Suggested citation: Mileham K, Bruinooge S, Aggarwal C, et al: Changes over time in COVID-19 severity and mortality in patients undergoing cancer treatment in the U.S.: Initial report from the ASCO registry DOI: 10.1200/OP.21.00394 JCO Oncology Practice.

Title:

Changes over time in COVID-19 severity and mortality in patients undergoing cancer treatment in the U.S.: Initial report from the ASCO registry

Authors:

1. Kathryn F. Mileham*
    a. Degree: MD
    b. Affiliation: Atrium Health – Levine Cancer Institute
    c. Full Address: 1021 Morehead Medical Drive, Suite 30500, Charlotte, NC 28204
2. Suanna S. Bruinooge*
    a. Degree: MPH
    b. Affiliation: American Society of Clinical Oncology
    c. Full Address: 2318 Mill Road, Suite 800, Alexandria, VA, 22314
3. Charu Aggarwal
    a. Degree: MD
    b. Affiliation: University of Pennsylvania School of Medicine, Abramson Cancer Center
    c. Full Address: 3400 Civic Center Blvd, Philadelphia, PA 19104
4. Alicia L. Patrick
    a. Degree: MA
    b. Affiliation: Atrium Health – Levine Cancer Institute
    c. Full Address: 1021 Morehead Medical Drive, Suite 30500, Charlotte, NC 28204
5. Christiana Davis
    a. Degree: MD
    b. Affiliation: University of Pennsylvania School of Medicine, Abramson Cancer Center
    c. Full Address: 3400 Civic Center Blvd, Philadelphia, PA 19104
6. Daniel J. Mesenhowski
    a. Degree: BA
    b. Affiliation: Virginia Cancer Specialists, US Oncology Research
    c. Full Address: 8503 Arlington Blvd, Suite 400 |Fairfax, VA 22031
7. Alexander Spira
    a. Degree: MD, PhD
    b. Affiliation: Virginia Cancer Specialists, US Oncology Research, Johns Hopkins Oncology
    c. Full Address: 8613 Lee highway, Fairfax VA 22031
8. Eric J. Clayton
    a. Degree: MS
    b. Affiliation: OHC, Cincinnati OH/an Affiliate of US Oncology
    c. Full Address: 4350 Malsbary Road, Cincinnati, Ohio 45242
9. David Waterhouse
    a. Degree: MD, MPH
    b. Affiliation: OHC, Cincinnati OH/an Affiliate of US Oncology
    c. Full Address: 4350 Malsbary Road, Cincinnati, OH 45242
10. Susan Moore
    a. Degree: CNS
    b. Affiliation: Virginia Cancer Institute
    c. Full Address: 6605 W Broad St Ste A, Richmond, VA 23230
11. Abdul-Rahman Jazieh
    a. Degree: MD

   b. Affiliation: Cincinnati Cancer Advisors
   c. Full Address: 4746 Montgomery Rd. Suite 201, Cincinnati, OH 45212
12. Ronald C. Chen
   a. Degree: MD
   b. Affiliation: University of Kansas Cancer Center
   c. Full Address: 4001 Rainbow Blvd. Kansas City, KS 66160
13. Melinda Kaltenbaugh
   a. Degree: MBA
   b. Affiliation: American Society of Clinical Oncology
   c. Full Address: 2318 Mill Road, Suite 800, Alexandria, VA, 22314
14. Jen Hanley Williams
   a. Degree: MA
   b. Affiliation: American Society of Clinical Oncology
   c. Full Address: 2318 Mill Road, Suite 800, Alexandria, VA, 22314
15. Julie R. Gralow
   a. Degree: MD
   b. Affiliation: American Society of Clinical Oncology
   c. Full Address: 2318 Mill Road, Suite 800, Alexandria, VA, 22314
16. Richard L. Schilsky**
   a. Degree: MD
   b. Affiliation: American Society of Clinical Oncology
   c. Full Address: 2318 Mill Road, Suite 800, Alexandria, VA, 22314
17. Elizabeth Garrett-Mayer**
   a. Degree: PhD
   b. Affiliation: American Society of Clinical Oncology
   c. Full Address: 2318 Mill Road, Suite 800, Alexandria, VA, 22314

***** Dr. Mileham and Ms. Bruinooge contributed equally as co-first authors.

** Drs. Schilsky and Garrett-Mayer contributed equally as co-senior authors.

Role of the funding source: Conquer Cancer, the ASCO Foundation, funds the ASCO Registry and had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication.

Corresponding Author: Suanna S. Bruinooge, suanna.bruinooge@asco.org, Phone: 571-483-1613, 2318 Mill Road, Suite 800, Alexandria, VA, 22314

Running Head: COVID-19 severity and mortality: ASCO Registry

Presentations: Poster presentation and discussion session at 2021 ASCO Annual Meeting

Abstract (246 of 250 words)

Introduction

People with cancer are at increased risk for SARS-Cov-2 infection. ASCO's COVID-19 registry promotes systematic data collection across U.S. oncology practices.

Methods

Participating practices enter data on patients with SARS-CoV-2 infection in cancer treatment. In this analysis, we focus on all patients with hematologic or regional/metastatic solid tumor malignancies. Primary outcomes are 30- and 90-day mortality rates and change over time.

Results

38 practices provided data for 453 patients from April-October 2020. 62% had regional/metastatic solid tumors. Median age was 64 years. 43% were current or previous cigarette users. Patients with B-cell malignancies aged 61-70 had twice mortality risk (HR=2.1 (95% CI: 1.3-3.3) and those >70 had 4.5 times mortality risk (95% CI: 1.8-11.1) compared with patients ≤60. Association between survival and age was not significant in patients with metastatic solid tumors (p=0.12). Tobacco users had 30-day mortality estimate of 21% compared to 11% for never users (log-rank p=0.005). Patients diagnosed with SARS-CoV-2 prior to June 2020 had 30-day mortality rate of 20% (95% CI: 14%-25%) compared to 13% (8%-18%) for those diagnosed in/after June 2020 (p=0.08). The 90-day mortality rate for pre-June patients was 28% (21%-34%) compared with 21% (13%-28%) (p=0.20).

Conclusions

Older patients with B-cell malignancies were at increased risk for death (unlike older patients with metastatic solid tumors), as were all patients with cancer who smoke tobacco. Diagnosis of SARS-CoV-2 later in 2020 was associated with more favorable 30- and 90-day mortality likely related to more asymptomatic cases and improved clinical management.

MANUSCRIPT (3121 OF 3000 WORDS)

Introduction:

People living with cancer are at increased risk for SARS-Cov-2 infection[1] COVID-19, and mortality.[2-5] The American Society of Clinical Oncology (ASCO) has a mission of helping oncology clinicians through research, education, and promotion of the highest quality and equitable patient care. Thus, ASCO created a registry to track acute and chronic effects of COVID-19 on cancer care delivery, treatments, and outcomes.

ASCO's Registry collects data from mostly community-based, non-academic medical oncology practices and supports longitudinal data collection to track outcomes over time. Outcomes of interest include all-cause mortality, COVID-19 symptoms and treatments, cancer treatment at the time of and following COVID-19 diagnosis, and changes to cancer treatment plans. In this initial report, our primary objective is to describe the impact of SARS-CoV-2 infection on patients with cancer undergoing anticancer treatment during 2020.

