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Authors

Grivas, P
Khaki, AR
Wise-Draper, TM
et al.

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ORIGINAL ARTICLE

Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium[☆]

P. Grivas^{1*†}, A. R. Khaki^{1,33†}, T. M. Wise-Draper^{2†}, B. French^{3†}, C. Hennessy³, C.-Y. Hsu³, Y. Shyr³, X. Li⁴, T. K. Choueiri⁵, C. A. Painter⁶, S. Peters⁷, B. I. Rini³, M. A. Thompson⁸, S. Mishra³, D. R. Rivera⁹, J. D. Acoba¹⁰, M. Z. Abidi¹¹, Z. Bakouny⁵, B. Bashir¹², T. Bekaii-Saab¹³, S. Berg¹⁴, E. H. Bernicker¹⁵, M. A. Bilen¹⁶, P. Bindal¹⁷, R. Bishnoi¹⁸, N. Bouganim¹⁹, D. W. Bowles¹¹, A. Cabal²⁰, P. F. Caimi^{21,22}, D. D. Chism²³, J. Crowell²⁴, C. Curran⁵, A. Desai²⁵, B. Dixon²⁴, D. B. Doroshov²⁶, E. B. Durbin²⁷, A. Elkrif¹⁹, D. Farmakiotis²⁸, A. Fazio²⁹, L. A. Fecher³⁰, D. B. Flora²⁴, C. R. Friese³⁰, J. Fu²⁹, S. M. Gadgeel³¹, M. D. Galsky²⁶, D. M. Gill³², M. J. Glover³³, S. Goyal³⁴, P. Grover², S. Gulati², S. Gupta³⁵, S. Halabi³⁶, T. R. Halfdanarson²⁵, B. Halmos³⁷, D. J. Hausrath⁴, J. E. Hawley³⁸, E. Hsu^{39,40}, M. Huynh-Le³⁴, C. Hwang³¹, C. Jani⁴¹, A. Jayaraj³⁹, D. B. Johnson³, A. Kasi⁴², H. Khan²⁸, V. S. Koshkin⁴³, N. M. Kuderer⁴⁴, D. H. Kwon⁴³, P. E. Lammers⁴⁵, A. Li⁴⁶, A. Loaiza-Bonilla⁴⁷, C. A. Low³², M. B. Lustberg⁴⁸, G. H. Lyman¹, R. R. McKay²⁰, C. McNair¹², H. Menon⁴⁹, R. A. Mesa⁵⁰, V. Mico¹², D. Mundt⁸, G. Nagaraj⁵¹, E. S. Nakasone¹, J. Nakayama^{22,52}, A. Nizam³⁵, N. L. Nock^{21,22}, C. Park², J. M. Patel¹⁷, K. G. Patel⁵³, P. Peddi⁵⁴, N. A. Pennell³⁵, A. J. Piper-Vallillo¹⁷, M. Puc⁵⁵, D. Ravindranathan¹⁶, M. E. Reeves⁵¹, D. Y. Reuben⁵⁶, L. Rosenstein⁵⁷, R. P. Rosovsky⁵⁸, S. M. Rubinstein⁵⁹, M. Salazar⁵⁰, A. L. Schmidt⁵, G. K. Schwartz³⁸, M. R. Shah⁶⁰, S. A. Shah³³, C. Shah¹⁸, J. A. Shaya²⁰, S. R. K. Singh³¹, M. Smits⁶¹, K. E. Stockerl-Goldstein⁶², D. G. Stover⁴⁸, M. Streckfuss⁸, S. Subbiah⁶³, L. Tachiki¹, E. Tadesse⁸, A. Thakkar³⁷, M. D. Tucker³, A. K. Verma³⁷, D. C. Vinh¹⁹, M. Weiss⁶¹, J. T. Wu³³, E. Wulf-Burchfield⁴¹, Z. Xie²⁵, P. P. Yu³⁹, T. Zhang³⁶, A. Y. Zhou⁶², H. Zhu⁶⁴, L. Zubiri⁵⁸, D. P. Shah^{50†}, J. L. Warner^{3†} & GdL. Lopes^{65†}

¹University of Washington/Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Seattle; ²University of Cincinnati Cancer Center, Cincinnati; ³Vanderbilt University Medical Center, Nashville; ⁴Vanderbilt University School of Medicine, Nashville; ⁵Dana-Farber Cancer Institute, Boston; ⁶Broad Institute, Cancer Program, Cambridge, USA; ⁷Lausanne University, Lausanne, Switzerland; ⁸Advocate Aurora Health, Milwaukee; ⁹Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville; ¹⁰University of Hawaii Cancer Center, Honolulu; ¹¹University of Colorado School of Medicine, Aurora; ¹²Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia; ¹³Mayo Clinic Cancer Center, Phoenix; ¹⁴Cardinal Bernardin Cancer Center, Loyola University Medical Center, Maywood; ¹⁵Houston Methodist Cancer Center, Houston; ¹⁶Winship Cancer Institute of Emory University, Atlanta; ¹⁷Beth Israel Deaconess Medical Center, Boston; ¹⁸University of Florida, Gainesville, USA; ¹⁹McGill University Health Centre, Montréal, Canada; ²⁰University of California San Diego, Moores Cancer Center, La Jolla; ²¹University Hospitals Seidman Cancer Center, Cleveland; ²²Case Western Reserve University, Cleveland; ²³Thompson Cancer Survival Center, Knoxville; ²⁴St. Elizabeth Healthcare, Edgewood; ²⁵Mayo Clinic Cancer Center, Rochester; ²⁶Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York; ²⁷Markey Cancer Center, University of Kentucky, Lexington; ²⁸The Warren Alpert Medical School of Brown University, Providence; ²⁹Tufts Medical Center Cancer Center, Boston and Stoneham; ³⁰University of Michigan Rogel Cancer Center, Ann Arbor; ³¹Henry Ford Cancer Institute/Henry Ford Health System, Detroit; ³²Intermountain Healthcare, Salt Lake City; ³³Stanford University, Stanford; ³⁴George Washington University, Washington DC; ³⁵Cleveland Clinic Taussig Cancer Institute, Cleveland; ³⁶Duke University, Durham; ³⁷Albert Einstein Cancer Center/Montefiore Medical Center, Bronx; ³⁸Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York; ³⁹Hartford HealthCare, Hartford; ⁴⁰University of Connecticut, Farmington; ⁴¹Mount Auburn Hospital, Cambridge; ⁴²University of Kansas Medical Center, Kansas City; ⁴³University of California, San Francisco, San Francisco; ⁴⁴Advanced Cancer Research Group, LLC, Kirkland; ⁴⁵Baptist Cancer Center, Memphis; ⁴⁶Baylor College of Medicine, Houston; ⁴⁷Cancer Treatment Centers of America, Philadelphia; ⁴⁸The Ohio State University, Columbus; ⁴⁹Penn State Health/Penn State Cancer Institute/St. Joseph Cancer Center, Hershey; ⁵⁰Mays Cancer Center at UT Health San Antonio MD Anderson, San Antonio; ⁵¹Loma Linda University Cancer Center, Loma Linda; ⁵²University Hospitals Cleveland Medical Center, Cleveland; ⁵³University of California Davis Comprehensive Cancer Center, Sacramento; ⁵⁴Willis-Knighton Cancer Center, Shreveport; ⁵⁵Virtua Health, Marlton; ⁵⁶Medical University of South Carolina, Charleston; ⁵⁷Gundersen Health System, La Crosse; ⁵⁸Massachusetts General Hospital, Harvard Medical School, Boston; ⁵⁹University of North Carolina, Chapel Hill; ⁶⁰Rutgers Cancer Institute of New Jersey, New Brunswick; ⁶¹ThedaCare Regional Cancer Center, Appleton; ⁶²Siteman Cancer Center, Washington University School of Medicine, St. Louis; ⁶³Stanley S. Scott Cancer Center, LSU Health Sciences Center, New Orleans; ⁶⁴Department of Medicine, Icahn School of Medicine at Mount Sinai, New York; ⁶⁵University of Miami/Sylvester Comprehensive Cancer Center, Miami, USA



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*Correspondence to: Dr Petros Grivas, Associate Professor, Department of Medicine, Division of Medical Oncology, University of Washington, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, 1144 Eastlake Avenue E, LG-465, Seattle, WA 98109, USA. Tel: +1-206-606-1943
E-mail: pgrivas@uw.edu (P. Grivas).

