Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System

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ABSTRACT

Cancer patients are presumed to be at increased risk from COVID-19 infection fatality due to underlying malignancy, treatment-related immunosuppression, or increased comorbidities. A total of 218 COVID-19 positive patients from March 18th-April 8th, 2020 with a malignant diagnosis were identified. A total of 61 (28%) cancer patients died from COVID-19 with a case fatality rate (CFR) of 37% (20/54) for hematologic malignancies and 25% (41/164) for solid malignancies. 6/11 (55%) lung cancer patients died from COVID-19 disease. Increased mortality was significantly associated with older age, multiple comorbidities, need for ICU support, and elevated levels of D-Dimers, LDH and lactate on multivariable analysis. Age-adjusted CFRs in cancer patients compared to non-cancer patients at our institution and NYC reported a significant increase in case fatality for cancer patients. These data suggest the need for proactive strategies to reduce likelihood of infection and improve early identification in this vulnerable patient population.

Statement of Signficance:

COVID-19 in cancer patients is associated with a significantly increased risk for case fatality suggesting the need for proactive strategies to reduce likelihood of infection and improve early identification in this vulnerable patient population.

INTRODUCTION

The novel coronavirus COVID-19, or severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2), has spread rapidly throughout the world since its emergence in December 2019.(1) The virus has currently infected approximately 2.9 million people in over 200 countries with over 200,000 deaths at the time of writing.(2) [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200408-sitrep-79-covid-19.pdf]. Most recently, the United States has become the epicenter of this pandemic, reporting an estimated 956,000 cases of COVID-19 infections, with the largest concentration in New York City and its surrounding areas (approximately >203,000 cases or 35% of all U.S. infections).(3) [https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html]

Early data suggests that 14-19% of the infected patients will develop significant sequelae with acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure(1, 4, 5), and approximately 1-4% will die from the disease.(2) Recent meta-analyses have demonstrated an almost 6-fold increase in the odds of mortality for patients with COPD and 2.5 fold for those with diabetes, possibly due to the underlying pulmonary and immune dysfunction.(6, 7) Given the above findings, patients with cancer would ostensibly be at a higher risk of developing and succumbing to COVID-19 due to immunosuppression, increased co-existing medical conditions, and, in cases of lung malignancy, underlying pulmonary compromise. Hematologic cancer patients, or those that are receiving active chemo- or immunotherapy, may be particularly susceptible due to increased immunosuppression and/or dysfunction.

According the National Cancer Institute, there were approximately 15.5 million cancer survivors and an estimated 1,762,450 new cases of cancer diagnosed in the United States in

2019.(8) Early case series from China and Italy have suggested that patients with malignancy are more susceptible to severe infection and mortality from COVID-19(9-12), a phenomenon that has been noted in other pandemics.(13) Many of these descriptive studies have included small patient cohorts and have lacked cancer site-specific mortality data or information regarding active cancer treatment. As New York has emerged as the current epicenter of the pandemic, we sought to investigate the risk posed by COVID-19 to our cancer population with more granular data regarding cancer type and active treatment, and identify factors that placed cancer patients at highest risk of fatality from COVID-19.

RESULTS

Outcomes of 218 cancer patients with COVID-19 shows high overall mortality with tumor specific patterns

A total of 218 patients with cancer and COVID-19 infection were treated in Montefiore Health system, New York from March 18th to April 8th, 2020. These included 164 (75%) patients with solid tumors and 54 (25%) with hematologic malignancies. This cohort included 127 (58%) males and 91 (42%) females. The cohort was predominantly composed of adult patients (215/218, 98.6%) with a median age of 69 years (range 10-92 years).

Sixty-one (28%) patients expired as a result of COVID-19 disease at the time of analysis (Table 1). The mortality was 25% of all solid tumor patients and was seen to occur at higher rates in lung cancers (55%), gastrointestinal cancers (colorectal (38%), pancreas (67%), upper GI

(38%)) and gynecologic malignancies (38%). Genitourinary (15%), and breast cancers (14%) were associated with relatively lower mortality with COVID-19 infection.

Hematologic malignancies were associated with higher rate of mortality with COVID-19 (37%). Myeloid malignancies (MDS/AML/MPN) showed a trend for higher mortality compared to lymphoid neoplasms (NHL/CLL/ALL/MM/HL) (Table 1). Rates of ICU admission and ventilator use were slightly higher for hematologic malignancies than solid tumors (26% vs 19% and 11% vs 10%, respectively), but this did not achieve statistical significance.

