



Increased Risk of Covid-19 Related Death among Cancer Survivors: A Real-World Data Study

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Abstract

The coronavirus disease 2019 (COVID-19) has maintained a massive impact on global public health and the economy during pandemic. Increased risk of COVID-19 related death has been reported among cancer survivors. However, due to limited sample size in those studies, to what extent the previous cancer diagnosis may play a role in the determination of COVID-19 related death is still unclear. Using aggregated real-world data extracted from TriNetx electronic medical record data from 34 hospitals around the United States, we intended to fill the gap by assessing the relationship between prior cancer diagnosis in the past 5 years and COVID-19 related death within one month after the diagnosis of virus contraction. Our data showed significant increased COVID-19 related death among cancer survivors. The elevated risk was particularly evident among those who had cancers in respiratory, digestive tract, and blood.

Keywords: COVID-19; Pandemic; Cancer Survivors

Abbreviations: COVID-19: Coronavirus Disease 2019; EMRs: Electronic Medical Records; RR: Risk Ratio; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease.

Introduction

The coronavirus disease 2019 (COVID-19) has maintained a massive impact on global public health and the economy during pandemic. From March 2020 to October 2021, COVID-19 is the third leading cause of death after heart disease and cancer in the United States. The pandemic may also have indirectly led to increases in other causes of death, including heart disease, diabetes, Alzheimer disease, and unintentional injuries [1-3]. Increased risk of COVID-19 related death has been reported among cancer survivors. However, due to limited sample size in those studies, to what

extent the previous cancer diagnosis may play a role in the determination of COVID-19 related death is still unclear. To fill the gap, we comprehensively examined the relationship between cancer status and COVID-19 related death among cancer survivors.

Methods

Data Source

TriNetX is a cloud-based federated network which aggregated de-identified longitudinal clinical data directly from the electronic medical records (EMRs) of the participating hospitals HCOs continuously. TriNetX allows real-time access to these aggregated real-world data along with the analytics to analyze research questions. TriNetX received a waiver from Western IRB since only statistical summaries of de-identified information, but no protected

health information was included. In this study, we applied the searching criteria suggested by Zhao H, et al. [4] to search TriNetx electronic medical record data from 34 hospitals around from January 20th to May 4th, 2020, and identify COVID-19 cases and collect patient characteristics (e.g. cancer status, demographics, other chronic diseases). As the first case in U.S. was recorded on January 20th, we set the time period as from January 20th to May 4th, 2020. The outcome variable was death within a month after the COVID-19 diagnosis.

Statistical Analysis

In this study, we intend to examine the relationship between cancer status and COVID-19 related death among cancer survivors. The statistical tool embedded in TriNetx was used. Each patient characteristic variable, pre-existing chronic diseases, outcome variable (death), were treated as the categorical variable. First, we use the univariate analysis to calculate risk ratio (RR) to examine the association between all cancers and COVID-19 related death among COVID-19 patients. Stratified analyses by race, gender and cancer type were performed.

Propensity score matching was applied to adjust potential covariates, including demographics (e.g., age, gender, race), and pre-existing common chronic diseases [e.g., obesity, diabetes, hypertension, heart disease, asthma, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD)]. Additionally, we applied Kaplan-Meier analysis to evaluate the differences in survival between patients with malignant tumors and patients with no cancer.

Results

Our retrospective cohort included a total of 24,534 patients aged 18-80 years old who were diagnosed with COVID-19 from January 20th to May 4th, 2020. First, we examined the association between all cancers and COVID-19 related death among COVID-19 patients (Table 1). Among the COVID-19 patients identified, 3,619 were cancer survivors with prior cancer diagnosis in the past 5 years. Death rate is much in cancer survivors compared to patients with no cancer. Among them, 4.53% of all patients, 3.69% of pts with no cancer, and 9.40% of cancer survivors die within 1 month after the diagnosis of virus contraction, respectively. In the univariate analysis, we found that cancer patients had 2.55-fold increased risk ratio (RR) of death than those without cancer. After the adjustment of demographics including age, gender and race, the risk was decreased, but still significant. The risk ratio was 1.46. Given that patient characteristics were associated with COVID-19-related death, we attempted to adjust them using 1 to 1 propensity score matching. The matching criteria included age of diagnosis, gender, race, obesity, diabetes, hypertension, heart disease, asthma, COPD, and CKD as appropriate (Table 1). After the adjustment of these demographics and other pre-existing chronic diseases, the risk was decreased, but still significant. The risk ratio was 1.42. Next, we performed the survival analysis using Kaplan-Meier estimate (Figure 1). Survival time here was the time from the date of COVID-19 diagnosis to patient death. The Kaplan-Meier survival curve showed that cancer survivors and COVID-19 patients with no cancer had statistically significant difference in the survivals ($P < 0.0001$). Cancer survivors had worse survival rates compared to COVID-19 patients with no cancer.