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[†] Contributed equally.

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Background: Patients with cancer may be at high risk of adverse outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We analyzed a cohort of patients with cancer and coronavirus 2019 (COVID-19) reported to the COVID-19 and Cancer Consortium (CCC19) to identify prognostic clinical factors, including laboratory measurements and anticancer therapies.

Patients and methods: Patients with active or historical cancer and a laboratory-confirmed SARS-CoV-2 diagnosis recorded between 17 March and 18 November 2020 were included. The primary outcome was COVID-19 severity measured on an ordinal scale (uncomplicated, hospitalized, admitted to intensive care unit, mechanically ventilated, died within 30 days). Multivariable regression models included demographics, cancer status, anticancer therapy and timing, COVID-19-directed therapies, and laboratory measurements (among hospitalized patients).

Results: A total of 4966 patients were included (median age 66 years, 51% female, 50% non-Hispanic white); 2872 (58%) were hospitalized and 695 (14%) died; 61% had cancer that was present, diagnosed, or treated within the year prior to COVID-19 diagnosis. Older age, male sex, obesity, cardiovascular and pulmonary comorbidities, renal disease, diabetes mellitus, non-Hispanic black race, Hispanic ethnicity, worse Eastern Cooperative Oncology Group performance status, recent cytotoxic chemotherapy, and hematologic malignancy were associated with higher COVID-19 severity. Among hospitalized patients, low or high absolute lymphocyte count; high absolute neutrophil count; low platelet count; abnormal creatinine; troponin; lactate dehydrogenase; and C-reactive protein were associated with higher COVID-19 severity. Patients diagnosed early in the COVID-19 pandemic (January–April 2020) had worse outcomes than those diagnosed later. Specific anticancer therapies (e.g. R-CHOP, platinum combined with etoposide, and DNA methyltransferase inhibitors) were associated with high 30-day all-cause mortality.

Conclusions: Clinical factors (e.g. older age, hematological malignancy, recent chemotherapy) and laboratory measurements were associated with poor outcomes among patients with cancer and COVID-19. Although further studies are needed, caution may be required in utilizing particular anticancer therapies.

Clinical trial identifier: NCT04354701

Key words: SARS-CoV2, neoplasm, cancer, anticancer therapy, laboratory measurements, outcomes

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has resulted in at least 1.5 million deaths worldwide.^{1,2} Patients with cancer may have increased risk for SARS-CoV-2 infection^{3–5} and worse outcomes.^{6–13} Estimates of 30-day mortality associated with coronavirus 2019 (COVID-19) for patients with cancer range from 13% to 33%,^{6,7} compared with 0.5% to 2% in the general population.^{1,14}

Patients with cancer comprise a heterogeneous population, and a better understanding of specific risk factors associated with poor outcomes may help guide clinical management. The COVID-19 and Cancer Consortium (CCC19) is an international consortium that collects data on patients with cancer and COVID-19.^{6,15,16} Studies from CCC19 and other cohorts have suggested that older age, male sex, smoking status, worse performance status (PS), presence of comorbidities, hematological malignancies, and active cancer are associated with more severe outcomes.^{6–9,13}

Prior studies were limited by modest statistical power. There is also conflicting data regarding the impact of timing and modality of recent anticancer therapy on COVID-19 severity.^{7,8,17} In addition, few studies have investigated the role of laboratory measurements as possible prognostic indicators, particularly among patients with cancer hospitalized with COVID-19.

Leveraging detailed information from almost 5000 patients with COVID-19 and cancer, we evaluated the hypothesis that specific demographic characteristics, clinical factors, and laboratory measurements would be associated

with higher COVID-19 severity. We also explored the impact of specific anticancer therapies on COVID-19 severity and 30-day all-cause mortality.

METHODS

Study design

CCC19 maintains a centralized multi-institution registry of patients with COVID-19 who have a current or past diagnosis of cancer. Details of the schema and data elements have been previously described.^{6,13} Study data are collected and managed using REDCap software hosted at Vanderbilt University Medical Center.^{18,19}

Reports were accrued from 17 March to 18 November 2020 and included patients who had a laboratory-confirmed diagnosis of SARS-CoV-2 by PCR and/or serology. Patients with noninvasive cancers including nonmelanoma skin cancer, *in situ* carcinoma (except bladder carcinoma *in situ*), or precursor hematologic neoplasms (e.g. monoclonal gammopathy of undetermined significance) were excluded. Reports with low-quality data (quality score >4 using our previously defined metric²⁰; [Supplementary Table S1](#), available at <https://doi.org/10.1016/j.annonc.2021.02.024>) or incomplete outcome ascertainment, resulting in unknown status of the primary outcome, were also excluded.

This study was exempt from Institutional Review Board (IRB) review (VUMC IRB#200467) and was approved by IRBs at participating sites per respective institutional policy. This ongoing study is registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04354701).

Outcome definitions

The primary outcome was a five-level ordinal scale of COVID-19 severity based on a patient's most severe reported disease status: none of the following complications (hereafter, uncomplicated); admitted to the hospital, admitted to an intensive care unit (ICU), mechanically ventilated at any time after COVID-19 diagnosis; or died from any cause within 30 days of COVID-19 diagnosis. We performed a secondary analysis of 30-day all-cause mortality and a descriptive analysis of patterns of anticancer therapy received within 3 months of COVID-19 diagnosis.

Prognostic factors

Potential prognostic variables were identified *a priori* and included age; sex; race/ethnicity; country of patient residence (United States versus non-United States); month of COVID-19 diagnosis (January-April, May-August, September-November; year 2020); smoking status; obesity; cardiovascular and pulmonary comorbidities; renal disease; diabetes mellitus; Eastern Cooperative Oncology Group (ECOG) PS; type of malignancy (solid tumor, hematological neoplasm); cancer status at time of COVID-19 diagnosis; timing of the most recent anticancer therapy; modality of anticancer therapy received within 3 months of COVID-19 diagnosis; and anti-COVID-19 treatments. Cancer status was defined as remission or no evidence of disease versus active disease, with active further defined as responding to therapy, stable, or progressing. Timing of anticancer therapy was categorized as never treated, 0-4 weeks, 1-3 months, and >3 months prior to COVID-19 diagnosis. Anticancer modalities were defined as cytotoxic chemotherapy, immunotherapy, targeted therapy, endocrine therapy, locoregional therapy (radiation and/or surgery), and other (Supplementary Table S2, available at <https://doi.org/10.1016/j.annonc.2021.02.024>). Anti-COVID-19 treatments included hydroxychloroquine, corticosteroids, remdesivir, and other (Supplementary Table S3, available at <https://doi.org/10.1016/j.annonc.2021.02.024>).