Disease characteristics of cancer patients with COVID-19 demonstrates the effect of age, co-morbidities and laboratory biomarkers on mortality

Analysis of patient characteristics with mortality did not show any gender bias (Table 2). Older age was significantly associated with increased mortality with median age of deceased cohort at 76 years when compared to 66 years for the non-deceased group (P Value= 0.0006, Cochran Armitage test). No significant associations with race and mortality were seen.

COVID-19 disease severity, as evident from patients who needed ICU care and ventilator support, was significantly associated with increased mortality. Interestingly, active disease (< 1 year) and advanced metastatic disease showed a trend for increased mortality, but the association did not achieve statistical significance ($p = 0.09$ and 0.06, respectively). Active chemotherapy and radiation therapy treatment were not associated with increased case fatality. Very few patients in this cohort were on immunotherapy, and this did not show any associations with mortality.

Analysis of co-morbidities demonstrated increased risk of dying from COVID-19 in cancer patients with concomitant heart disease (HTN, CAD and CHF) and chronic lung disease (Table 2). Diabetes and chronic kidney disease were not associated with increased mortality in univariate analysis (Table 2).

We also analyzed lab values obtained prior to diagnosis of COVID-19 and during the time of nadir after COVID-19 positivity in our cancer cohort. Relative anemia pre-COVID-19 was associated with increased mortality, while pre-COVID platelet and lymphocyte counts were not (Table 3). Post-COVID-19 infection, a lower hemoglobin, higher total WBC count and higher absolute neutrophil counts were associated with increased mortality (Table 3). Analysis of other serologic biomarkers demonstrated that elevated D-Dimer, lactate and LDH in patients were significantly correlated with dying (Table 3).

Next, we conducted multivariate analyses and used variables that showed a significant association with mortality in univariate analysis (p value <0.05 in univariate was seen with age, ICU admission, hypertension, chronic lung disease, CAD, CHF, baseline hemoglobin, nadir hemoglobin, WBC counts, D-Dimer, Lactate and LDH). Gender was forced in the model and we used a composite score of comorbidities from the sum of indicators for DM, HTN, Chronic Lung Disease, CKD, CAD, CHF capped at a maximum of 3. In the multivariate model (Supp Table 1), we observed that older age (age <65 OR=0.23, 95% CI 0.07-0.6), higher composite comorbidity score (OR=1.52, 95%CI 1.02-2.33), ICU admission (OR=4.83, 95% CI 1.46-17.15) and elevated inflammatory markers (D-Dimer, Lactate and LDH) were significantly associated with mortality after multivariate comparison in patients with cancer and COVID-19.

Interaction with the healthcare environment was a prominent source of exposure for cancer patients

A detailed analysis of deceased patients (N=61) (Supplementary table 2) demonstrated that many were either nursing home or shelter (n=22) residents, and/or admitted as an inpatient or presented to the emergency room within the 30 days prior to their COVID-19 positive test (21/61). Altogether, 37/61 (61%) of the deceased cohort were exposed to the health care environment at the outset of the COVID-19 epidemic. Few of the patients in the cohort were on active oncologic therapy. The vast majority had a poor ECOG PS (51/61 with an ECOG PS of 2 or higher) and carried multiple co-morbidities.

Cancer patients demonstrate a markedly increased COVID-19 mortality rate compared to non-cancer and all New York City COVID-19 patients

An age and sex-matched cohort of 1090 patients at a 5:1 ratio of non-cancer to cancer COVID-19 patients from the same time period and from the same hospital system was also obtained after propensity matching and used as control to estimate the increased risk posed to our cancer population (Table 4). We observed case fatality rates were elevated in all age cohorts in cancer patients and achieved statistical significance in the age groups 45-64 and in patients older than 75years of age.

To also compare our case-fatality rates with a larger dataset from the greater New York City (NYC) region, we obtained official cases numbers from NY State (current up to April 12th, 2020).(3) In all cohorts, the percentage of deceased patients was found to rise sharply with

increasing age (Table 4). Strikingly, case-fatality rates in cancer patients with COVID-19 were significantly, many-fold higher in all age groups when compared to all NYC cases (Table 4).

DISCUSSION

To our knowledge, this is the first large report of COVID-19 case fatality rates among patients with cancer in the United States. The overall case-fatality among COVID-19 infected cancer patients in an academic center located within the current epicenter of the global pandemic exceeded 25%. Additionally, striking tumor-specific discrepancies were seen with marked increased susceptibility for those with hematologic malignancies and lung cancer. Case fatality rates were 2-3 times the age-specific percentages seen in our non-cancer population and the greater New York City area for all COVID-19 patients.

