encounter (known as the critical visit within N3C).[19] This allowed the identification of the most important or critical COVID-related encounter in a patient's clinical record and the most critical non-COVID–related visit for COVID-negative controls. Hence, an important strength of our study is the inclusion of non-COVID controls in our cohort, allowing us to estimate independent effects of COVID-19 infection on mortality risk in patients with cancer. The manner that the COVID-19–negative cohort was constructed, however, is not without limitations. Initially, all COVID-19–negative patients were included from the contributing sites. Starting December 2020, COVID-19–negative controls are being randomly selected from each of the

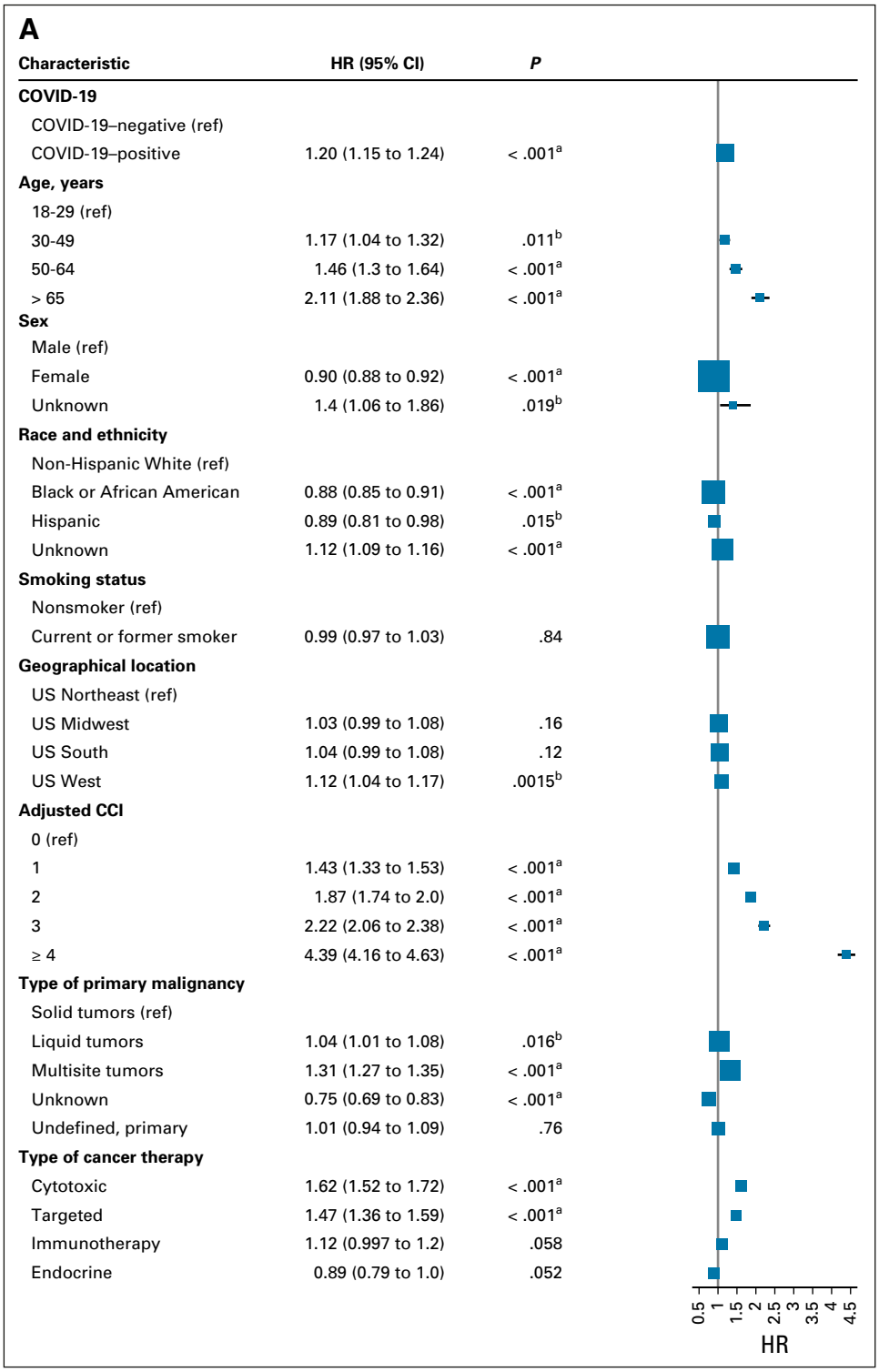


FIG 4. Adjusted HRs Cox proportional hazard model for association of potential risk factors with 1-year all-cause mortality in (A) entire cohort, and (B) COVID-19–positive patients only. CCI, Charlson Comorbidity Index; HR, hazard ratio; ref, reference. [a]$P < .001$. [b]$P < .05$. (continued on following page)

data contributing sites using a 2:1 ratio to match the overall prevalence of age, sex, and race of COVID-19 cases from those sites. Future studies could explore more detailed and consistent matching strategies within the cohort. Data missingness from EHR is a well-known problem for studies using clinical records. Although some patient records may be completely captured by a given hospital system, other records are only partially captured, when a patient sought