Survey respondents were instructed to report the earliest measured laboratory measurements during the COVID-19 disease course. Laboratory measurements included absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet count, creatinine, D-dimer, troponin, lactate dehydrogenase (LDH), and C-reactive protein (CRP). Hematological measurements (ALC, ANC, platelets) were recorded as high, normal, or low; nonhematological measurements were defined as normal or abnormal. Except for low ALC, which was centrally defined as ALC <1500/ μ l, ascertainment of upper and lower limits of normal was left to the discretion of survey respondents.

Statistical methods

All statistical methods were specified before database lock (18 November 2020) and the subsequent initiation of the analysis.

Standard descriptive statistics were used to summarize baseline prognostic factors overall and stratified by levels of

the ordinal COVID-19 severity outcome. Adjusted odds ratios and 95% confidence intervals for COVID-19 severity and 30-day mortality were estimated from multivariable ordinal and binary logistic regression models, respectively.²¹ Exploratory analyses with smoothing splines were used to determine the association of age (as a continuous variable) with outcomes,²² which appeared nonlinear (Supplementary Figure S1, available at <https://doi.org/10.1016/j.annonc.2021.02.024>). A linear regression spline with a knot at 40 years, which allowed a different linear association less than and greater than 40 years, provided an adequate fit. All other covariates were categorical.

For analyses among all patients, we included all pre-specified covariates in a single model, given a sufficient number of events (and corresponding degrees of freedom) to enable full multivariable models. In the primary analysis for COVID-19 severity, we did not adjust for anti-COVID-19 treatments due to suspected confounding by indication¹⁶; these were adjusted for in a sensitivity analysis. Results between minimally adjusted (age, sex, and race/ethnicity) and fully adjusted models, variance inflation factors, and clinical judgment were used to assess stability of the results. We considered interactions among specific comorbidities (cardiovascular, pulmonary, renal disease), specific anti-COVID-19 treatments (hydroxychloroquine, corticosteroids, other), specific anticancer therapies (cytotoxic chemotherapy, immunotherapy, targeted therapy), and between timing and modality of anticancer therapy.

Associations of laboratory measurements with outcomes were assessed among hospitalized patients due to current common clinical practice to avoid a laboratory blood draw for outpatients.²³ Because of the reduced sample size, we adjusted for a smaller set of potential clinical confounders: age, sex, race/ethnicity, country of patient residence, month of COVID-19 diagnosis, type of malignancy, cancer status, and active anticancer therapy. No interactions were considered for this analysis.

Multiple imputation using additive regression, bootstrapping, and predictive mean matching was used to impute missing and unknown data for all variables included in the analysis,²⁴ with the following exceptions: unknown ECOG PS and unknown cancer status were included as 'unknown' categories; and laboratory values were imputed only among hospitalized patients. Separate imputation models were developed for the full cohort (10 iterations; missingness rates were <5%) and the hospitalized cohort (20 iterations; missingness rates for laboratory values were >10%).

We conducted an exploratory analysis of specific anticancer drug exposures, which are collected in optional free-text fields. Two curators (JLW and XL) independently abstracted the fields for all patients with systemic anticancer therapy reported (cytotoxic chemotherapy, immunotherapy, endocrine therapy, and/or targeted therapy) within 3 months prior to COVID-19 diagnosis; disagreements were resolved by consensus. Specific drugs were grouped by similar mechanisms of action (Supplementary Table S2, available at <https://doi.org/10.1016/j.annonc.2021.02.024>).

2021.02.024) based on consensus among authors. The results were visualized using UpSet plots.²⁵

Analyses were performed in R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), including the Hmisc, rms, and UpSetR²⁶ extension packages.

RESULTS

A total of 6968 reports were evaluable in the REDCap database and 4966 were included in our analysis after exclusions (Supplementary Figure S2, available at <https://doi.org/10.1016/j.annonc.2021.02.024>). Among these patients, who had a median follow-up of 42 days [interquartile range (IQR) 22-90 days], 2872 (58%) were hospitalized during their COVID-19 course (Table 1). The median age of the entire cohort and hospitalized subgroup was 66 (IQR 56-76) and 70 (IQR 60-79) years, respectively. Approximately half of the patients were female and non-Hispanic white in each group, while non-Hispanic black patients represented 22% and 24%, respectively. Approximately 80% had solid tumors, 51% had cancer in remission, and 40% received anticancer therapy within 3 months of COVID-19 diagnosis. Altogether, 61% had cancer that was present, active, or treated within the past year. Additional baseline characteristics are summarized in Table 1.

Supplementary Table S4, available at <https://doi.org/10.1016/j.annonc.2021.02.024>, provides unadjusted rates of hospitalization and 30-day mortality. Of note, the 30-day mortality rate (95% CI) for patients diagnosed with COVID-19 during January-April, May-August, and September-November was 21% (20%-23%), 10% (9%-11%), and 7% (5%-10%), respectively.

COVID-19 severity

Of the 4966 patients, 2072 had an uncomplicated disease course (Table 2). For the 2894 patients with complications, 1675 were admitted to the hospital but did not require ICU care or mechanical ventilation and did not die. An additional 232 were admitted to the ICU without mechanical ventilation, 292 required mechanical ventilation, and 695 died within 30 days. Patients who died were older (median age 75 versus 61-69 years for other outcomes). Males had worse COVID-19 severity compared with females, as indicated by greater proportions of males among those who received mechanical ventilation or died. Table 2 and Supplementary Table S5, available at <https://doi.org/10.1016/j.annonc.2021.02.024>, provide summaries stratified by the ordinal outcome for the entire cohort and the hospitalized subgroup, respectively.

Multivariable analysis revealed higher COVID-19 severity among patients older than 40 years, males, and non-Hispanic black and Hispanic patients compared with non-Hispanic white patients (Table 3). In addition, obesity, cardiovascular and pulmonary comorbidities, renal disease, diabetes mellitus, worse ECOG PS, and hematological malignancy were associated with higher COVID-19 severity. Active and progressing cancer, recent active cytotoxic chemotherapy, and COVID-19-directed treatments were

also associated with higher severity. Notably, noncytotoxic systemic anticancer therapies including immunotherapy, targeted therapy, and endocrine therapy were not associated with higher COVID-19 severity. Of the 483 patients receiving endocrine therapy, 214 (44%) were in remission, which was a higher proportion than for those receiving cytotoxic chemotherapy (11%), targeted therapy (15%), or immunotherapy (6%).

More recent diagnosis of COVID-19 compared with diagnosis earlier in the pandemic (between January and April) was associated with lower COVID-19 severity. Significant interactions were observed among anti-COVID-19 treatments (Supplementary Table S6, available at <https://doi.org/10.1016/j.annonc.2021.02.024>). However, there were no meaningful interactions among medical comorbidities, anticancer therapies, or between timing of anticancer therapy and modality of anticancer therapies (Supplementary Table S7, available at <https://doi.org/10.1016/j.annonc.2021.02.024>).

Many characteristics associated with higher COVID-19 severity, including cytotoxic chemotherapy, were also associated with 30-day mortality (Table 3). Factors such as Hispanic ethnicity and cardiovascular comorbidities had a weaker association that was no longer statistically significant. COVID-19-directed treatments had a substantial attenuation of the association in the 30-day mortality analysis, although all retained statistical significance.