Our results seem to mirror the typical prognosis of the various cancer types. Among the most common malignancies within the US population (lung, breast, prostate and colorectal), there was 55% mortality among lung, 14% for breast, 20% for prostate, and 38% for colorectal (CRC) cancer patients. This pattern reflects the overall known lethality of these cancers. The % annual mortality (ratio of annual deaths/new diagnosis) is 59.3% for lung cancer, 15.2% for breast, 17.4% for prostate and 36% for CRC.(8) This suggests that COVID-19 infection amplifies the risk of death regardless of the cancer type.

Patients with hematological malignancies demonstrate a higher mortality than those with solid tumors. These patients tend to be treated with more myelosuppressive therapy, and are often severely immunocompromised due to underlying disease. There is accumulating evidence that one major mechanism of injury may be a cytokine-storm syndrome secondary to hyper-

inflammation, which results in pulmonary damage. Hematologic malignancy patients may be potentially more susceptible to cytokine-mediated inflammation due to perturbations in myeloid and lymphocyte cell compartments.(14)

Many of the predictive risk factors for mortality in our cancer cohort were similar to published data among all COVID-19 patients. A recent meta-analysis highlighted the association of chronic diseases including hypertension (OR: 2.29), diabetes (OR: 2.47), chronic obstructive pulmonary disease (COPD) (OR: 5.97), cardiovascular disease (OR: 2.93), and cerebrovascular disease (OR: 3.89) with a risk for developing severe COVID-19 infection among all patients.(15) In our cancer patient dataset, a large proportion of patients had at least one of these concurrent risk factors. In a univariate model, we observed significant associations of death from COVID 19 infection in patients with hypertension, chronic lung disease, coronary heart disease, and congestive heart failure. Serologic predictors in our dataset predictive for mortality included anemia at time of infection, and elevated LDH, D-dimer, and lactic acid, which correlate with available data from all COVID-19 patients.

Rapidly accumulating reports suggest that age and race may play a role in the severity of COVID-19 infection. In our cancer cohort, the median age of the patients succumbing to COVID-19 was 76 years, which was10 years older than patients who have remained alive. The CDC has reported a disproportionate number of African Americans are affected by COVID-19 in the United States accounting for 33% of all hospitalized patients while constituting only 13% of the U.S. population(15). However, the racial breakdown of our patients was proportional to the Bronx population as a whole and race was not a significant predictor of mortality in our univariate or multivariable models. Our data might argue that the increased mortality noted in the

larger NYC populations might be also likely driven by socioeconomic and health disparities in addition to underlying biological factors. Overall mortality with COVID-19 has been higher in the Bronx, which is a socioeconomically disadvantaged community with an average mean per capita income of $19,721.(16, 17) [https://www.census.gov/quickfacts/fact/table/bronxcountybronxboroughnewyork/SEX255218]. Our cancer patients were predominantly from the Bronx and potentially had increased mortality in part due to socioeconomic and comorbidities. Even after accounting for the increased mortality seen in COVID-19 in the Bronx, the many-fold magnitude increase in death rates within in our cancer cohort can potentially be attributed to the vulnerability of oncology patients. This was evident in the comparison with a control group from the same hospital system that demonstrated a significant association of cancer with mortality in patients between 45-64 and over 75 years of age.

Interaction with the healthcare environment prior to widespread knowledge of the epidemic within New York City was a prominent source of exposure for our cancer patients. Many of those who succumbed to COVID-19 infection were older and frail with significant impairment of pulmonary and/or immunologic function. These findings could be utilized to risk stratify cancer patients during this pandemic, or in future viral airborne outbreaks, and inform mitigation practices for high-risk individuals. These strategies could include early and aggressive social distancing, resource allocation towards more outpatient-based care and telemedicine, testing of asymptomatic high-risk patients, and institution of strict infection control measures. Indeed, such strategies were implemented early in the pandemic at our center possibly explaining the relatively low number of infected patients on active therapy.

There were several limitations to our study. Data regarding do not resuscitate or intubate (DNR/I) orders were not included in the analysis and could have significantly impacted the decision making and mortality surrounding these patients. While an attempt was made to control for those receiving active cancer treatment or additional comorbidities, we could not fully account for the patients' pre-existing health condition prior to COVID-19 infection. Differential treatments paradigms for COVID-19 infection and sequelae were not controlled for in our analysis. Due to the limited follow up, the full clinical course of these patients may not be included. Future comparative studies to non-cancer patients will be needed to fully ascertain the risk posed to oncology patients. Finally, while our data does include those who were tested and discharged within our health system, we cannot fully account for those who were tested in non-affiliated outpatient settings, which may potentially bias our study to more severe cases. We also acknowledge that the mortality rate is highly dependent on the breadth of testing, and therefore understand that more widespread detection of viral infection would likely alter the results.