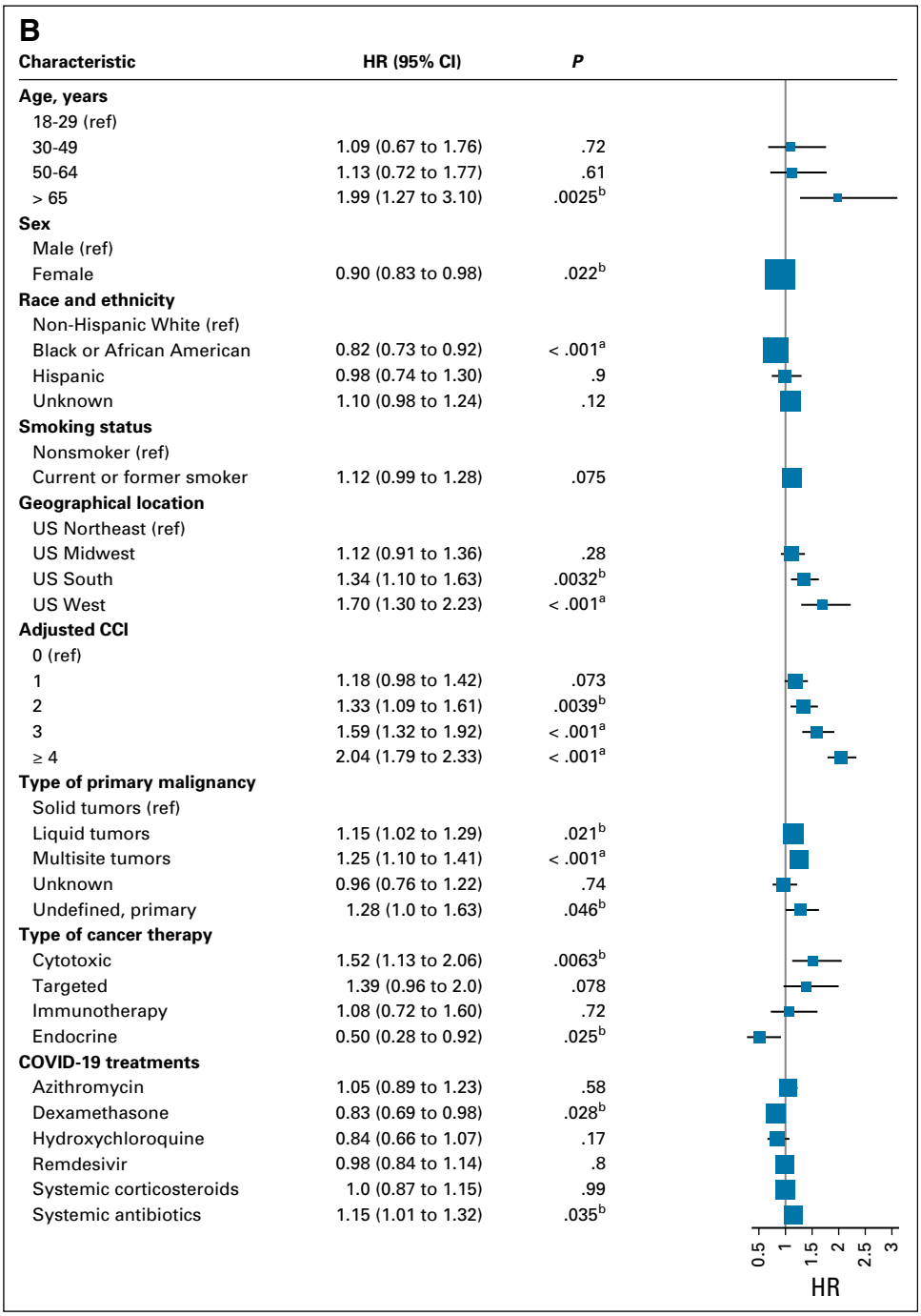


FIG 4. (Continued).

care at a different facility not affiliated with the given hospital system. This limitation extends to all clinical data domains including death information. Many hospital systems link their records with state death records to close this gap, but this is often done on a semiannual basis and it may not be done at every site. All-cause mortality, our primary study outcome, may be under-represented in the data; however, the scope and scale of the N3C data repository potentially overcome the limitations of individual sites.

In conclusion, through constructing the largest COVID-19 and cancer cohort within the United States, we examined risks of adverse outcomes associated with COVID-19–positive patients with cancer, particularly all-cause mortality. Despite the known limitations of large-scale data networks such as N3C, the consortium represents an unmatched resource for clinicians and researchers to examine the effects of cancer on COVID-19 outcomes and vice versa. Consistent with previous literature, older age, male gender, and increasing

comorbidities were associated with higher mortality in patients with cancer and COVID-19. The N3C data set also confirmed that patients with cancer and COVID-19 who received recent immunotherapies or targeted therapies were not at higher risks of overall mortality. Future studies of the cohort will provide insights into the evolving effect of COVID-19 on patients with cancer and additional evidence to guide the clinical management of this patient population.

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DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Authorship was determined using ICMJE recommendations.

PRIOR PRESENTATION

Presented in part at the ASCO 2021 Virtual Meeting, June 4-8, 2021.

SUPPORT

Supported by NCATS U24 TR002306 and the National Institute of General Medical Sciences, 5U54GM104942-04, and the analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave (https://covid.cd2h.org/enclave). This work was also partially financially supported by the Indiana University Precision Health Initiative funded to J.S. U.T. was partially supported by the Cancer Center Support Grant from the National Cancer Institute to the Comprehensive Cancer Center of Wake Forest Baptist Medical Center (P30 CA012197). U.T. and Q.S. were supported in part by Bioinformatics Shared Resources under the NCI Cancer Center Support Grant to the Comprehensive Cancer Center of Wake Forest University Health Sciences (P30 CA012197). Additional support for Q.S. was provided by a Fellowship to Wei Zhang from the National Foundation for Cancer Research. N.S. was supported by the Leukemia and Lymphoma Society Career Development Award (LLS 3386-19). T.B. and J.G. were supported by the Bill and Melinda Gates Foundation (INV-018455).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.01074.