Laboratory measurements among hospitalized patients

Laboratory measurements collected during SARS-CoV-2 diagnosis were analyzed among the hospitalized subgroup of 2872 patients (Figure 1, Supplementary Table S8, available at <https://doi.org/10.1016/j.annonc.2021.02.024>). High ALC; low ALC; high ANC; and low platelets; as well as abnormal levels of creatinine; troponin; or LDH; were each associated with higher COVID-19 severity and 30-day mortality. Abnormal CRP was associated with higher COVID-19 severity.

Anticancer therapies

Of the 1803 patients receiving systemic anticancer therapy within 3 months of COVID-19 diagnosis, 1626 (90%) had extractable free-text drug exposure with 125 distinct drugs/classes reported. Most exposures ($n = 856$, 53%) were to a single drug or class; 357 (22%) patients received at least three drugs in combination. Drug/class exposures noted in at least 10 patients are shown in Figure 2. The three treatment regimens with the lowest and highest observed 30-day and overall all-cause mortality are described in Table 4. Platinum-etoposide, R-CHOP-like, and DNA methyltransferase inhibitor regimens were associated with the highest observed 30-day and overall all-cause mortality.

DISCUSSION

COVID-19 poses a substantial risk to patients with cancer. It is essential to understand factors associated with high risk of adverse outcomes to inform clinical decision making. In

Table 1. Baseline prognostic factors among all patients and hospitalized patients

	All patients (n = 4966)	Hospitalized patients (n = 2872)
Median age ^a , years (IQR)	66 (56-76)	70 (60-79)
Sex		
Female	2527 (51)	1323 (46)
Male	2436 (49)	1546 (54)
Missing/unknown	3 (<1)	3 (<1)
Race and ethnicity ^b		
Non-Hispanic white	2485 (50)	1371 (48)
Non-Hispanic black	1068 (22)	697 (24)
Hispanic	722 (15)	390 (14)
Other	578 (12)	359 (12)
Missing/unknown	113 (2)	55 (2)
Smoking status		
Never	2615 (53)	1356 (47)
Ever	2161 (44)	1386 (48)
Missing/unknown	190 (4)	130 (5)
Obesity status		
Not obese	3220 (65)	1909 (66)
Obese	1704 (34)	944 (33)
Missing/unknown	42 (1)	19 (1)
Comorbidities ^b		
Cardiovascular	1582 (32)	1175 (41)
Pulmonary	1091 (22)	762 (27)
Renal disease	831 (17)	644 (22)
Diabetes mellitus	1385 (28)	994 (35)
Missing/unknown	56 (1)	26 (1)
ECOG performance status		
0	1731 (35)	725 (25)
1	1296 (26)	794 (28)
≥2	806 (16)	675 (24)
Unknown	1121 (23)	671 (23)
Missing	12 (<1)	7 (<1)
Type of malignancy ^b		
Solid tumor	4021 (81)	2260 (79)
Hematological neoplasm	1097 (22)	717 (25)
Cancer status		
Remission or no evidence of disease	2546 (51)	1366 (48)
Active and responding	556 (11)	293 (10)
Active and stable	813 (16)	467 (16)
Active and progressing	613 (12)	452 (16)
Unknown	426 (9)	283 (10)
Missing	12 (<1)	11 (<1)
Timing of anticancer therapy		
Never treated	413 (8)	252 (9)
0-4 weeks	1609 (32)	907 (32)
1-3 months	375 (8)	231 (8)
>3 months	2344 (47)	1324 (46)
Missing/unknown	225 (5)	158 (6)
Modality of active anticancer therapy ^{b,c}		
None	2807 (57)	1625 (57)
Cytotoxic chemotherapy	802 (16)	491 (17)
Immunotherapy	248 (5)	137 (5)
Targeted therapy	693 (14)	426 (15)
Endocrine therapy	483 (10)	229 (8)
Locoregional therapy	422 (8)	249 (9)
Other	33 (1)	18 (1)
Missing/unknown	176 (4)	110 (4)
Anti-COVID-19 treatment ^b		
None	2816 (57)	1048 (36)
Remdesivir	438 (9)	435 (15)
Hydroxychloroquine	829 (17)	796 (28)
Corticosteroids	708 (14)	634 (22)
Other	1166 (23)	1023 (36)
Missing/unknown	259 (5)	143 (5)
Country of patient residence		
United States	4739 (95)	2714 (94)
Outside United States	227 (5)	158 (6)

Continued

Table 1. Continued

	All patients (n = 4966)	Hospitalized patients (n = 2872)
Month of COVID-19 diagnosis		
January-April	1927 (39)	1284 (45)
May-August	2508 (51)	1325 (46)
September-November	433 (9)	211 (7)
Missing/unknown	98 (2)	52 (2)
Absolute lymphocyte count ^d		
Low	—	1402 (49)
Normal	—	891 (31)
High	—	74 (3)
Missing/unknown	—	505 (18)
Absolute neutrophil count ^d		
Low	—	217 (8)
Normal	—	1739 (61)
High	—	474 (17)
Missing/unknown	—	442 (15)
Platelet count ^d		
Low	—	733 (26)
Normal	—	1675 (58)
High	—	119 (4)
Missing/unknown	—	345 (12)
Creatinine ^d		
Normal	—	1498 (52)
Abnormal	—	1049 (37)
Missing/unknown	—	325 (11)
D-dimer ^d		
Normal	—	236 (8)
Abnormal	—	1321 (46)
Missing/unknown	—	1315 (46)
Troponin ^d		
Normal	—	983 (34)
Abnormal	—	608 (21)
Missing/unknown	—	1281 (45)
Lactate dehydrogenase ^d		
Normal	—	358 (12)
Abnormal	—	1128 (39)
Missing/unknown	—	1386 (48)
C-reactive protein ^d		
Normal	—	137 (5)
Abnormal	—	1434 (50)
Missing/unknown	—	1301 (45)

Data presented as n (%) unless otherwise indicated. The 'Missing/unknown' category indicates either missingness due to nonresponse for optional survey questions or a response of unknown; an unknown category was provided for all survey questions. COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

^a For patients younger than 18 years (n = 9), age was truncated to 18 years; for patients older than 89 years (n = 161), age was truncated to 90 years. Truncation was done in concordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and to reduce the risk of re-identifiability.

^b Percentages could sum to >100% because categories are not mutually exclusive.

^c Within 3 months of COVID-19 diagnosis.

^d Laboratory data were systemically not collected for nonhospitalized patients.

this study, we used a novel ordinal outcome of COVID-19 severity and a cohort of almost 5000 patients with cancer to identify demographic factors (age, male sex, race/ethnicity), clinical factors (comorbidities, ECOG PS, hematological malignancy, active and progressing cancer, recent cytotoxic chemotherapy), and laboratory measurements (high or low ALC; high ANC; low platelets; abnormal creatinine, troponin, or LDH) associated with higher COVID-19 severity. While these data can certainly inform providers regarding prognostic factors and risk stratification, and also significantly broaden our understanding in this important

Table 2. Baseline prognostic factors stratified by levels of COVID-19 severity^a among all patients