Our data suggests significant risk posed to cancer patients infected with COVID-19 with an observed signficant increase in mortality. The highest susceptibility appears to be in hematologic or lung malignancies, suggesting that proactive strategies to reduce likelihood of infection and improve early identification of COVID-19 positivity in the cancer patient population are clearly warranted. Overall, we hope and expect that our data from the current epicenter of the COVID-19 epidemic will help inform other healthcare systems, cancer patients, and the public about the particular vulnerability of oncologic patients to this disease.

METHODS

Study Design and Participants

Data regarding all patients who had tested positive for COVID-19 from March 18th, 2020 until April 8th, 2020 were extracted from the electronic medical record from a single, urban, academic medical center. These records were cross-referenced with an existing cancer database, and a retrospective review was done by senior authors to extract additional data on patients with a history of malignancy. Reverse transcriptase qPCR assay was utilized to determine SARS-CoV-2 status. Baseline characteristics, laboratory data and clinical outcomes were tabulated with data collection finalized on April 12th, 2020. All patients who were tested were symptomatic for COVID-19 at the time of testing due to the unavailability of asymptomatic, prophylactic testing early in the epidemic. Cases identified as having benign neoplasms were excluded. Information collected included demographic data, medical history including comorbidities, cancer diagnosis, chemotherapy and/or radiation in the last 30 days, curative vs palliative treatment, laboratory data pre- (when available) and post-infection [white blood cell (WBC), hemoglobin (Hgb), platelet count (plt), differential counts, ferritin, d-dimer, lactate, lactate dehydrogenase (LDH)], hospital course (admission, discharge, intensive care unit (ICU), need for ventilator support and/or dialysis), and mortality. Case fatality rates of cancer patients with COVID-19 at our institution were compared to age and sex-matched control cohort within our hospital system, as well as publicly available New York City (NYC) COVID-19 mortality data.(16) [https://www1.nyc.gov/assets/doh/downloads/pdf/imm/covid-19-deaths-confirmed-probable-daily-04142020.pdf]. Our institutional ethics review board reviewed and approved the study and waived the need for informed consent.

Statistical Analysis

For categorical data, percentages of each variable were calculated after dichotomization based on mortality status. Medians with range were determined for age, and means were calculated and utilized for lab values. For continuous data, Wilcoxon rank sum test or student's t-test were used to compare continuous data for patients in the alive or deceased cohorts. Fischer's exact test was performed for the categorical variables. Multivariable analysis was done utilizing logistic regression with inclusion of variables significant in univariate testing ($p<0.05$). The multivariate logistic model was built from a two sided stepwise regression based on AIC. Missing datapoints for some lab values were imputed with the R package using the MissForest-non-parametric missing value imputation for mixed-type data method. Propensity-score based case matching was then utilized to match non-cancer COVID-19 patients as controls to COVID-19 cancer patients based on age and sex at a 5:1 ratio. Odds ratios for mortality were calculated via logistic regression comparing both cohorts in their entirety and broken down by age group. All statistical analysis were done using R (version 3.5.3; The R Foundation).

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Table 1: Outcomes in patients with cancer and COVID-19

	Alive	Deceased
Total	157 (72%)	61 (28%)
Solid tumors	123(75%)	41 (25%)
Genitourinary	39 (85%)	7 (15%)
Breast	24 (86%)	4 (14%)
Colorectal	13 (62%)	8 (38%)
Gynecologic	8 (62%)	5 (38%)
Lung	5 (45%)	6 (55%)
Head and Neck	7 (88%)	1 (13%)
Neuro	7 (88%)	1 (13%)
Upper GI	5 (63%)	3 (38%)
Hepatobiliary	5 (71%)	2 (29%)
Bone / Soft Tissue	4 (80%)	1 (20%)
Neuro-endocrine	3 (100%)	0 (0%)
Pancreas	1 (33%)	2 (67%)
Skin	2 (67%)	1 (33%)
Hematologic malignancies	34 (63%)	20 (37%)
NHL	10 (67%)	5 (33%)
MDS	2 (40%)	3 (60%)
MPN	5 (71%)	2 (29%)
ALL	4 (100%)	0 (0%)
AML	1 (100%)	0 (0%)
MM	8 (62%)	5 (38%)
CML	0 (0%)	1 (100%)
Hodgkin's	2 (40%)	3 (60%)
CLL	2 (67%)	1 (33%)
Myeloid Malignancy	8 (57%)	6 (43%)
Lymphoid Malignancy	26 (65%)	14 (35%)