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ACKNOWLEDGMENT

The authors would like to extend special thanks to Amin Mannaa for providing support on the analytic platform.
We gratefully acknowledge contributions from the following N3C core teams: Principal Investigators: Melissa A. Haendel*, Christopher G. Chute*, Kenneth R. Gersing, and Anita Walden; Workstream, Subgroup, and Administrative Leaders: Melissa A. Haendel*, Tellen D. Bennett, Christopher G. Chute, David A. Eichmann, Justin Guinney, Warren A. Kibbe, Hongfang Liu, Philip R.O. Payne, Emily R. Pfaff, Peter N. Robinson, Joel H. Saltz, Heidi Spratt, Justin Starren, Christine Suver, Adam B. Wilcox, Andrew E. Williams, and Chunlei Wu; Key liaisons at data partner sites; Regulatory staff at data partner sites; Individuals at the sites who are responsible for creating the data sets and submitting data to N3C; Data Ingest and Harmonization Team: Christopher G. Chute*, Emily R. Pfaff*, Davera Gabriel, Stephanie S. Hong, Kristin Kostka, Harold P. Lehmann, Richard A. Moffitt, Michele Morris, Matvey B. Palchuk, Xiaohan Tanner Zhang, and Richard L. Zhu; Phenotype Team (individuals who create the scripts that the sites use to submit their data, on the basis of the COVID and Long COVID definitions): Emily R. Pfaff*, Benjamin Amor, Mark M. Bissell, Marshall Clark, Andrew T. Girvin, Stephanie S. Hong, Kristin Kostka, Adam M. Lee, Robert T. Miller, Michele Morris, Matvey B. Palchuk, and Kellie M. Walters; Project Management and Operations Team: Anita Walden*, Usman Sheikh, Yooree Chae, Connor Cook, Alexandra Dest, Racquel R. Dietz, Thomas Dillon, Patricia A. Francis, Rafael Fuentes, Alexis Graves, Julie A. McMurry, Andrew J. Neumann, Shawn T. O'Neil, Andréa M. Volz, and Elizabeth Zampino; Partners From NIH and Other Federal Agencies: Christopher P. Austin*, Kenneth R. Gersing*, Samuel Bozzette, Mariam Deacy, Nicole Garbarini, Michael G. Kurilla, Sam G. Michael, Joni L. Rutter, and Meredith Temple-O'Connor; Analytics Team (individuals who build the Enclave infrastructure, help create codesets and variables, and help Domain Teams and project teams with their data sets): Benjamin Amor*, Mark M. Bissell, Katie Rebecca Bradwell, Andrew T. Girvin, Amin Manna, and Nabeel Qureshi; Publication Committee Management Team: Mary Morrison Saltz*, Christine Suver*, Christopher G. Chute, Melissa A. Haendel, Julie A. McMurry, Andréa M. Volz, and Anita Walden; Publication Committee Review Team: Carolyn Bramante, Jeremy Richard Harper, Wenndy Hernandez, Farrukh M. Koraishy, Federico Mariona, Saidulu Mattapally, Amit Saha, and Satyanarayana Vedula.
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This research was possible because of the patients whose information is included within the data from participating organizations (https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories) and scientists (https://covid.cd2h.org/duas) who have

contributed to the on-going development of this community resource doi.org/10.5281/zenodo.3979622.
The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol No. IRB00249128 or individual site agreements with NIH. The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources. *Denotes N3C core team leads.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Outcomes of COVID-19 in Patients With Cancer: Report From the National COVID Cohort Collaborative (N3C)

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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Research Funding: AstraZeneca, Bristol Meyers Squib, Roche/Genentech

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Stock and Other Ownership Interests: CareDirections

No other potential conflicts of interest were reported.

APPENDIX 1

Methods: Algorithm to Define a Single Index Encounter Representing the Critical COVID-19–Related Visit for Each Patient

We followed N3C definitions to select one single index encounter per person by COVID status and severity. Among multiple recorded encounters per patient, the most appropriate single encounter for analysis is chosen using the following procedure:

1. Select visits with an associated COVID-positive test result, if available
2. Select visits with an associated COVID-negative test result, if available
3. Select visits with a suspected COVID diagnosis, if available
4. Select inpatient visits, if available
5. Select emergency department visits, if available
6. Select hospital visits, if available
7. If the patient is recorded as dead, select the most recent visit
8. Select visits that included extracorporeal membrane oxygenation or mechanical ventilation, if available
9. Select the longest visit
10. Select the most recent visit

APPENDIX 2

Addendum of the National COVID Cohort Collaborative (N3C) core authors and affiliations

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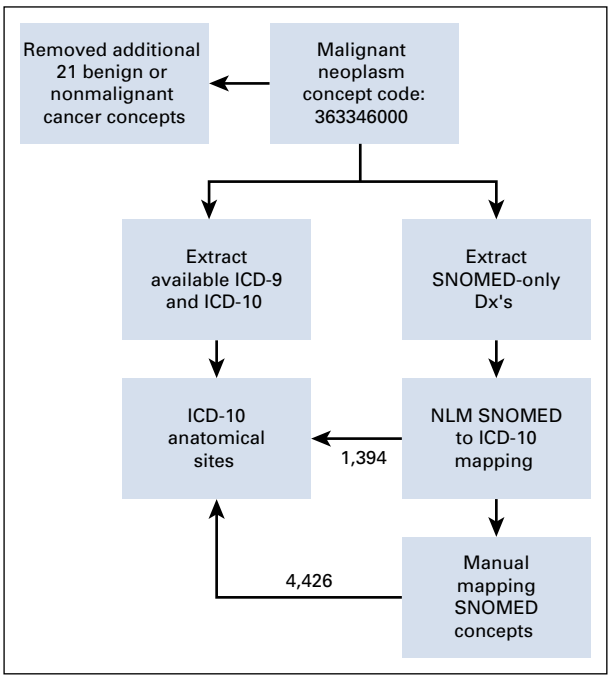

FIG A1. Primary cancer type mapping process. Dx, diagnosis; ICD, International Classification of Diseases.