Methods:

Study Design: The ASCO Survey on COVID-19 in Oncology Registry is a cohort study launched in April 2020. Participating oncology practices identify patients with a positive SARS-CoV-2 test who are also actively undergoing cancer treatment. The limited identifiers include birth date, home zip code, and event dates. Birth date, home zip code, and practice name are used to link data from the same patient. Electronic health record data are manually entered by staff into REDCap electronic data capture tools (a secure, web-based software platform) hosted at ASCO.[6,7] The recommended data entry schedule is at positive SARS-CoV-2 test and then at the following one, two, three, six, nine, and 12 months, although practices may submit initial data at any time. ASCO is implementing a Registry update that will extend data collection to 18 and 24 months, enabling tracking of additional vaccine doses and SARS-CoV-2 reinfections. Practices joining the registry are asked to submit data retrospectively for eligible patients who experienced illness earlier in the pandemic. The study involves a limited dataset and requires data use agreements with participating institutions; WCG IRB reviewed the study protocol and determined it was not human subject research. This study (ClinicalTrials.gov:NCT04659135) continues to add data from new and continuing patients (retrospectively and prospectively).

Practice participation: 77 practices in the United States are currently participating, with 38 having submitted data on at least one patient at data cutoff (October 24, 2020).

Eligibility: Patients who test positive for SARS-CoV-2 and (a) have active cancer or (b) are receiving adjuvant treatment for a cancer resected within the past 12 months are eligible for registry inclusion. For this analysis, we focused on patients with hematologic malignancies or regional/metastatic solid tumors who were receiving anticancer drug therapy when they tested positive for SARS-CoV-2.

Data Collection: The registry collects information on demographics, risk factors (e.g., comorbidities, smoking history), cancer (e.g., type, treatments, treatment delays), SARS-CoV-2 infection (e.g., symptoms, treatments, hospitalizations, long-term sequelae), and mortality at initial data entry. Follow-up information on acute SARS-CoV-2 infection is collected at one, two, and three months; long term symptoms and sequelae are collected at six, nine, and 12 months after a diagnostic SARS-CoV-2 test (supplemental figure 1). Patients' cancer status and anticancer treatment are collected at all entries.

Outcomes: We focus primarily on 30- and 90-day mortality – all-cause and due to COVID-19. Because of changes in availability of diagnostic testing, clinical experience in managing patients, and revisions to U.S. guidelines in 2020, we hypothesized that we would find differences among patients who tested positive for the virus earlier vs. later in 2020. Therefore, we examined patient outcomes before and after June 1, 2020, separately.

Statistical Analysis: Descriptive statistics summarized patient characteristics. Proportions were estimated with exact 95% confidence intervals (CI). Comparisons were made using Fisher's exact test, or Chi-square test. Hypothesis tests involving categorical variables with "unknown" categories were performed without including "unknown" data. Overall survival (OS) is defined as time from SARS-CoV-2 positive test result to death. Kaplan-Meier methods were used to estimate 30- and 90- day mortality estimates within subgroups, with 95% CIs; 90-day mortality was compared using a Z-test. Logrank tests were used for comparing survival distributions. Cox regression evaluated the association between OS and age and cancer type. Age was included as ordinal with age groups ≤60, 61-70, >70. Interactions between age and cancer type were included to assess differences in association between age and OS by cancer type. Adherence to ordinality was assessed by fitting the model with age groups as nominal. Fit was almost identical based on estimated hazard ratios and likelihood statistics; the model with age group as ordinal is reported due to improved precision of estimates. Sample size was not determined based on a power calculation or other justification because of the observational aspect. Therefore, findings are hypothesis generating. Data cutoff was based on timing of study revisions. While there was sufficient sample size for some comparisons, certain subgroup analyses were underpowered. As a result, inferences relied primarily on point estimates and 95% CIs with less reliance on p-values.

Results:

Patient characteristics. Of the 755 patients entered in the registry by October 24 (one practice provided batched data on November 15), 453 met inclusion criteria for this analysis (supplemental figure 2). Most patients (76%) were entered by 31 non-academic practices within hospitals/health systems or free-standing (table 1). Half of patients (53%) had metastatic solid tumors; 38% had hematologic malignancies; 9% had regional solid tumors. The most common cancer diagnosis was multiple myeloma (17%) followed by metastatic lung and metastatic breast cancers (11% each). Half of patients (53%) have 30 days or more of follow-up data after SARS-CoV-2 test or died ≤30 days from SARS-CoV-2 test.

61% percent of patients were white, 27% black, and 12% other or unknown race. Most patients were female (53%); median age was 64 years (IQR: 54, 74). Most patients had no documented history of tobacco smoking (52%); 43% were current or previous cigarette users (5% unknown). Due to their association with COVID-19[8,9], hypertension, diabetes, and pulmonary disease (not including lung cancer) were examined; 36% of patients had one of these comorbidities; 23% had two comorbidities; no patients had all three. 35% of patients had no reported comorbidities (except cancer diagnosis). Most patients were either overweight (34%) or obese (36%) according to body mass index scale.

Impact on cancer treatment. At the time of initial data entry, about one-third of patients (35%) were continuing their anticancer drug treatments without change; half of patients (49%) had delayed one or more anticancer drug treatments but did not discontinue any treatments. 73 patients (16%) had discontinued one or more of their anticancer drug treatments, with and without antecedent delays. Most patients without drug treatment changes (72%) and those with delayed treatments (68%) were age ≤70 years. In those who had one or more drug discontinuations, 49% were >70 years old (supplemental table 2). Most patients with anticancer drug discontinuations were hospitalized for COVID-19 (72%), including 30% who received intensive care. Of patients without drug treatment changes, 41% were hospitalized with only 12% receiving intensive care. A similar percentage of patients with delays were hospitalized (38%; 10% receiving intensive care).

Patient outcomes. A total of 95 patients in the cohort had died prior to data cutoff. Most of these deaths (61%) were attributed to COVID-19 or its complications. Cancer progression was the second most common cause of death (22%), with causes of the remaining deaths unknown (8%), unrelated to cancer or COVID-19 (3%), or not reported (5%).

Preliminary analyses showed associations between OS and age (≤60, 61-70, >70, p=0.001). There was no significant difference in OS comparing patients with B-cell malignancies versus those with metastatic solid tumors. Looking within cancer types, however, an age association was observed in patients with B-cell malignancies (Figure 1). Among patients with metastatic solid tumors, those aged 61-70 were not at significantly increased risk of death compared to patients ≤60 (HR=1.29 (95% CI: 0.93-1.79), and similarly for those aged >70 vs. ≤60 (HR=1.67, 95% CI: 0.87-3.19). In contrast, patients with B-cell malignancies aged 61-70 were at more than twice the risk of death (HR=2.11 (95% CI:1.34-3.32), and patients >70 years old were at 4.47 times the risk of death (95% CI: 1.80-11.06) compared with patients ≤60 years old.