Prognostic factor	No complications	Admitted to hospital	Admitted to ICU	Received mechanical ventilation	Died within 30 days
	(n = 2072, 42%)	(n = 1675, 34%)	(n = 232, 5%)	(n = 292, 6%)	(n = 695, 14%)
Median age ^b , years (IQR)	61 (50-70)	69 (59-78)	66.5 (58-76)	66 (57-72.25)	75 (66-83)
Sex					
Female	1193 (58)	832 (50)	109 (47)	111 (38)	282 (41)
Male	879 (42)	841 (50)	123 (53)	180 (62)	413 (59)
Missing/unknown	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)
Race and ethnicity ^c					
Non-Hispanic white	1100 (53)	802 (48)	116 (50)	125 (43)	342 (49)
Non-Hispanic black	369 (18)	389 (23)	51 (22)	76 (26)	183 (26)
Hispanic	328 (16)	239 (14)	27 (12)	46 (16)	82 (12)
Other	217 (10)	211 (13)	36 (16)	38 (13)	76 (11)
Missing/unknown	58 (3)	34 (2)	2 (1)	7 (2)	12 (2)
Smoking status					
Never	1248 (60)	842 (50)	105 (45)	154 (53)	266 (38)
Ever	764 (37)	768 (46)	113 (49)	126 (43)	390 (56)
Missing/unknown	60 (3)	65 (4)	14 (6)	12 (4)	39 (6)
Obesity status					
Not obese	1293 (62)	1125 (67)	148 (64)	165 (57)	489 (70)
Obese	756 (36)	538 (32)	82 (35)	125 (43)	203 (29)
Missing/unknown	23 (1)	12 (1)	2 (1)	2 (1)	3 (<1)
Comorbidities ^c					
Cardiovascular	393 (19)	629 (38)	96 (41)	110 (38)	354 (51)
Pulmonary	323 (16)	414 (25)	65 (28)	67 (23)	222 (32)
Renal disease	179 (9)	331 (20)	49 (21)	63 (22)	209 (30)
Diabetes mellitus	385 (19)	540 (32)	82 (35)	113 (39)	265 (38)
Missing/unknown	30 (1)	15 (1)	2 (1)	4 (1)	5 (1)
ECOG performance status					
0	1004 (48)	476 (28)	65 (28)	96 (33)	90 (13)
1	499 (24)	490 (29)	62 (27)	79 (27)	166 (24)
≥2	115 (6)	328 (20)	50 (22)	35 (12)	278 (40)
Unknown	449 (22)	378 (23)	54 (23)	80 (27)	160 (23)
Missing	5 (<1)	3 (<1)	1 (<1)	2 (1)	1 (<1)
Type of malignancy ^c					
Solid tumor	1744 (84)	1361 (81)	167 (72)	213 (73)	536 (77)
Hematological neoplasm	373 (18)	368 (22)	74 (32)	91 (31)	191 (27)
Cancer status					
Remission	1173 (57)	831 (50)	125 (54)	148 (51)	269 (39)
Active and responding	262 (13)	194 (12)	17 (7)	27 (9)	56 (8)
Active and stable	344 (17)	275 (16)	38 (16)	48 (16)	108 (16)
Active and progressing	153 (7)	243 (15)	23 (10)	32 (11)	162 (23)
Unknown	139 (7)	129 (8)	29 (12)	34 (12)	95 (14)
Missing	1 (<1)	3 (<1)	0 (0)	3 (1)	5 (1)
Timing of anticancer therapy					
Never treated	159 (8)	144 (9)	21 (9)	26 (9)	63 (9)
0-4 weeks	697 (34)	530 (32)	66 (28)	96 (33)	220 (32)
1-3 months	139 (7)	130 (8)	14 (6)	15 (5)	77 (11)
>3 months	1012 (49)	793 (47)	113 (49)	137 (47)	289 (42)
Missing/unknown	65 (3)	78 (5)	18 (8)	18 (6)	46 (7)
Modality of active anticancer therapy ^{c,d}					
None	1171 (57)	953 (57)	142 (61)	167 (57)	374 (54)
Cytotoxic chemotherapy	305 (15)	293 (17)	29 (12)	31 (11)	144 (21)
Immunotherapy	108 (5)	75 (4)	15 (6)	11 (4)	39 (6)
Targeted therapy	264 (13)	243 (15)	34 (15)	48 (16)	104 (15)
Endocrine therapy	252 (12)	149 (9)	11 (5)	24 (8)	47 (7)
Locoregional therapy	173 (8)	140 (8)	20 (9)	24 (8)	65 (9)
Other	15 (1)	9 (1)	0 (0)	2 (1)	7 (1)
Missing/unknown	65 (3)	63 (4)	10 (4)	14 (5)	24 (3)
Anti-COVID-19 treatment ^c					
None	1752 (85)	744 (44)	54 (23)	44 (15)	222 (32)
Remdesivir	<5 (<1)	210 (13)	72 (31)	69 (24)	84 (12)
Hydroxychloroquine	32 (2)	380 (23)	57 (25)	122 (42)	238 (34)
Corticosteroids	73 (4)	281 (17)	92 (40)	104 (36)	158 (23)
Other	142 (7)	465 (28)	100 (43)	175 (60)	284 (41)
Missing/unknown	112 (5)	84 (5)	11 (5)	14 (5)	38 (5)
Country of patient residence					
United States	2004 (97)	1573 (94)	221 (95)	282 (97)	659 (95)
Outside United States	68 (3)	102 (6)	11 (5)	10 (3)	36 (5)

Continued

Table 2. Continued					
Prognostic factor	No complications	Admitted to hospital	Admitted to ICU	Received mechanical ventilation	Died within 30 days
	(n = 2072, 42%)	(n = 1675, 34%)	(n = 232, 5%)	(n = 292, 6%)	(n = 695, 14%)
Month of COVID-19 diagnosis					
January-April	627 (30)	651 (39)	75 (32)	163 (56)	411 (59)
May-August	1177 (57)	842 (50)	129 (56)	115 (39)	245 (35)
September-November	222 (11)	148 (9)	26 (11)	6 (2)	31 (4)
Missing/unknown	46 (2)	34 (2)	2 (1)	8 (3)	8 (1)

Data presented as n (%) unless otherwise indicated. The 'Missing/unknown' category indicates either missingness due to nonresponse for optional survey questions or a response of unknown; an unknown category was provided for all survey questions.

COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; ICU, intensive care unit; IQR, interquartile range.

^a Five-level ordinal scale based on a patient's most severe reported disease status. For example, patients who were admitted to the intensive care unit without mechanical ventilation and did not die within 30 days of COVID-19 diagnosis are classified as 'admitted to intensive care unit', whereas patients who were admitted to the intensive care unit with mechanical ventilation and did not die within 30 days of COVID-19 diagnosis are classified as 'received mechanical ventilation'.

^b For patients younger than 18 years, age was truncated to 18 years; for patients older than 89 years, age was truncated to 90 years.

^c Percentages could sum to >100% because categories are not mutually exclusive.

^d Within 3 months of COVID-19 diagnosis.

topic, our findings are hypothesis generating and might not directly modify daily clinical practice.

Our findings confirm those from an earlier study from CCC19 and other studies.^{6-10,17} In particular, older age and male sex have been identified as negative prognostic factors among patients with or without cancer, although our study is the first, to our knowledge, to demonstrate a nonlinear relationship between age and risk.^{6-10,17,27}

We also noted higher COVID-19 severity for patients of non-Hispanic, non-white race/ethnicity and higher 30-day mortality for non-Hispanic black patients. These differences may suggest disparities in health care access, delivery, and research,²⁸ especially in the context of our prior finding and a recent systematic review suggesting that non-Hispanic black patients were less likely to receive novel anti-COVID-19 treatments.^{16,29} Future research from CCC19 is planned to investigate these disparities further.