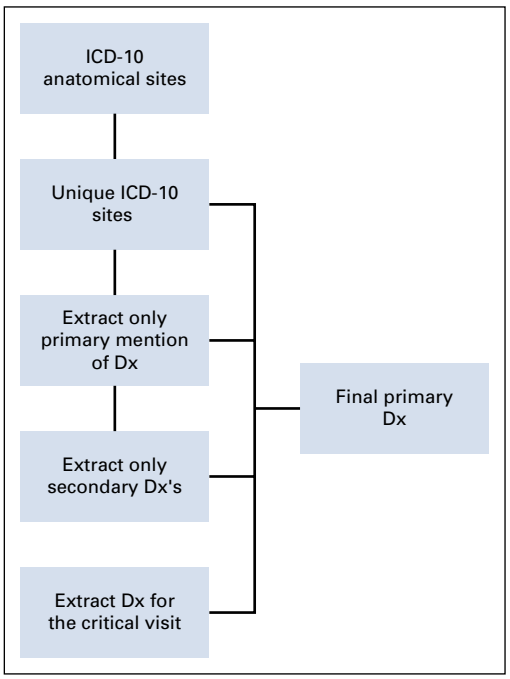

FIG A2. Primary cancer type identification process. Dx, diagnosis; ICD, International Classification of Diseases.

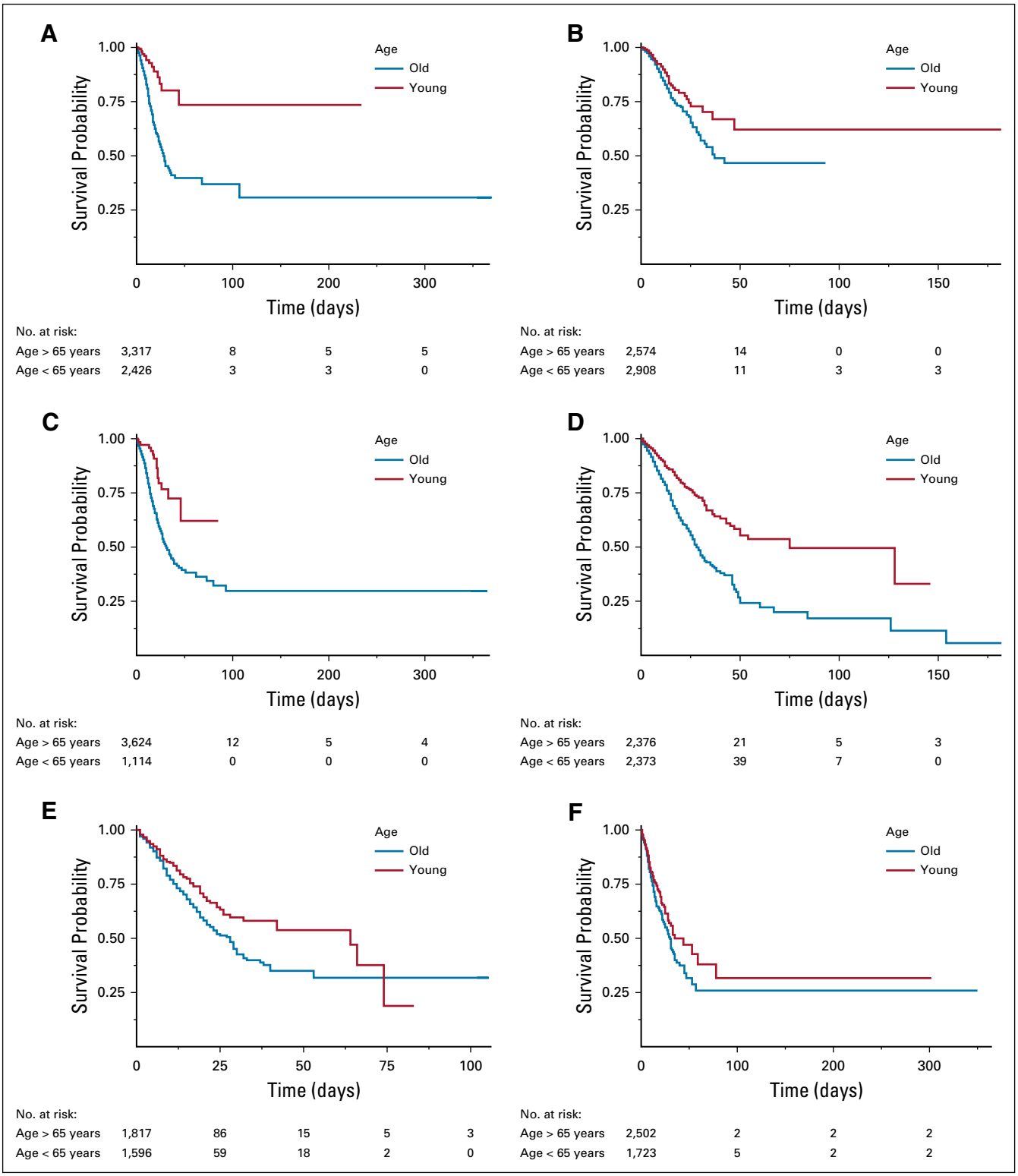

FIG A3. Survival probability curves by cancer type and age for COVID-19–positive patients. (A) Skin cancers, (B) breast cancer, (C) prostate cancer, (D) hematologic cancers, (E) GI cancers, and (F) multisite tumors.