All-cause mortality rates at the 30- and 90-day timepoints for all patients were 16% (95% CI: 12%-20%) and 24% (95% CI: 20%-29%), respectively. Many differences emerged over time in univariable analyses (supplemental table 1). Prior to June, testing was limited; the main reason for testing was COVID-19 symptoms (74%). Beginning in June 2020, significantly fewer patients were tested due to symptoms (49%, p<0.001), and significantly more patients were tested during routine oncology care (35% after vs. 7% before, p<0.001). Significantly more patients who tested positive before June had COVID-19 related pneumonia compared to those who tested positive in/after June (46% vs. 23%, p<0.001). Hospitalization for COVID-19, with and without ICU admission, decreased for patients diagnosed in/after June compared with those diagnosed before June (p<0.001 for both) (supplemental figure 3). Patients diagnosed before June were significantly more likely to have received supplemental oxygen (44% vs. 21% p<0.001) and been placed on a ventilator (16% vs. 6%, p=0.001) than those diagnosed in/after June.

Figure 2 demonstrates 30- and 90-day mortality rates in patients diagnosed before June and those diagnosed in/after June. Patients diagnosed prior to June had a 30-day mortality rate of 20% (95% CI: 14%-25%) compared to 13% (8%-18%) for those diagnosed in/after June (p=0.08). The 90-day mortality rate for patients with pre-June diagnoses was also higher at 28% (21%-34%) compared with 21% (13%-28%) although not significant (p=0.20). Patients with pre-June diagnosis admitted to the ICU had a 54% (33%,68%) mortality rate at 30 days and 63% (42%-76%) at 90 days. Patients with pre-June diagnosis who were hospitalized without intensive care had a 22% (12%-29%) mortality rate at 30 days and 35% rate (23%-44%) at 90 days. Mortality rates for patients with a diagnosis in/after June who were hospitalized without intensive care were lower at 30 days (11%; 95%CI: 2%-19%) and 90 days (23%; 95%CI: 5%-35%).

The only patient subgroups diagnosed in/after June whose 30- and 90-day mortality rates were substantially higher than for those diagnosed before June were patients who discontinued anticancer therapy and patients admitted to intensive care. Some comparisons across the time periods are limited due to sample size. People with current or past tobacco use had increased mortality rates in both the pre-June and in/after June period. As shown in supplemental figure 4, ever having smoked is a risk factor for mortality with a 30-day mortality estimate of 21% compared to only 11% for never smokers (HR=1.81, p=0.005). We found no association between BMI and mortality and adjusting for BMI did not diminish the association between tobacco use and mortality (HR=1.78, p=0.008).

Discussion:

During 2020, availability of SARS-CoV-2 tests, emerging data on use of antivirals and steroids as COVID-19 therapeutic interventions[10-13] and increasing recognition of asymptomatic transmission as an important element of infection[14] led to changes in COVID-19 screening, testing, and care delivery and cancer treatment. We observed temporal differences in COVID-19 symptomatology, as well as COVID-19 and cancer disease management and outcomes in patients receiving treatment for their cancer and COVID-19. Changes in COVID-19 management and patient outcomes also reflect clinicians' growing understanding of the disease and how best to manage severe complications, as well as increasing availability of disease management options. This analysis is among the first to identify these temporal changes in the care of patients with cancer undergoing active cancer therapy, and the first to describe 90-day mortality rates for patients with cancer and COVID-19.

We observed a 30-day mortality rate of 20% for patients diagnosed with SARS-CoV-2 prior to June 2020, which is greater than other reports. For example, the 30-day mortality rate of 13% reported in a similar period using COVID-19 and Cancer Consortium (CCC19) data likely reflects differences between the registry populations. The ASCO Registry restricts reporting to patients in active cancer treatment and receives most reporting from community/non-academic practices (76%); a minority (39%) of the CCC19 cohort analyzed were in active anticancer treatment and most (92%) were treated at academic centers where testing might have been more readily available earlier in the pandemic, possibly identifying milder cases. As a result, our respective cohorts may not be directly comparable. Notably, during the same pre-June 2020 interval, the rates of 30-day mortality are similar among those admitted to the hospital, 22% in CCC19 and 23% in the ASCO Registry. For those admitted to intensive care, however, large differences emerge; patients in the ASCO Registry who received intensive care had a 30-day

mortality rate of 58% compared with 38% in CCC19[15], likely reflective of clinical care setting and/or impact of active cancer therapy.

This analysis from the ASCO Registry reveals an increased mortality risk with increasing age in patients, especially those with B-cell malignancies. There is nominal (and not significant) increased risk of mortality with age in those with solid tumor malignancies. The identification of more than twice the risk of death (HR = 2.11 and 4.47, respectively) for patients with B-cell malignancies aged 61-70 and >70 years, is strengthened by the inclusion of large percentages of patients over 71 years (33%) and patients with B-cell malignancies (32%). Older age has been established as one of the main risk factors for severe COVID-19,[16] and other COVID-19 and cancer registry analyses report an association between increased age and mortality.

Other analyses[17-19] have also found an increased risk for COVID-19 mortality among patients with hematologic malignancies with varying findings based on the type of hematologic malignancy.[1821] Passamonti et al observed worse survival among patients with acute myeloid leukemia, indolent non-Hodgkin lymphoma, aggressive non-Hodgkin lymphoma, and plasma cell neoplasms. Mortality association in Dai et al was observed in patients with leukemia, lymphoma, or myeloma. The American Society of Hematology Registry found that those with Hodgkin lymphoma had the highest percentage of deaths, followed by acute leukemia, multiple myeloma/amyloid light chain, and chronic lymphocytic leukemia.[19] The biological basis for increased COVID-19 mortality among patients with hematologic cancers is presumed to be due to decreased SARS-CoV-2-specific antibodies (IgM and IgG) in response to infection along with quantitative defects in CD4 and B cells (either due to the underlying disease or to its treatment) as compared to patients with solid tumor malignancies.[20] Reports from BNT162b2 mRNA SARS-CoV-2 vaccination studies bolster this hypothesis finding a lower antibody response rate for patients with chronic lymphocytic leukemia[22] and older patients with multiple myeloma (median age of 83 years; range: 59-92).[23] Our analysis found an association of mortality with age for patients with all B-cell malignancies, which included multiple myeloma, non-Hodgkin lymphoma, lymphoid leukemia, and Hodgkin lymphoma. As the number of patients and length of follow-up data grow, we plan to conduct more in-depth analyses within patients with B-cell malignancies.

Our analysis did not find an association between race, sex, and comorbidity index (including hypertension, diabetes, and pulmonary disease) and OS in our cohort of patients with regional/metastatic solid or hematologic malignancies receiving anticancer therapy. Reports from other registries[17,8,18] earlier in the pandemic provided different findings across more diverse populations,

including those with early-stage disease and survivors. Kuderer et al found a mortality association for progressive cancer, smoking (former and current), male sex, race, number of comorbidities, and ECOG performance status $\geq$ two.[15] An international analysis of 650 patients with multiple myeloma found that age, renal disease, and high-risk or poorly controlled multiple myeloma were independent predictors of mortality.[26] In this analysis of the ASCO Registry, mortality was only associated with current/former tobacco use and older age in patients with B-cell malignancies. Because all the patients included in our cohort had advanced cancer and were receiving anticancer therapy, advanced cancer and active cancer treatment may have greater impacts than other risk factors in determining patient outcome.