Abbreviations: MDS: Myelodysplastic syndromes, ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia
MPN: Myeloproliferative neoplasm; MM: Multiple myeloma; CML: Chronic Myeloid Leukemia; CLL: Chronic Lymphoid Leukemia

Table 2: Disease characteristics of cancer patients with COVID-19 and association with mortality

	Alive	Deceased	P Val
Total	157 (72%)	61 (28%)	
Males	91 (72%)	36 (28%)	0.6
Females	66 (73%)	25 (27%)	0.6
Median Age (Range)	66 (10-92)	76 (10-92)	0.0006
Race			0.602
Caucasian	14 (64%)	8 (36%)	
Hispanic	58 (76%)	18 (24%)	
African American	67(73%)	25 (27%)	
Asian	5 (71%)	2 (29%)	
Other	13 (62%)	8 (38%)	
	N/Total Alive (%)	**N/Total Deceased (%)**	
ICU admission	8 (5%)	15 (24%)	9.10E-05
Ventilator support	10 (6%)	35 (57%)	1.74E-15
Hemodialysis	10 (6%)	6 (10%)	0.37
Metastasis (Solids only)	27 (22%)	15 (37%)	0.06
Active Cancer (<1yr)	60 (38%)	32 (52%)	0.09
Active ChemoTx	34 (22%)	8 (13%)	0.2
Immunotherapy	4 (3%)	1 (2%)	1
Radiation Therapy	38 (24%)	11 (18%)	0.33
DM	53 (34%)	27 (44%)	0.116
HTN	100 (64%)	47 (77%)	0.047
Chronic Lung Dis	34 (22%)	28 (46%)	0.0003
Chronic Kidney Dis	33 (21%)	21 (34%)	0.052
Coronary Artery Dis	24 (15%)	19 (31%)	0.012
CHF	18 (11%)	15 (25%)	0.019

Table 3: Lab values of cancer patients with COVID-19 and association with mortality

	Alive	Deceased	P Val
Total	157 (72%)	61 (28%)	
Pre-COVID-19 (Means)			
Hemoglobin	11.99	11.22	0.048
Platelet Count	225	256	0.16
WBC	7.33	7.55	0.12
ANC	4.9	5.8	0.18
Total Lymphocyte Count	1.6	1.7	0.5
Post-COVID-19 (Means)			
Hemoglobin	10.7	9.9	0.047
Platelet Count	177	171	0.7
WBC	5.8	8.8	0.01
ANC	4.4	6.6	0.017
Total Lymphocyte Count	0.7	0.6	0.6
Ferritin	1491	2136	0.21
D Dimer	4.1	8.8	0.002
Lactate	2	4	0.001
LDH	438	683	0.01

Table 4: Comparison of Cancer and COVID-19 mortality with all NYC cases (official NYC numbers upto 5pm, April 12th, 2020) and a control group from the same healthcare facility. The NYC cohort and the control group were compared independently to the Cancer-COVID-19 cohort and the P Values and Odds ratio are shown.

Age Groups	Cancer COVID-19 Cases	Cancer COVID-19 Deaths	%	Control Group Cases	Control Group Deaths	%	Odds Ratio	P Val	NYC Cases	NYC Deaths	%	Odds Ratio	P Val
Total	**218**	**61**	**28%**	**1090**	**149**	**14%**	**2.45**	**8.46E-07**	**104185**	**6182**	**6%**	**6.160**	**< 2.2e-16**
0-17	3	1	**33%**	5	0	**0%**	na	0.375	2025	3	**0%**	304.66	0.006
18-44	13	1	**8%**	75	2	**3%**	2.99	0.38466	39704	284	**1%**	11.56	0.088
45-64	64	10	**16%**	320	13	**4%**	4.35	0.00161	37851	1449	**4%**	4.65	0.0001
65-74	59	13	**22%**	282	41	**15%**	1.66	0.169939	13128	1511	**12%**	2.17	0.020
>75	79	36	**46%**	408	93	**23%**	2.83	7.34E-05	11477	2935	**26%**	2.44	0.0001

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CANCER DISCOVERY

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