TABLE A1. Excluded Concepts From the Standard Malignant Neoplastic Disease Concept Set (SNOMED Concept Code 363346000)

Concept ID	Concept Code	Concept Name	Domain	Standard or Concept
45586684	J91	Pleural effusion in conditions classified elsewhere	Condition	Nonstandard
254061	60046008	Pleural effusion	Condition	Standard
1569505	J91	Pleural effusion in conditions classified elsewhere	Condition	Nonstandard
4304002	386789004	Eosinophil count raised	Condition	Standard
4154632	271472001	Benign neoplasm of nose, middle ear, and accessory sinuses	Condition	Standard
135214	109992005	Polycythemia vera (clinical)	Condition	Standard
140064	307651005	Myelosclerosis with myeloid metaplasia	Condition	Standard
40571991	393573009	Hypereosinophilic syndrome	Condition	Standard
4308623	423294001	Idiopathic hypereosinophilic syndrome	Condition	Standard
132277	269496008	Neoplasm of uncertain behavior of endocrine glands and nervous system	Condition	Standard
45940956	135214	Malignant neoplasm of carpal bone—lunate	Condition	Nonstandard
45595761	D45	Polycythemia vera	Condition	Nonstandard
45537914	D47.0	Histiocytic and mast cell tumors of uncertain and unknown behavior	Condition	Nonstandard
45576400	D47.3	Essential (hemorrhagic) thrombocythemia	Condition	Nonstandard
42619338	D47.4	Osteomyelofibrosis	Condition	Nonstandard
1595515	D03.111	Melanoma in situ of right upper eyelid, including canthus	Condition	Nonstandard
432582	118616009	Neoplastic disease of uncertain behavior	Condition	Standard
438383	109994006	Essential thrombocythemia	Condition	Standard
4033836	109274007	Melanoma in situ of eyelid, including canthus	Condition	Standard
1595516	D03.112	Melanoma in situ of right lower eyelid, including canthus	Condition	Nonstandard
45547566	D03.20	Melanoma in situ of unspecified ear and external auricular canal	Condition	Nonstandard
45600575	D03.21	Melanoma in situ of right ear and external auricular canal	Condition	Nonstandard
45561885	D03.22	Melanoma in situ of left ear and external auricular canal	Condition	Nonstandard
45547567	D03.30	Melanoma in situ of unspecified part of face	Condition	Nonstandard
45557052	D03.39	Melanoma in situ of other parts of face	Condition	Nonstandard
35206527	D14.0	Benign neoplasm of middle ear, nasal cavity, and accessory sinuses	Condition	Nonstandard
35206666	D45	Polycythemia vera	Condition	Nonstandard
35206676	D47.0	Mast cell neoplasms of uncertain behavior	Condition	Nonstandard
35206679	D47.3	Essential (hemorrhagic) thrombocythemia	Condition	Nonstandard
45595763	D47.4	Osteomyelofibrosis	Condition	Nonstandard
45600602	D49.7	Neoplasm of unspecified behavior of endocrine glands and other parts of nervous system	Condition	Nonstandard
45571627	D49.81	Neoplasm of unspecified behavior of retina and choroid	Condition	Nonstandard
35206777	D72.1	Eosinophilia	Condition	Nonstandard
725245	D72.110	Idiopathic hypereosinophilic syndrome	Condition	Nonstandard
725247	D72.118	Other hypereosinophilic syndrome	Condition	Nonstandard
725248	D72.119	Hypereosinophilic syndrome, unspecified	Condition	Nonstandard
45543278	J91.0	Malignant pleural effusion	Condition	Nonstandard
3655266	860792009	Pleural effusion because of malignant neoplastic disease	Condition	Standard
45561883	D03	Melanoma in situ	Condition	Nonstandard
1567722	D03	Melanoma in situ	Condition	Nonstandard
4031756	109266006	Melanoma in situ of skin (clinical)	Condition	Standard