Finally, our analysis offers insight about changes to cancer care delivery for patients diagnosed with COVID-19. We report a high percentage of patients with treatment delays (49%) and discontinuations (16%) with or without delays. Interpretation of these findings is challenging because of limited ability to discern whether the changes were driven by the patient's COVID-19 severity, their cancer status, or both. In addition, practices may have implemented policies to pause anticancer treatment for all patients for one or more time periods to reduce exposure risks to other patients and staff within infusion space. We plan more in-depth analysis on delays and discontinuations of cancer therapies, as well as rationale for the delays and discontinuations and associations with COVID-19 symptoms and severity and patient outcomes in future work. In addition, with longer follow-up and a larger sample size, we will have power to perform analyses with greater attention to adjustment for potential confounders, including evaluation of COVID-19-related versus non-COVID-19-related OS.

This observational research study is reliant largely on data collected from ambulatory oncology clinics. As a result, ready access to inpatient and clinical data not directly related to oncology treatment varies. We directed practices to inquire with hospitals to obtain this information. We also recognize that this initial patient cohort is not representative of all patients with cancer, and sample size for this analysis is modest. To improve external validity, we are recruiting practices from additional geographic locations and enhancing inclusion of cases including the most frequent incident cancers. Differential duration of follow-up for those diagnosed early versus later in the pandemic may lead to bias, but most hospitalizations and COVID-19 symptoms are reported on the initial registry form, so the potential differential follow-up bias is somewhat mitigated. Initial analysis of data collected regarding cancer treatment delays and discontinuations led us to recognize that more detailed data was needed (e.g., start/stop dates, drug names) to better characterize lengths of delays and identify treatments that were

changed or discontinued. Our data collection forms have now been revised to capture this information and will provide greater detail to expand this analysis in future research.

Although U.S. outbreaks have slowed, our findings continue to be relevant in areas with low vaccination rates and surging SARS-CoV-2 variant infections. Additionally, for patients with cancer who exhibit decreased vaccine response, our findings that life can be extended with early diagnosis (testing of asymptomatic individuals) and aggressive care (as implemented after June 2020) are important, as SARS-CoV-2 remains a public health problem in the U.S as well as in many countries, especially low- and middle-income countries around the world with limited access to vaccines.

Conclusions:

Among patients with regional or metastatic solid tumor and hematologic cancers, those with both B-cell malignancies and older age were at increased risk for death, along with people who previously or currently smoke tobacco. Patients in the U.S. diagnosed with SARS-CoV-2 during the first six months of 2020 were more likely to receive intensive COVID-19 interventions and were at greater mortality risk. Delays and discontinuations of cancer treatment were common and future analyses will provide more in-depth analysis of this data.

Acknowledgments:

The ASCO Registry is supported by Conquer Cancer, the ASCO Foundation's COVID Impacts Cancer Fund (https://p2p.conquer.org/covidresponse?cmpid=learn_more_homepage_secondary_pane). ASCO thanks the oncology practices that are participating in the ASCO Survey on COVID-19 in Oncology (ASCO) Registry (https://www.asco.org/asco-coronavirus-information/coronavirus-registry), taking the time to enter data on their patients' experiences with cancer and COVID-19.

References

1. Wang Q, Berger NA, Xu R. Analyses of Risk, Racial Disparity, and Outcomes Among US Patients With Cancer and COVID-19 Infection. JAMA Oncol. 2021 Feb 1;7(2):220-227. doi: 10.1001/jamaoncol.2020.6178. PMID: 33300956; PMCID: PMC7729584.
2. He, W., Chen, L., Chen, L. *et al.* COVID-19 in persons with haematological cancers. *Leukemia* 34, 1637–1645 (2020). https://doi.org/10.1038/s41375-020-0836-7
3. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, Bogler Y, Caldararo M, Figueroa CJ, Glickman MS, Joanow A, Kaltsas A, Lee YJ, Lucca A, Mariano A, Morjaria S, Nawar T, Papanicolaou GA, Predmore J, Redelman-Sidi G, Schmidt E, Seo SK, Sepkowitz K, Shah MK, Wolchok JD, Hohl TM, Taur Y, Kamboj M. Determinants of COVID-19 disease severity in patients with cancer. Nat Med. 2020 Aug;26(8):1218-1223. doi: 10.1038/s41591-020-0979-0. Epub 2020 Jun 24. PMID: 32581323; PMCID: PMC7785283.
4. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, Li C, Ai Q, Lu W, Liang H, Li S, He J. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020 Mar;21(3):335-337. doi: 10.1016/S1470-2045(20)30096-6. Epub 2020 Feb 14. PMID: 32066541; PMCID: PMC7159000.
5. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. JAMA Oncol. 2020 Jul 1;6(7):1108-1110. doi: 10.1001/jamaoncol.2020.0980. PMID: 32211820; PMCID: PMC7097836.
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010. Epub 2008 Sep 30. PMID: 18929686; PMCID: PMC2700030.
7. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN; REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019 Jul;95:103208. doi: 10.1016/j.jbi.2019.103208. Epub 2019 May 9. PMID: 31078660; PMCID: PMC7254481.
8. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, Abosalif KOA, Ahmed Z, Younas S. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020 Dec;13(12):1833-1839. doi: 10.1016/j.jiph.2020.07.014. Epub 2020 Aug 4. PMID: 32788073; PMCID: PMC7402107.
9. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, Gan H, Sun YL, Fu W, Li W, Liang HL, Cao YY, Yan Q, Cao C, Gao HY, Brüggen MC, van de Veen W, Sokolowska M, Akdis M, Akdis CA. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021 Feb;76(2):428-455. doi: 10.1111/all.14657. Epub 2020 Dec 4. PMID: 33185910.
10. M.L. Holshue, C. DeBolt, S. Lindquist, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med, 382 (10) (2020), pp. 929-936.
11. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020;382(24):2327–2336.
12. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020 May 12;323(18):1824-1836. doi: 10.1001/jama.2020.6019. PMID: 32282022.

13. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin PF, Du B, Emberson J, Fisher D, Giraudeau B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT, Horby P, Jüni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, Meziani F, Møller MH, Perner A, Petersen MW, Savovic J, Tomazini B, Veiga VC, Webb S, Marshall JC. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Oct 6;324(13):1330-1341. doi: 10.1001/jama.2020.17023. PMID: 32876694; PMCID: PMC7489434.
14. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control Covid-19. N Engl J Med. 2020 May 28;382(22):2158-2160. doi: 10.1056/NEJMe2009758. Epub 2020 Apr 24. PMID: 32329972; PMCID: PMC7200054.
15. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, Shete S, Hsu CY, Desai A, de Lima Lopes G Jr, Grivas P, Painter CA, Peters S, Thompson MA, Bakouny Z, Batist G, Bekaii-Saab T, Bilen MA, Bouganim N, Larroya MB, Castellano D, Del Prete SA, Doroshow DB, Egan PC, Elkrief A, Farmakiotis D, Flora D, Galsky MD, Glover MJ, Griffiths EA, Gulati AP, Gupta S, Hafez N, Halfdanarson TR, Hawley JE, Hsu E, Kasi A, Khaki AR, Lemmon CA, Lewis C, Logan B, Masters T, McKay RR, Mesa RA, Morgans AK, Mulcahy MF, Panagiotou OA, Peddi P, Pennell NA, Reynolds K, Rosen LR, Rosovsky R, Salazar M, Schmidt A, Shah SA, Shaya JA, Steinharter J, Stockerl-Goldstein KE, Subbiah S, Vinh DC, Wehbe FH, Weissmann LB, Wu JT, Wulff-Burchfield E, Xie Z, Yeh A, Yu PP, Zhou AY, Zubiri L, Mishra S, Lyman GH, Rini BI, Warner JL; COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020 Jun 20;395(10241):1907-1918. doi: 10.1016/S0140-6736(20)31187-9. Epub 2020 May 28. Erratum in: Lancet. 2020 Sep 12;396(10253):758. PMID: 32473681; PMCID: PMC7255743.
16. Derosa, L., Melenotte, C., Griscelli, F. et al. The immuno-oncological challenge of COVID-19. Nat Cancer 1, 946–964 (2020). https://doi.org/10.1038/s43018-020-00122-3
17. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, Angelucci E, Krampera M, Cairoli R, Della Porta MG, Fracchiolla N, Ladetto M, Gambacorti Passerini C, Salvini M, Marchetti M, Lemoli R, Molteni A, Busca A, Cuneo A, Romano A, Giuliani N, Galimberti S, Corso A, Morotti A, Falini B, Billio A, Gherlinzoni F, Visani G, Tisi MC, Tafuri A, Tosi P, Lanza F, Massaia M, Turrini M, Ferrara F, Gurrieri C, Vallisa D, Martelli M, Derenzini E, Guarini A, Conconi A, Cuccaro A, Cudillo L, Russo D, Ciambelli F, Scattolin AM, Luppi M, Selleri C, Ortu La Barbera E, Ferrandina C, Di Renzo N, Olivieri A, Bocchia M, Gentile M, Marchesi F, Musto P, Federici AB, Candoni A, Venditti A, Fava C, Pinto A, Galieni P, Rigacci L, Armiento D, Pane F, Oberti M, Zappasodi P, Visco C, Franchi M, Grossi PA, Bertù L, Corrao G, Pagano L, Corradini P; ITA-HEMA-COV Investigators. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol. 2020 Oct;7(10):e737-e745. doi: 10.1016/S2352-3026(20)30251-9. Epub 2020 Aug 13. PMID: 32798473; PMCID: PMC7426107.
18. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, Zhang Z, You H, Wu M, Zheng Q, Xiong Y, Xiong H, Wang C, Chen C, Xiong F, Zhang Y, Peng Y, Ge S, Zhen B, Yu T, Wang L, Wang H, Liu Y, Chen Y, Mei J, Gao X, Li Z, Gan L, He C, Li Z, Shi Y, Qi Y, Yang J, Tenen DG, Chai L, Mucci LA, Santillana M, Cai H. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during

the COVID-19 Outbreak. Cancer Discov. 2020 Jun;10(6):783-791. doi: 10.1158/2159-8290.CD-20-0422. Epub 2020 Apr 28. PMID: 32345594; PMCID: PMC7309152.
19. Wood WA, Neuberg DS, Thompson JC, Tallman MS, Sekeres MA, Sehn LH, Anderson KC, Goldberg AD, Pennell NA, Niemeyer CM, Tucker E, Hewitt K, Plovnick RM, Hicks LK. Outcomes of patients with hematologic malignancies and COVID-19: a report from the ASH Research Collaborative Data Hub. Blood Adv. 2020 Dec 8;4(23):5966-5975. doi: 10.1182/bloodadvances.2020003170. PMID: 33278301; PMCID: PMC7724912.
20. Huang A, Bange E, Han N, Wileyto EP, Kim J, Gouma S, Robinson J, Greenplate A, Porterfield F, Owoyemi O, Naik K, Zheng C, Galantino M, Weisman A, Ittner C, Kugler E, Baxter A, Weirick M, McAllister C, Babady NE, Kumar A, Widman A, Dewolf S, Boutemine S, Roberts C, Budzik K, Tollett S, Wright C, Perloff T, Sun L, Mathew D, Giles J, Oldridge D, Wu J, Alanio C, Adamski S, Vella L, Kerr S, Cohen J, Oyer R, Massa R, Maillard I, Maxwell K, Maslak P, Vonderheide R, Wolchok JD, Hensley S, Wherry E, Meyer N, DeMichele A, Vardhana S, Mamtani R, Oniyide O, Agyekum R, Dunn T, Jones T, Giannini H, Garfall A, Reilly J. CD8 T cells compensate for impaired humoral immunity in COVID-19 patients with hematologic cancer. Res Sq [Preprint]. 2021 Feb 2:rs.3.rs-162289. doi: 10.21203/rs.3.rs-162289/v1. PMID: 33564756; PMCID: PMC7872363.
21. Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K, Lu H, Liu J, Yang J, Dong Y, Pan D, Shu C, Li J, Wei J, Huang Y, Peng L, Wu M, Zhang R, Wu B, Li Y, Cai L, Li G, Zhang T, Wu G. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020 Jul;21(7):904-913. doi: 10.1016/S1470-2045(20)30310-7. Epub 2020 May 29. PMID: 32479787; PMCID: PMC7259917.
22. Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, Morales Moshiashvili M, Ziv-Baran T, Shorer Y, Scarfo L, Joffe E, Perry C, Ghia P. Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with Chronic Lymphocytic Leukemia. Blood. 2021 Apr 16:blood.2021011568. doi: 10.1182/blood.2021011568. Epub ahead of print. PMID: 33861303; PMCID: PMC8061088.
23. Terpos E, Trougakos IP, Gavriatopoulou M, Papassotiriou I, Sklirou AD, Ntanasis-Stathopoulos I, Papanagnou ED, Fotiou D, Kastritis E, Dimopoulos MA. Low Neutralizing Antibody Responses Against SARS-CoV-2 in Elderly Myeloma Patients After the First BNT162b2 Vaccine Dose. Blood. 2021 Apr 16:blood.2021011904. doi: 10.1182/blood.2021011904. Epub ahead of print. PMID: 33861315; PMCID: PMC8061093.
24. Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, Pradhan K, Thota R, Reissman S, Sparano JA, Gartrell BA, Smith RV, Ohri N, Garg M, Racine AD, Kalnicki S, Perez-Soler R, Halmos B, Verma A. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. Cancer Discov. 2020 Jul;10(7):935-941. doi: 10.1158/2159-8290.CD-20-0516. Epub 2020 May 1. PMID: 32357994; PMCID: PMC7334098.
25. Garassino MC, Whisenant JG, Huang LC, Trama A, Torri V, Agustoni F, Baena J, Banna G, Berardi R, Bettini AC, Bria E, Brighenti M, Cadranel J, De Toma A, Chini C, Cortellini A, Felip E, Finocchiaro G, Garrido P, Genova C, Giusti R, Gregorc V, Grossi F, Grosso F, Intagliata S, La Verde N, Liu SV, Mazieres J, Mercadante E, Michielin O, Minuti G, Moro-Sibilot D, Pasello G, Passaro A, Scotti V, Solli P, Stroppa E, Tiseo M, Viscardi G, Voltolini L, Wu YL, Zai S, Pancaldi V, Dingemans AM, Van Meerbeeck J, Barlesi F, Wakelee H, Peters S, Horn L; TERAVOLT investigators. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based,

cohort study. Lancet Oncol. 2020 Jul;21(7):914-922. doi: 10.1016/S1470-2045(20)30314-4. Epub 2020 Jun 12. PMID: 32539942; PMCID: PMC7292610.