Among patients with cancer, hematological malignancies,^{6,8,11} active cancer,^{6,9-11,17} and worse ECOG PS^{6,10,17} have been consistently associated with worse outcomes, which was also noted here. While prior studies observed a negative association between number of comorbidities and COVID-19 outcomes,^{6,7,9} few have investigated specific comorbidities as we included in our analysis.

In previous studies among patients without cancer, low ALC, low platelets, and abnormal CRP and creatinine were identified among laboratory values associated with severe COVID-19.^{30,31} Data among patients with cancer are limited, although prior studies suggested that abnormal CRP, LDH, and low ALC were associated with worse COVID-19 outcomes.^{10,17} Our study included a broader range of routinely collected laboratory measurements and identified new parameters associated with higher COVID-19 severity. However, we did not collect laboratory values now recognized to be associated with COVID-19 severity (e.g. ferritin³² and procalcitonin³³); future efforts will include automated extraction of these and longitudinal values directly from electronic health records.

Receipt of cytotoxic chemotherapy was associated with higher COVID-19 severity and 30-day mortality. However, there is substantial variability of anticancer regimens, such

that no one regimen containing cytotoxics was received by >31 patients (Figure 2). Some regimens may be subject to unmeasured confounding, for example, extent of lung involvement in patients with lung cancer receiving platinum doublets. It was very concerning to note the high mortality among those receiving R-CHOP, especially because most received it with curative intent. While grade 5 toxicities with R-CHOP may occur,³⁴ a mortality rate >40% is very high. Although the exact etiology remains unclear, this regimen is broadly immunosuppressive. In addition to B-cell lymphodepleting effects, rituximab is known to alter the T-cell compartment, which may contribute to cytokine storm.^{13,35} On the contrary, the finding of relatively lower mortality among patients with multiple myeloma receiving daratumumab + IMiD + corticosteroid seems paradoxical given the high risk of infection in this patient population. Interestingly, inhibition of the CD38 pathway may reduce the inflammatory response.³⁶ This relatively favorable prognosis is supported by several studies.³⁷⁻³⁹

Notably, immunotherapy alone was not associated with higher COVID-19 severity. This is in contrast to an earlier report in lung cancer,⁴⁰ which was subsequently disproven after adjustment for smoking status from the same group.⁴¹ This finding is encouraging as immuno-therapeutics (specifically, immune checkpoint inhibitors) are the most prescribed regimen in our cohort and >40% of patients with advanced cancer may be eligible for immunotherapy.⁴²

Similarly, endocrine therapy was not associated with higher COVID-19 severity, after adjustment for cancer status. There is a hypothetical possibility that antiandrogens could downregulate TMPRSS2 in the lung, limiting SARS-CoV-2 infection.^{13,43} Further investigation is needed.

The pandemic has substantially changed oncology practice in many deleterious ways, which may worsen cancer-related outcomes.^{13,44} Since the beginning, clinicians have attempted to balance the risks and benefits of cancer therapy by developing consensus-based algorithms to assist decision making⁴⁵⁻⁴⁸; our data could further guide the optimization and refinement of those algorithms. Our finding of lower COVID-19 severity later in the pandemic may also suggest an overall improvement in COVID-19 care.

Table 3. Adjusted associations of baseline prognostic factors with COVID-19 severity (primary) and 30-day all-cause mortality (secondary) among all patients

	COVID-19 severity	30-day mortality
	OR ^a (95% CI)	OR ^b (95% CI)
Age, per decade ^c		
Age <40 years	0.91 (0.72-1.15)	0.58 (0.35-0.97)
Age >40 years	1.38 (1.31-1.45)	1.75 (1.59-1.93)
Sex, male versus female	1.47 (1.31-1.65)	1.46 (1.20-1.77)
Race and ethnicity, versus non-Hispanic white		
Non-Hispanic black	1.46 (1.27-1.68)	1.38 (1.09-1.75)
Hispanic	1.38 (1.16-1.64)	1.31 (0.96-1.80)
Other	1.27 (1.05-1.53)	0.97 (0.70-1.36)
Smoking status, ever versus never	1.10 (0.98-1.24)	1.20 (0.98-1.46)
Obesity status, obese versus not obese	1.14 (1.01-1.29)	1.09 (0.88-1.35)
Cardiovascular comorbidities, yes versus no	1.46 (1.29-1.67)	1.17 (0.95-1.43)
Pulmonary comorbidities, yes versus no	1.52 (1.33-1.74)	1.34 (1.09-1.66)
Renal disease, yes versus no	1.38 (1.19-1.60)	1.31 (1.05-1.63)
Diabetes mellitus, yes versus no	1.53 (1.35-1.73)	1.23 (1.00-1.50)
ECOG performance status, versus 0		
1	1.42 (1.22-1.64)	1.53 (1.14-2.05)
≥2	3.44 (2.88-4.10)	4.48 (3.34-6.00)
Unknown	1.75 (1.50-2.04)	2.04 (1.51-2.76)
Type of malignancy, versus solid tumor		
Hematological neoplasm	1.70 (1.46-1.99)	1.44 (1.10-1.87)
Multiple ^d	1.21 (1.01-1.44)	1.30 (1.00-1.70)
Cancer status, versus remission or no evidence of disease		
Active and responding	0.84 (0.67-1.04)	0.79 (0.52-1.18)
Active and stable	0.97 (0.81-1.16)	1.06 (0.77-1.44)
Active and progressing	2.19 (1.80-2.67)	2.88 (2.13-3.90)
Unknown	1.93 (1.55-2.41)	2.19 (1.56-3.07)
Timing of anticancer therapy, versus >3 months		
Never treated	1.05 (0.83-1.32)	1.10 (0.75-1.62)
0-4 weeks	1.04 (0.79-1.36)	1.10 (0.70-1.72)
1-3 months	1.03 (0.75-1.41)	1.39 (0.84-2.29)
Modality of active anticancer therapy ^e		
Cytotoxic chemotherapy, yes versus no	1.28 (1.04-1.58)	1.61 (1.15-2.24)
Immunotherapy, yes versus no	0.86 (0.64-1.16)	0.91 (0.56-1.47)
Targeted therapy, yes versus no	1.09 (0.87-1.36)	0.90 (0.63-1.31)
Endocrine therapy, yes versus no	0.79 (0.61-1.03)	0.68 (0.43-1.09)
Locoregional therapy, yes versus no	1.18 (0.93-1.50)	0.96 (0.65-1.42)
Other, yes versus no	0.97 (0.47-2.00)	1.31 (0.44-3.94)
Anti-COVID-19 treatment ^f		
Remdesivir, yes versus no	—	1.55 (1.10-2.18)
HCQ alone, yes versus no	—	1.64 (1.16-2.32)
Corticosteroids alone, yes versus no	—	1.86 (1.35-2.56)
Other alone, yes versus no	—	1.64 (1.23-2.17)
HCQ + corticosteroids, yes versus no	—	1.91 (1.21-3.01) ^g
HCQ + other, yes versus no	—	2.98 (2.24-3.97) ^g
Country of residence, United States versus outside United States	1.07 (0.81-1.41)	0.85 (0.54-1.35)
Month of COVID-19 diagnosis, versus January-April		
May-August	0.50 (0.45-0.57)	0.43 (0.35-0.54)
September-November	0.42 (0.34-0.52)	0.26 (0.16-0.41)

Models for COVID-19 severity and 30-day all-cause mortality include all variables listed, except where noted. There were no indications of model instability, except for timing of anticancer therapy (variance inflation factor 5.4); however, multicollinearity is not unexpected because timing and modality are both defined by receipt of anticancer therapy. CI, confidence interval; COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; HCQ, hydroxychloroquine; OR, odds ratio.