TABLE A2. List of Cancer Therapies Captured Within Each Therapy Category

Therapy Category	Therapy Captured
Cytotoxic therapy	ABRAXANE, Doxorubicin, Adrucil, ALIMTA, Alkeran, Altretamine, ARRANON, Arsenic, Arsenic Trioxide, Asparaginase, Asparlas, Azacitidine, AZEDRA, BELRAPZO, Bendamustine, BENDEKA, BiCNU, Bleomycin, Bleomycin Sulfate, Bromocriptine, Busulfan, Busulfex, Cabazitaxel, Calaspargase, Calaspargase pegol-mknl, Camptosar, Capecitabine, Carboplatin, Carmustine, CeeNU, Chlorambucil, Cisplatin, Cladribine, Clofarabine, Clolar, Cosmegen, Cyclophosphamide, CYSTAGON, Cysteamine, Cysteamine Bitartrate, Cytarabine, Cytoxan, Dacarbazine, Dacogen, Dactinomycin, Daunorubicin, Daunorubicin Hydrochloride, Daunoxome, Decitabine, DepoCyt, Docefrez, Docetaxel, Docetaxel Anhydrous, Doxil, Doxorubicin, Doxorubicin Hydrochloride, Doxorubicin Hydrochloride Liposome, Efudex, Ellence, Eloxatin, Elspar, Emcyt, Epirubicin, Eribulin, Erwinaze, Estramustine, Estramustine Phosphate Sodium, ETOPOPHOS, Etoposide, Etoposide Phosphate, Evomela, Floxuridine, Fludara, Fludarabine, Fludarabine Phosphate, Fluorouracil, FOLOTYN, Gemcitabine, Gemzar, Gleostine, Gliadel, HALAVEN, Hexalen, Hicon, Hycamtin, Hydrea, Hydroxyurea, Iodine-131, I-131 Mini, Idamycin, Idamycin PFS, Idarubicin, Idarubicin Hydrochloride, IFEX, Ifosfamide, Infugem, Iobenguane, Iobenguane I-131, Irinotecan, Irinotecan Hydrochloride, Ixabepilone, Ixempra, JEVTANA, Leukeran, Lipodox 50, Lomustine, LONSURF, Lurbinectedin, Lutathera, Lutetium, Lutetium LU 177 Dotatate, Lysodren, Marqibo, Matulane, MAVENCLAD, Mechlorethamine, Mechlorethamine Hydrochloride, Melphalan, Mercaptopurine, Methotrexate, Methotrexate Sodium, Methoxsalen, Mitomycin, Mitotane, Mitoxantrone, Mitoxantrone Hydrochloride, Mustargen, MUTAMYCIN, Myleran, N/A, Navelbine, Nelarabine, NIPENT, Omacetaxine Mepesuccinate, Oncaspar, ONIVYDE, Oxaliplatin, Sodium Phosphate P32, Sodium Phosphate P 32, P32 Sodium Phosphate, Paclitaxel, Paraplatin, Parlodel, Pegaspargase, Pemetrexed, Pemetrexed Disodium, Pentostatin, Photofrin, Platinol, Platinol-AQ, Porfimer Sodium, Pralatrexate, Procarbazine, Procarbazine Hydrochloride, Procysbi, Purixan, Radium 223 Dichloride, Radium Dichloride 223, Rubex, Sodium Iodide I 131, Sodium Iodide I-131, Streptozocin, Synribo, Tabloid, Taxotere, Temodar, Temozolomide, Teniposide, TEPADINA, Thioguanine, Thiotepa, Toposar, Topotecan, Topotecan Hydrochloride, Trabectedin, TREANDA, Trexall, Trisenox, UVADEX, VALCHLOR, Valrubicin, Valstar, Vidaza, Vinblastine, Vinblastine Sulfate, Vincasar PFS, Vincristine, Vincristine Sulfate, Vinorelbine, Vinorelbine Tartrate, VYXEOS, XATMEP, Xeloda, Xofigo, YONDELIS, Zanosar, Zepzelca
Targeted therapy	Abemaciclib, Acalabrutinib, Ado-Trastuzumab, Ado-Trastuzumab Emtansine, Afatinib, AFINITOR, AFINITOR DISPERZ, Aldara, ALECENSA, Alectinib, Alemtuzumab, Aliqopa, Alpelisib, ALUNBRIG, Avapritinib, Axitinib, AYVAKIT, BALVERSA, Beleodaq, Belinostat, Bevacizumab, Binimetinib, Bortezomib, BOSULIF, Bosutinib, BRAFTOVI, Brigatinib, BRUKINSA, CABOMETYX, Cabozantinib, CALQUENCE, Capmatinib, CAPRELSA, Carfilzomib, Ceritinib, Cetuximab, Cobimetinib, COMETRIQ, Copanlisib, COPIKTRA, COSELA, COTELLIC, Crizotinib, Dabrafenib, Dacomitinib, Dasatinib, DAURISMO, Denosumab, Dinutuximab, Dinutuximab, Duvelisib, Enasidenib, Encorafenib, Enfortumab, Entrectinib, Erdafitinib, Erivedge, Erlotinib, Erlotinib Hydrochloride, Everolimus, FARYDAK, Fedratinib, Fedratinib Hydrochloride, GAVRETO, Gefitinib, GILOTRIF, Gilteritinib, Glasdegib, GLEEVEC, IBRANCE, Ibritumomab, Ibritumomab Tiuxetan, Ibrutinib, ICLUSIG, Idelalisib, IDHIFA, Imatinib, Imatinib Mesylate, IMBRUVICA, INLYTA, INREBIC, IRESSA, ISTODAX, Ivosidenib, Ixazomib, Jakafi, KISQALI, KOSELUGO, KYPROLIS, Lapatinib, Larotrectinib, Lenvatinib, LENVIMA, LORBRENA, Lorlatinib, LYNPARZA, Margetuximab, Mekinist, MEKTOVI, Midostaurin, Naxitamab, Necitumumab, Neratinib, NERLYNX, Nexavar, Nilotinib, NINLARO, Nintedanib, Niraparib, ODOMZO, OFEV, Olaparib, Olaratumab, Osimertinib, Palbociclib, Panitumumab, Panobinostat, Pazopanib, Pazopanib Hydrochloride, PEMAZYRE, Pemigatinib, Pertuzumab, Pexidartinib, PIQRAY, Ponatinib, Ponatinib Hydrochloride, Pralsetinib, Prolia, QINLOCK, Ramucirumab, Regorafenib, Retevmo, Ribociclib, Ripretinib, Romidepsin, ROZLYTREK, Rubraca, Rucaparib, Ruxolitinib, RYDAPT, Sacituzumab, Selinexor, Selpercatinib, Selumetinib, Sonidegib, Sorafenib, SPRYCEL, STIVARGA, Sunitinib, Sunitinib Malate, SUTENT, TABRECTA, TAFINLAR, TAGRISSO, Talazoparib, TALZENNA, Tarceva, TASIGNA, Tazemetostat, TAZVERIK, Temsirolimus, TEPMETKO, Tepotinib, Tepotinib Hydrochloride, TIBSOVO, TORISEL, Trametinib, Trastuzumab, Trastuzumab-Anns, Trastuzumab-Dttb, Trastuzumab-Pkrb, Trastuzumab-Qyyp