26. Chari A, Samur MK, Martinez-Lopez J, Cook G, Biran N, Yong K, Hungria V, Engelhardt M, Gay F, García Feria A, Oliva S, Oostvogels R, Gozzetti A, Rosenbaum C, Kumar S, Stadtmauer EA, Einsele H, Beksac M, Weisel K, Anderson KC, Mateos MV, Moreau P, San-Miguel J, Munshi NC, Avet-Loiseau H. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. Blood. 2020 Dec 24;136(26):3033-3040. doi: 10.1182/blood.2020008150. PMID: 33367546; PMCID: PMC7759145.

Table 1. Characteristics of Patients included in the Initial Analysis from the ASCO Registry

	Categories	N	%
TOTAL		453	100%
Number of Patients Entered by Practice Type	Non-Academic Hospital/Health System-Owned Practices (N=19)	229	52%
	Physician-owned, independent practices (N=12)	113	24%
	Academic Practices (N=7)	111	24%
U.S. Region	Midwest	109	24%
	Northeast	99	22%
	South	224	49%
	West	21	5%
Age at COVID-19 Diagnosis	<=60	174	38%
	61-70	129	28%
	71-80	108	24%
	>80	42	9%
Sex	Male	213	47%
	Female	239	53%
Race	White	275	61%
	Black	123	27%
	Asian	9	2%
	American Indian or Alaska Native	2	0%
	Other/Unknown	44	10%
Ethnicity	Hispanic or Latino	42	9%
	Not Hispanic or Latino	386	85%
	Unknown	25	6%
Cancer Groups	**Solid Tumor, Regional**	42	9%
	Breast	12	29%
	Lung	7	17%
	Colorectal	3	7%
	Pancreatic	3	7%
	Other	17	40%
	Solid Tumor, Metastatic	240	53%
	Lung	52	22%
	Breast	49	20%
	Colorectal	24	10%
	Prostate	21	9%
	Kidney	14	6%
	Pancreatic	7	3%
	Stomach	8	3%
	Uterine	8	3%

	Ovarian	7	3%
	Melanoma	7	3%
	Other	43	18%
	B-cell Hematologic Malignancies	144	32%
	Multiple myeloma	75	52%
	Non-Hodgkin lymphoma	41	28%
	Lymphoid leukemia	25	17%
	Hodgkin lymphoma	3	2%
	Other Hematologic Malignancies	27	6%
	Chronic myeloid leukemia	7	26%
	Cutaneous T cell lymphoma	3	11%
	Myeloid leukemia	3	11%
	Other leukemia	14	52%
Additional Malignancy (prior or concurrent)	Yes	133	30%
	No	312	70%
Smoking Status	Current Smoker	39	9%
	Former Smoker	156	34%
	Never Smoked	235	52%
	Unsure	23	5%
Body Mass Index	Underweight	18	4%
	Normal Weight	118	26%
	Overweight	153	34%
	Obese	160	36%
ECOG Performance Status at COVID-19 Diagnosis	0	99	22%
	1	129	28%
	2	45	10%
	$\geq$ 3	56	13%
	Unknown	124	27%
Hypertension	Yes	215	47%
	No	238	53%
Diabetes	Yes	103	23%
	No	350	77%
Pulmonary Disease	Yes	68	15%
	No	385	85%
Comorbidity Index (Hypertension, Diabetes, Pulmonary Disease)	None of these three comorbidities	187	41%
	One of three	162	36%
	Two of three	104	23%
	All three	0	0%
No Reported Comorbidities	Yes	157	35%
	No	296	65%

COVID-19 Symptoms (at any time)	Fever	201	44%
	Cough	189	42%
	Shortness of breath	177	39%
	Fatigue	126	28%
	Body or muscle aches	61	13%
	Diarrhea	59	13%
	Headache	42	9%
	Loss of taste or smell	39	9%
	Congestion or runny nose	38	8%
	Vomiting	35	8%
	Loss of appetite	33	7%
	Sore throat	26	6%
	Chest pain	22	5%
	Weakness	12	3%
	Chills	11	2%
	Nausea	10	2%
	Abdominal pain	4	1%
	No symptoms/Asymptomatic	115	25%
Hospitalization for COVID-19 or COVID-19 Complications	Yes, but no intensive care	138	30%
	Yes, and intensive care	64	14%
	No	251	55%
Pneumonia	Yes	145	33%
	No	300	67%
Use of a Ventilator	Yes	46	10%
	No	389	86%
	Unsure/unknown	18	4%
Use of Supplemental Oxygen	Yes	135	30%
	No	292	64%
	Unsure/unknown	26	6%
Treatment with Anti-COVID-19 Drugs	Yes	101	22%
	No	316	70%
	Unsure/unknown	34	8%
Anti-COVID-19 drugs Used	remdesivir	39	9%
	dexamethasone	35	8%
	azithromycin	33	7%
	hydroxychloroquine	20	4%
	convalescent plasma	20	4%
	tocilizumab	4	1%
	chloroquine	2	<1%
	losartan	1	<1%
	Other	29	6%

	Unknown	1	0%
Cancer Treatment Status at Time of COVID-19 Diagnosis	Initial cancer diagnosis and deciding initial therapy	37	8%
	In active anti-cancer therapy	416	92%
Types of Therapies Ongoing or Planned at COVID Diagnosis	Surgery	10	2%
	Radiation	32	7%
	Drug-based	453	100%
Cancer-Directed, Drug-Based Treatment	Immunotherapy	75	17%
	Chemotherapy	241	53%
	Other Drug-based treatment	137	30%
Delayed, Discontinued, or Used Less Aggressive Drug Treatment	Neither delayed nor discontinued drug-based treatments	160	35%
	Delayed at least one component of drug-based therapy and no discontinuations	220	49%
	Discontinued one or more components of drug-based treatments (with or without delays of other components)	73	16%

Figure Captions

Figure 1. Overall survival by age in all patients (left; p = 0.001), patients with B-cell malignancy (center; p=0.002) and in patients with metastatic solid tumors (right; p=0.40).

Figure 2: Mortality rates in patients with positive SARS-CoV-2 test before June (left, N=191) or in/after June (right, N=262)

Supplemental Figure 1: Study Calendar for Patients in ASCO Survey on COVID-19 in Oncology Registry

Supplemental Figure 2. CONSORT Diagram for Registry Patients Selected for Analysis

Supplemental Figure 3: COVID-19 Interventions in patients diagnosed with SARS-CoV-2 before or after June 2020. Estimated percentages remove unknown percentages for each category of intervention from the percentage that is reported (see Table 1).