^a Odds ratios >1 indicate higher COVID-19 severity.

^b Odds ratios >1 indicate higher odds of 30-day all-cause mortality.

^c Obtained from a linear regression spline with a knot at age 40 years, such that odds ratios for 'Age <40 years' correspond to the per-decade difference in age for ages <40 years and odds ratios for 'Age >40 years' correspond to the per-decade difference in age for ages >40 years.

^d Includes two or more solid tumors or hematological neoplasms.

^e Within 3 months of COVID-19 diagnosis.

^f The model for COVID-19 severity did include anti-COVID-19 treatments due to suspected confounding by indication.

^g Interaction $P = 0.19$ (2 degrees of freedom).

Alternative explanations for this finding include that certain areas may have been overwhelmed earlier in the pandemic and that patients prone to severe disease and death, particularly those in skilled nursing facilities, may have been infected early. Notably, only 9% of included patients were diagnosed with COVID-19 during September-November, so

that the observed improvement in outcomes should not be extrapolated to the surge in November-December 2020. Ultimately, an individualized risk-benefit discussion is critical when choosing systemic treatment, balancing carefully risks of cancer progression, associated risk of anticancer therapy, and COVID-19 severity.

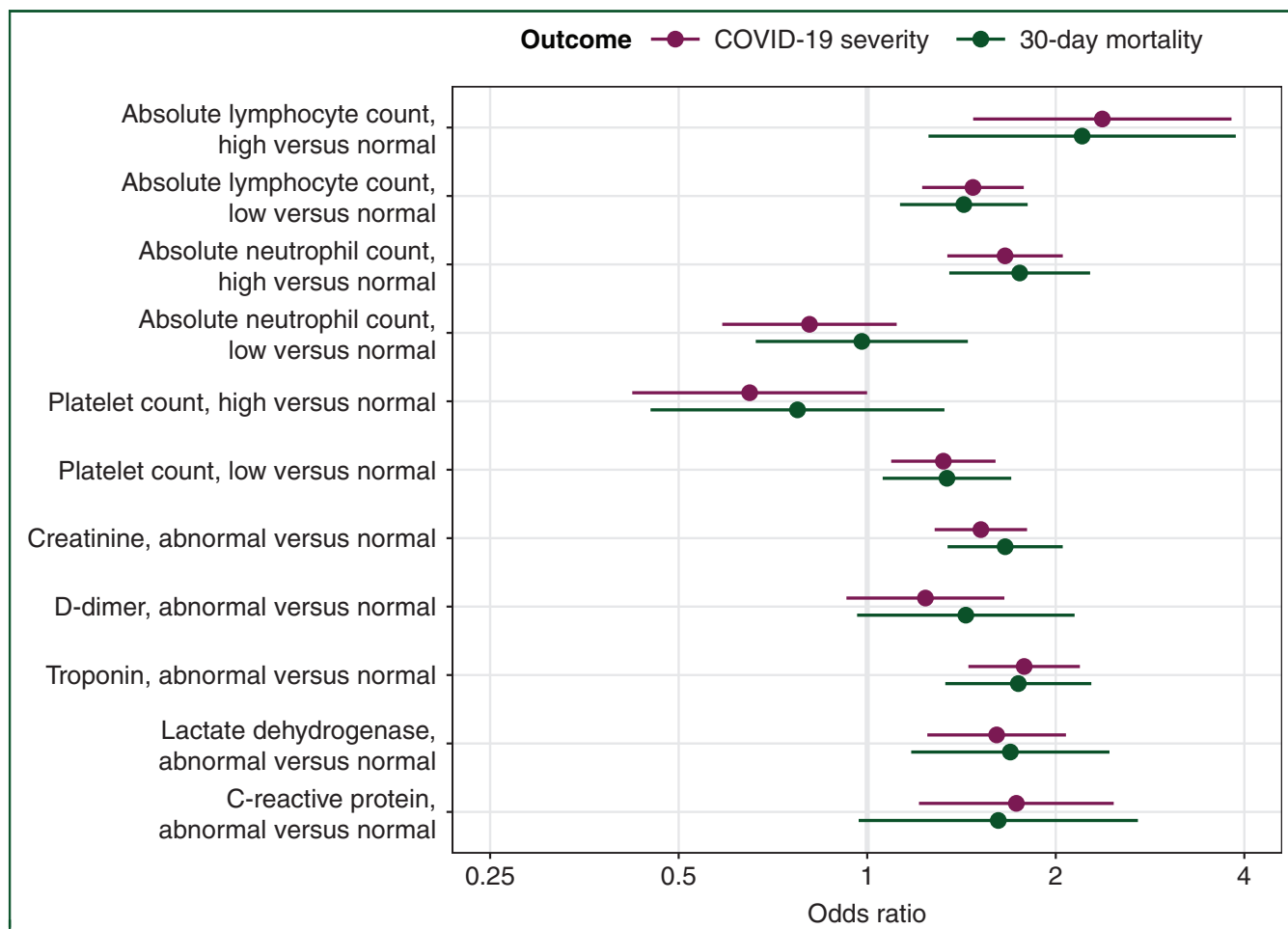


Figure 1. Adjusted odds ratios and 95% confidence intervals for laboratory measurements obtained from multivariable models for COVID-19 severity and 30-day all-cause mortality among hospitalized patients.

Odds ratios >1 indicate higher COVID-19 severity or higher odds of 30-day all-cause mortality. Adjusted for age, sex, race/ethnicity, country of patient residence, month of COVID-19 diagnosis, type of malignancy, cancer status, and active anticancer therapy. COVID-19, coronavirus disease 2019.

While the majority of prior studies have suggested poor outcomes for patients with cancer and COVID-19, a recent study using a case-matched study design found patients with cancer and COVID-19 had similar outcomes to those without cancer, when matched by age, sex, and comorbidities.⁴⁹ However, this study was limited to hospitalized patients in Manhattan, whereas our cohort includes any patient with cancer and COVID-19 and is diverse in multi-institutional representation.

Notable strengths of our study include detailed and granular information directly collected by health care professionals on a large and geographically diverse patient population with comprehensive follow-up. The novel ordinal scale of COVID-19 severity extends our previous research beyond 30-day mortality to capture other relevant complications of COVID-19 disease, and is consistent with newly recommended analytical approaches.⁵⁰ The analysis of anticancer therapy elucidated specific regimens associated with increased mortality, which warrants detailed exploration.

Our study has several limitations, including those inherent to a retrospective, observational cohort study.

Despite a robust data quality assurance system, survey-based data collection (voluntary, uncompensated) across multiple sites may result in selection biases, reporting errors, missing, and unknown data; the potential impact of these is mitigated by exclusion of low-quality reports and multiple imputation. Our results, particularly those for COVID-19 treatments, may be subject to confounding by indication and severity.¹⁶ Baseline laboratory measurements prior to COVID-19 diagnosis, which have been suggested to be associated with COVID-19 outcomes,⁵¹ were not collected due to the time-intensive nature of manually recording laboratories; automated data pulls from electronic health records may address this limitation in the future. Fixed dates are not captured due to the deidentified nature of the protocol; therefore time intervals are approximated at varying levels of granularity. We did not pursue subset analysis within individual cancer types, which is an area of future research.