(continued on following page)

TABLE A2. List of Cancer Therapies Captured Within Each Therapy Category (continued)

Therapy Category	Therapy Captured
Immunotherapy	ACTIMMUNE, ADCETRIS, Aldesleukin, Alemtuzumab, Arzerra, Atezolizumab, Avelumab, Axicabtagene, Axicabtagene Ciloleucel, Bacillus Calmette-Guerin, BAVENCIO, Belantamab, Besponsa, Bexxar, Bexxar Dosimetric, Blenrep, Blinatumomab, BLINCYTO, Brentuximab, Brexucabtagene, Breyanzi, Campath, Cemiplimab, Daratumumab, DARZALEX, Denileukin, Denileukin Diftitox, Durvalumab, Elotuzumab, Elzonris, EMPLICITI, GAZYVA, Gemtuzumab, Gemtuzumab Ozogamicin, Ibritumomab, Ibritumomab Tiuxetan, IMFINZI, IMLYGIC, Inotuzumab, Inotuzumab Ozogamicin, Interferon Alfa-2b, Interferon Gamma-1b, INTRON A, Ipilimumab, Isatuximab, KEYTRUDA, KYMRIAH, Lenalidomide, Libtayo, Lisocabtagene, Lisocabtagene Maraleucel, LUMOXITI, Margetuximab, Mogamulizumab-kpkc, MONJUVI, Moxetumomab, Moxetumomab Pasudotox-tdfk, Mylotarg, Nivolumab, Obinutuzumab, Ofatumumab, Ontak, OPDIVO, PEGASYS, Peginterferon Alfa-2a, Peginterferon Alfa-2b, Pembrolizumab, Polatuzumab, POLIVY, Pomalidomide, POMALYST, POTELIGEO, Proleukin, PROVENGE, REVLIMID, RITUXAN, RITUXAN HYCELA, Rituximab, Rituximab-abbs, Rituximab-pvvr, RUXIENCE, SARCLISA, Siltuximab, Sipuleucel-t, SYLATRON, SYLVANT, Tafasitamab, Tafasitamab-cxix, Tagraxofusp-erzs, Talimogene Laherparepvec, TECARTUS, TECENTRIQ, Thalidomide, Thalomid, TheraCys, TICE BCG, Tisagenlecleucel, Tositumomab, Tositumomab, Iodine I-131, TRUXIMA, YERVOY, YESCARTA, ZEVALIN
Endocrine therapy	Abiraterone, Absorica, Accutane, Alitretinoin, Amnesteem, Anastrozole, Android, ANDROXY, Apalutamide, Arimidex, Aromasin, Bexarotene, Bicalutamide, Casodex, Claravis, Darolutamide, Degarelix, Delatestryl, Delestrogen, Depo-Provera, Eligard, Enzalutamide, ERLEADA, Estrace, Estradiol, Estradiol Valerate, Conjugated Estrogen, Esterified Estrogen, Estrogens, Conjugated, Estrogens, Esterified, Evista, Exemestane, Fareston, Faslodex, Femara, Firmagon, Fluoxymesterone, Flutamide, Fulvestrant, Goserelin Acetate, Histrelin, Hydroxyprogesterone Caproate, Isotretinoin, KORLYM, Lanreotide, Lanreotide Acetate, Letrozole, Leuprolide, Leuprolide Acetate, LUPRON, LUPRON DEPOT, Medroxyprogesterone, Medroxyprogesterone Acetate, Megace, Megestrol, Megestrol Acetate, Menest, Methitest, Methyltestosterone, Mifepristone, Myorisan, Nilandron, Nilutamide, Nolvadex, NUBEQA, Octreotide, Octreotide Acetate, Orgovyx, Panretin, Premarin, Provera, Raloxifene, Raloxifene Hydrochloride, Relugolix, Sandostatin, Sandostatin LAR Depot, Soltamox, Somatuline, Somatuline Depot, Tamoxifen, Tamoxifen Citrate, Targretin, Testosterone Enanthate, Testred, THYROGEN, Thyrotropin Alfa, Toremifene Citrate, Trelstar, Tretinoin, Triptorelin, Triptorelin Pamoate, Vantas, Xtandi, YONSA, Zenatane, Zoladex, ZYTIGA

TABLE A3. Adjusted HRs for Association of Potential Risk Factors With All-Cause Mortality in Hematologic Malignancy Patients Compared With Solid Malignancy COVID-19–Positive Patients