Supplemental Figure 4. 30- and 90-day mortality estimates by patient subgroups

Supplemental Table 1: COVID-19 information, stratified by date of COVID-19 Diagnosis

Supplemental Table 2. Select baseline characteristics, stratified by patients who had no changes to their cancer treatment(s), delay(s) in one or more of their cancer treatments, or discontinuation(s) of one or more of their cancer treatment(s) (possibly in addition to delays)

Manuscript Title: Changes over time in COVID-19 severity and mortality in patients undergoing cancer treatment in the U.S.: Initial report from the ASCO registry
Clean – Track Changes Accepted for Resubmission

Figure 1. Overall survival by age in all patients (left; p = 0.001), patients with B-cell malignancy (center; p=0.002) and in patients with metastatic solid tumors (right; p=0.40).

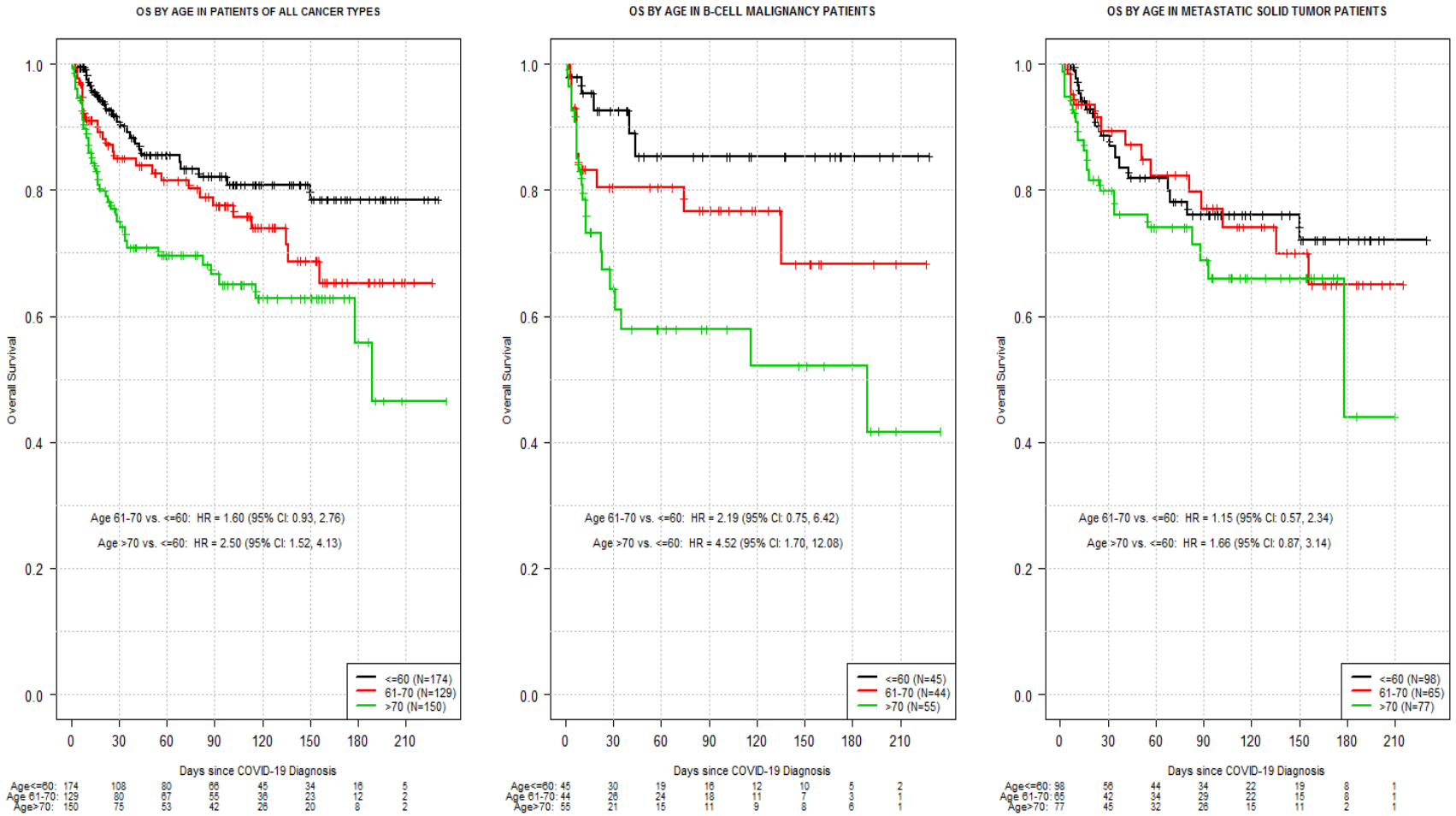
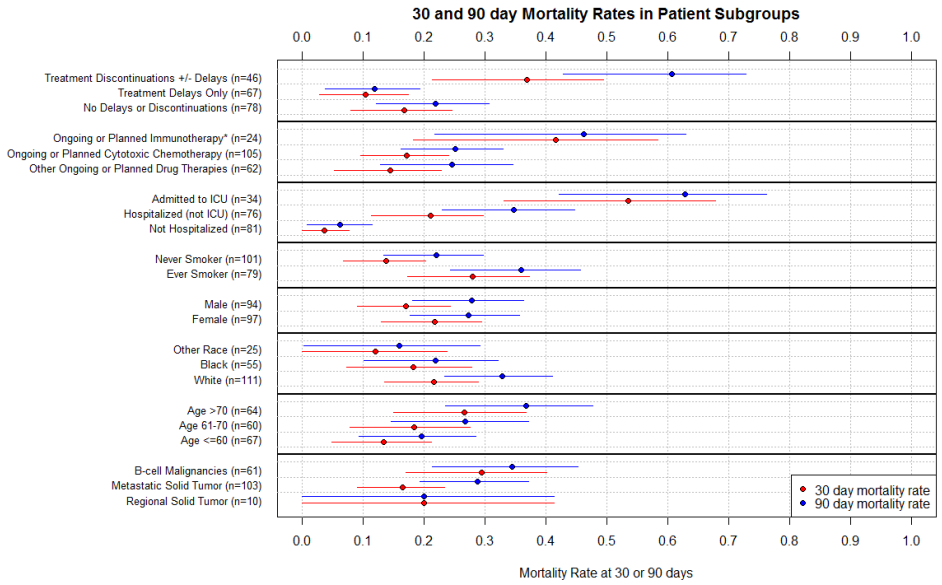
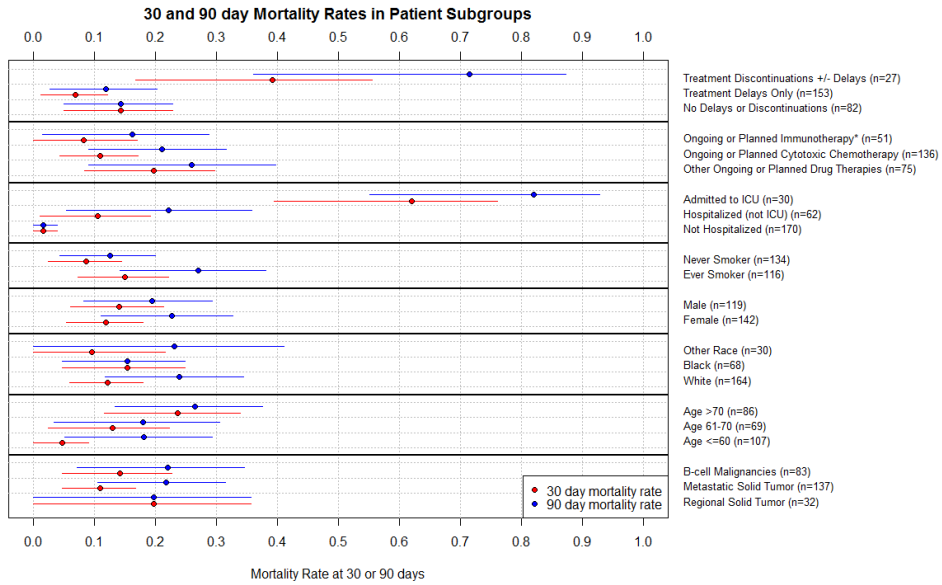