In conclusion, we confirmed high COVID-19 severity and mortality among patients with cancer, in particular for those of older age, male sex, non-Hispanic non-white race/ethnicity, worse ECOG PS, hematologic malignancy, and

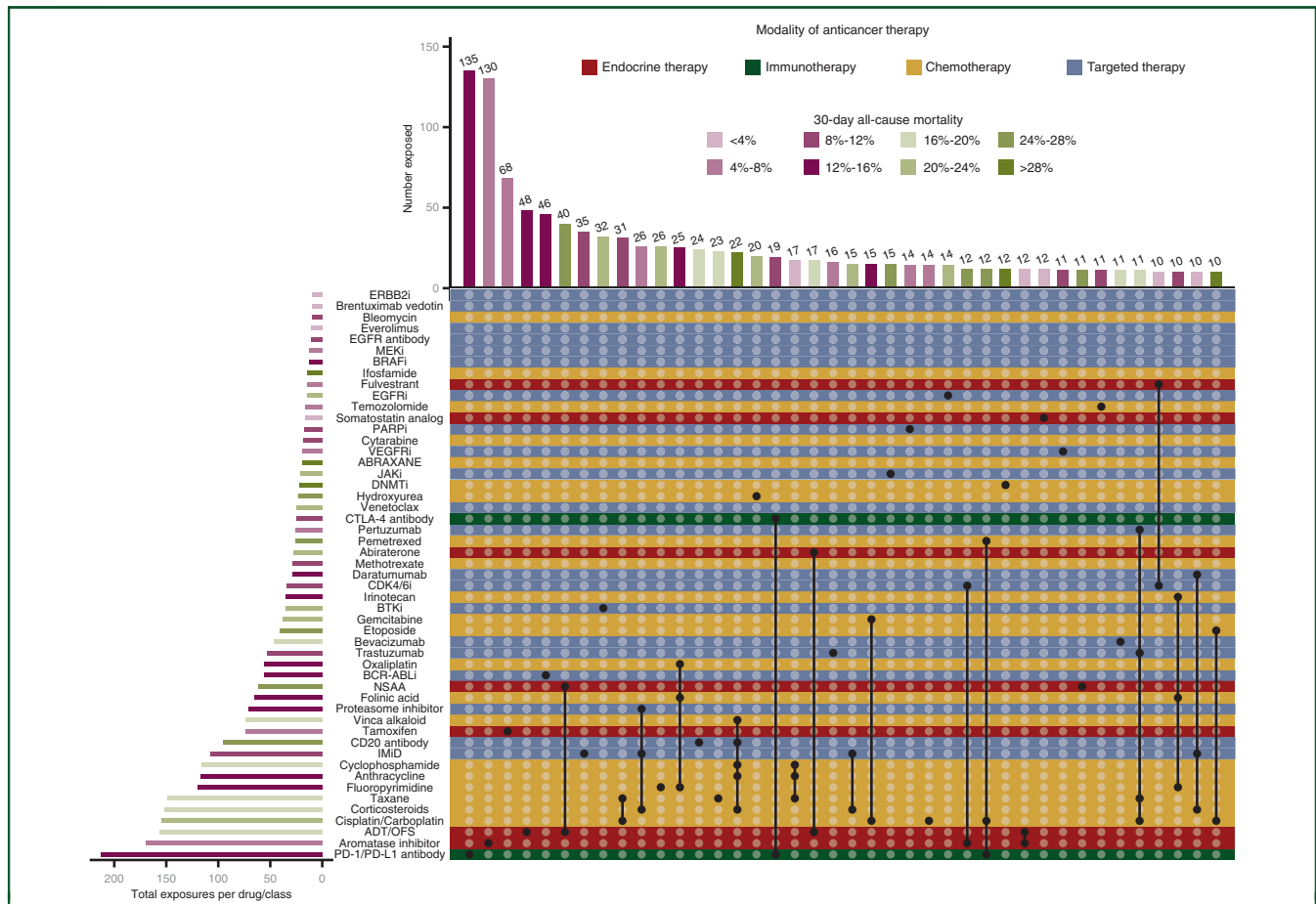


Figure 2. Visualization of the most prevalent cancer therapies and associated 30-day all-cause mortality. Individual anticancer drug exposures and their combinations are shown in an UpSet plot, which is an alternative to the Venn diagram for the visualization of high-dimensional data. Each row represents the individual anticancer therapies recorded as being given within 3 months of COVID-19 diagnosis that were present in ≥10 cases; rows are colored by treatment modality. Each column represents the intersection of one or more drugs given in combination (i.e. as a regimen) in ≥10 cases. A column with a single dark circle represents a monotherapy regimen; columns with multiple dark circles connected by dark lines represent multiagent regimens. Bars are colored by mortality for the patients receiving the drug or the combination, with darker hues representing higher mortality. This information is also shown in tabular format in [Supplementary Table 9](https://doi.org/10.1016/j.annonc.2021.02.024), available at <https://doi.org/10.1016/j.annonc.2021.02.024>. ADT, androgen-deprivation therapy; BCR-ABL_i, BCR-ABL tyrosine kinase inhibitor; BRAF_i, serine/threonine-protein kinase B-Raf inhibitor; BTK_i, Bruton tyrosine kinase inhibitor; DNMT_i, DNA methyltransferase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory imide drugs; IQR, interquartile range; MDS, myelodysplastic syndrome; MM, multiple myeloma; OFS, ovarian function suppression; PS, performance status; SCLC, small-cell lung cancer.

	Lowest observed mortality			Highest observed mortality		
	AC-T-like ^b (n = 17)	Dara-IMiD-Dex (n = 10)	OFS + AI (n = 12)	Platinum + Etoposide (n = 10)	R-CHOP-like ^c (n = 22)	DNMT _i (n = 12)
All-cause mortality						
30-day mortality	0 (0)	0 (0)	0 (0)	3 (30)	8 (36)	6 (50)
Any mortality	0 (0)	1 (10)	0 (0)	4 (40)	10 (45)	6 (50)
Most common primary cancer	Breast 17 (100)	MM 10 (100)	Breast 11 (92)	SCLC 5 (50)	DLBCL 17 (77)	MDS 7 (58)
Median (IQR) age, years	55 (49-62)	69 (64-80.5)	43.5 (41-46.5)	66.5 (60-74.5)	67.5 (45-79)	67.5 (59-87)
ECOG PS 0-1	16 (94)	5 (50)	11 (92)	6 (60)	18 (82)	7 (58)
Curative treatment intent	17 (100)	0 (0) ^d	10 (83)	2 (20)	18 (82)	1 (8)

Data presented as n (%) unless otherwise indicated.
 AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; COVID-19, coronavirus disease 2019; Dara, daratumumab; DLBCL, diffuse large B-cell lymphoma; DNMT_i, DNA methyltransferase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory imide drugs; IQR, interquartile range; MDS, myelodysplastic syndrome; MM, multiple myeloma; OFS, ovarian function suppression; PS, performance status; SCLC, small-cell lung cancer.
^a Not shown: somatostatin analogs, and CDK4/6i + fulvestrant.
^b Combination of anthracycline, cyclophosphamide, and taxane.
^c Combination of CD20 antibody, cyclophosphamide, anthracycline, vinca alkaloid, and corticosteroid.
^d All treatment for multiple myeloma except allogeneic stem cell transplant was considered palliative by definition.

select laboratory measurements. Certain chemotherapy regimens were associated with high all-cause mortality. These findings can inform novel translational research, clinical trial designs, and clinical decision making for patients with cancer and COVID-19. Future planned work from CCC19 includes further investigation into health care disparities, outcomes for specific cancer subtypes, and impact of particular anticancer therapies.

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