Outcome	HR (95% CI)	P
Age, years		
18-29 (ref)		
30-49	1.11 (0.69 to 1.8)	.67
50-64	1.16 (0.74 to 1.83)	.52
65+	2.03 (1.3 to 3.17)	.002
Sex		
Male (ref)		
Female	0.9 (0.83 to 0.99)	.03
Unknown	9.69 (1.34 to 70.28)	.02
Race and ethnicity		
Non-Hispanic White (ref)		
Black or African American	0.83 (0.73 to 0.93)	.002
Hispanic	0.99 (0.74 to 1.31)	.92
Unknown	1.1 (0.98 to 1.24)	.11
Geographical location		
US Northeast (ref)		
US Midwest	1.12 (0.92 to 1.37)	.26
US South	1.35 (1.11 to 1.63)	.003
US West	1.73 (1.32 to 2.26)	< .001
Smoking status		
Nonsmoker (ref)		
Current or former smoker	1.12 (0.98 to 1.27)	.09
Adjusted CCI		
0 (ref)		
1	1.18 (0.98 to 1.42)	.08
2	1.33 (1.1 to 1.61)	.004
3	1.6 (1.32 to 1.93)	< .001
≥ 4	2.05 (1.79 to 2.34)	< .001
Type of primary malignancy		
Solid tumors (ref)		
Myeloid leukemia	1.14 (0.82 to 1.6)	.44
Lymphoid leukemia	1.3 (1.04 to 1.64)	.02
Lymphoma	1.2 (0.99 to 1.45)	.07
Multiple myeloma	0.74 (0.57 to 0.97)	.03
Multisite[a]	1.24 (1.1 to 1.41)	< .001
Unknown[b]	1.17 (0.99 to 1.38)	.07
Undefined primary[c]	1.28 (1.01 to 1.63)	.04
Type of cancer therapy (yes)		
Cytotoxic	1.49 (1.1 to 2.02)	.009
Targeted	1.47 (1.02 to 2.11)	.04
Immunotherapy	1.23 (0.82 to 1.84)	.31
Endocrine	0.49 (0.27 to 0.89)	.02
COVID-19 treatment (yes)		
Systemic antibiotics	1.16 (1.01 to 1.32)	.03
Systemic steroids	1.01 (0.87 to 1.16)	.94
Azithromycin	1.04 (0.89 to 1.22)	.63
Hydroxychloroquine	0.85 (0.67 to 1.09)	.21
Remdesivir	0.99 (0.85 to 1.15)	.85
Dexamethasone	0.83 (0.7 to 0.98)	.03

Abbreviations: CCI, Charlson Comorbidity Index; HR, hazard ratio; ICD, International Classification of Diseases; ref, reference.

[a]More than one cancer site has been reported for these patients and insufficient data to differentiate subsequent malignancy versus metastasis.

[b]An SNOMED-reported cancer type that cannot be mapped to single ICD-10 anatomical site.

[c]Primary diagnosis mapped to ICD-10 codes of C76—malignant neoplasm of other and ill-defined sites or C80—malignant neoplasm without specification of site.

TABLE A4. Adjusted HRs for Association of Potential Risk Factors With All-Cause Mortality in Hematologic Malignancy COVID-19–Positive Patients

Outcome	HR (95% CI)	*P*
Age, years		
18-29 (ref)		
30-49	3.75 (1.12 to 12.58)	.03
50-64	5.26 (1.65 to 16.76)	.005
65+	7.77 (2.47 to 24.45)	< .001
Sex		
Male (ref)		
Female	0.91 (0.74 to 1.13)	.41
Unknown	20.7 (2.61 to 164.18)	.004
Race and ethnicity		
Non-Hispanic White (ref)		
Black or African American	0.99 (0.73 to 1.34)	.95
Hispanic	1.04 (0.52 to 2.05)	.92
Unknown	1.29 (0.98 to 1.69)	.07
Geographical location		
US Northeast (ref)		
US Midwest	1.22 (0.76 to 1.97)	.41
US South	1.69 (1.06 to 2.69)	.03
US West	1.5 (0.78 to 2.87)	.23
Smoking status		
Nonsmoker (ref)		
Current or former smoker	1.17 (0.86 to 1.6)	.32
Adjusted CCI		
0 (ref)		
1	1.07 (0.74 to 1.55)	.71
2	1.17 (0.78 to 1.75)	.46
3	1.29 (0.86 to 1.92)	.22
≥ 4	1.5 (1.13 to 2.0)	.005
Type of primary malignancy		
Myeloid leukemia (ref)		
Lymphoid leukemia	1.28 (0.85 to 1.93)	.23
Lymphoma	1.14 (0.78 to 1.68)	.5
Multiple myeloma	0.72 (0.46 to 1.11)	.13
Unknown[a]	1.47 (0.98 to 2.22)	.06
Type of cancer therapy (yes)		
Cytotoxic	0.75 (0.33 to 1.73)	.50
Targeted	1.14 (0.54 to 2.40)	.74
Immunotherapy	1.27 (0.65 to 2.46)	.48
COVID-19 treatment (yes)		
Systemic antibiotics	0.8 (0.56 to 1.14)	.22
Systemic steroids	1.6 (1.12 to 2.28)	.01
Azithromycin	0.89 (0.61 to 1.3)	.55
Hydroxychloroquine	1.07 (0.65 to 1.76)	.80
Remdesivir	1.05 (0.74 to 1.49)	.78
Dexamethasone	0.6 (0.4 to 0.89)	.01

(continued in next column)

TABLE A4. Adjusted HRs for Association of Potential Risk Factors With All-Cause Mortality in Hematologic Malignancy COVID-19–Positive Patients (continued)

Abbreviations: CCI, Charlson Comorbidity Index; HR, hazard ratio; ICD, International Classification of Diseases; ref, reference.

[a]An SNOMED-reported cancer type that cannot be mapped to single ICD-10 anatomical site.