Figure 2: Mortality rates in patients with positive SARS-CoV-2 test before June (left, N=191) or in/after June (right, N=262)



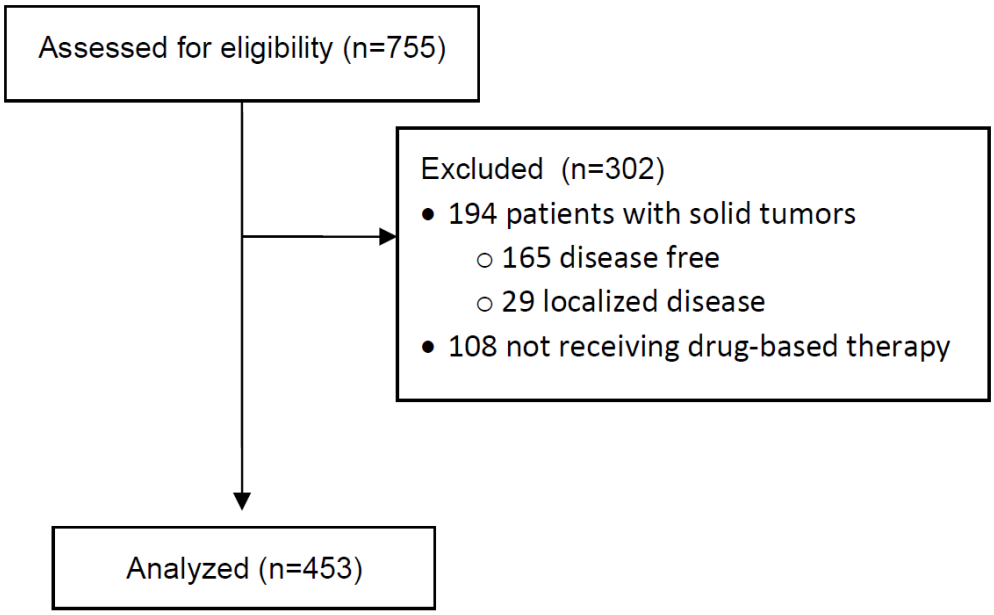


Supplemental Figure 1. **Study Calendar for Patients in ASCO Survey on COVID-19 in Oncology Registry**

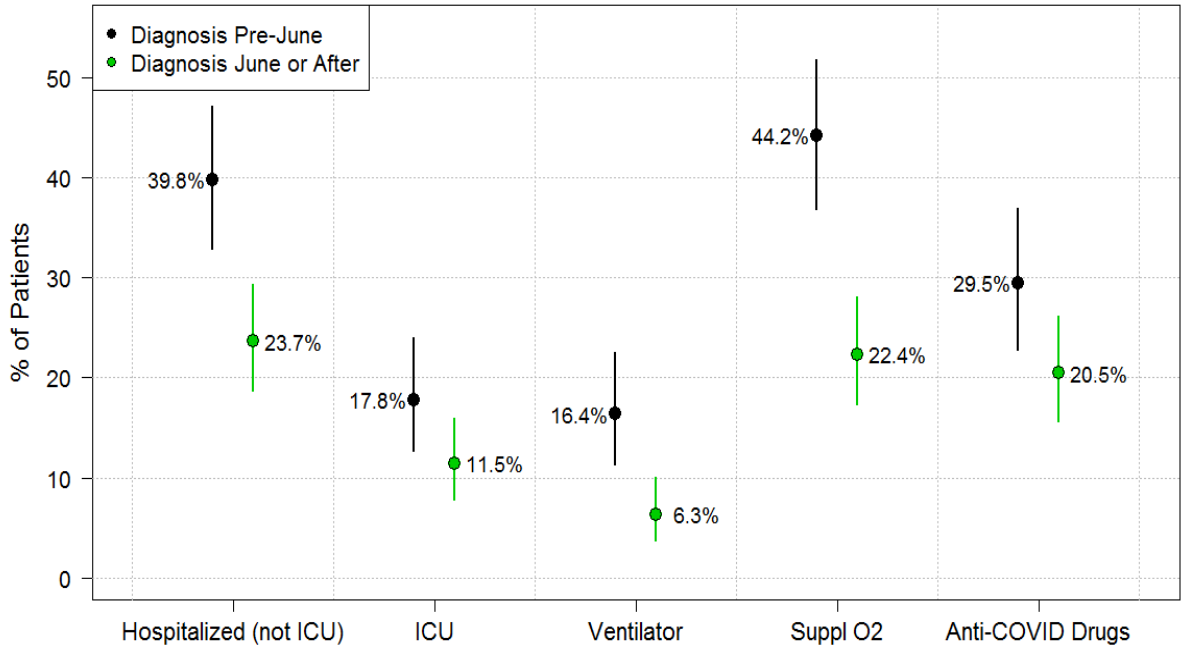
Phase	**Initial Entry**	**Short term Follow-up**			**Long-term Follow-up**
	Initial at time of positive SARS-CoV-2 test	1 month after positive SARS-CoV-2 test	2 months after positive SARS-CoV-2 test	3 months after positive SARS-CoV-2 test	6, 9 and 12 months after positive SARS-CoV-2 test
Initial Entry					
Initial Clinical and Demographic Information	●				
SARS-CoV-2 Related Symptoms, and Treatment	●				
Cancer Diagnosis, Status, and Treatment	●				
Short Term Follow-up					
SARS-CoV-2 Related Status Update		●	●	●	
Cancer Status Update		●	●	●	
Long Term Follow-up					
SARS-CoV-2 Related Long-term Update					●
Cancer Status Update					●

Note: The Registry was changed in August 2021 to add data collection for at 18 and 24 months after positive SARS-CoV-2 test. The full ASCO Registry protocol schema is available at https://www.asco.org/asco-coronavirus-information/coronavirus-registry.

Supplemental Figure 2. CONSORT Diagram for Registry Patients Selected for Analysis



Supplemental Figure 3: COVID-19 Interventions in patients diagnosed with SARS-CoV-2 infection before or after June 2020. Estimated percentages remove unknown percentages for each category of intervention from the percentage that is reported (see Table 1).



Supplemental Figure 4. 30- and 90-day mortality estimates by patient subgroups