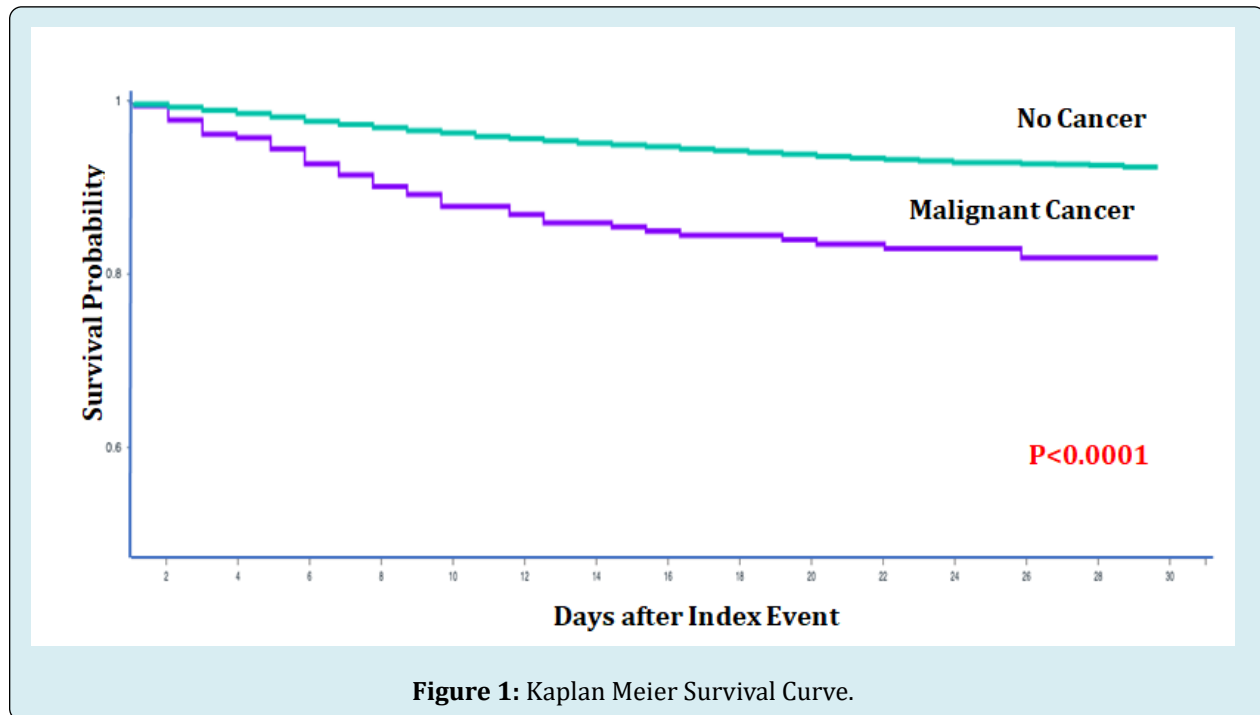
	Total	Patients with No Cancer	Patients with Malignant Tumors
Number of COVID-19 patients	24,534	20,915	3,619
Death ratio	4.53%	3.69%	9.40%
Risk ratio*		1	2.55 (2.25, 2.88)
Number of Death	1,112	772	340
Death ratio	4.53%	3.69%	9.40%
Risk ratio#		1.1	1.46 (1.24, 1.71)
P value			<0.001
Risk ratio*		1	2.55 (2.25, 2.88)
P value			<0.001

*. Univariate Analysis.

#. Adjusted by Age, Gender, and Race.

\$. Adjusted by Age, Gender, Race, Obesity, Diabetes, Hypertension, Heart Disease, Asthma, COPD, and CKD.

Table 1: Association between All Cancers and COVID-19 Related Death among COVID-19 Patients.



After that, we further assessed the relationship between selected cancers and COVID-19 related death among COVID-19 patients (Table 2). When stratified by cancer sites, significant associations were observed between respiratory, oral, digestive, breast, male genital, urinary, blood, and skin cancers with COVID-19 related death in the univariate analysis. The most significant cancer site was respiratory cancer with a risk ratio of 6.49. After the adjustment of demographics and other pre-existing chronic diseases, the significant associations were remained for

respiratory, digestive, and blood cancers (RR=1.89; RR=1.59; RR=2.08, respectively). Lastly, we examined the associations between death with race and gender among cancer patients contracting COVID-19 (Table 3). When stratified by gender and race, we found that male cancer survivors had higher risk of death than female with a risk ratio of 1.77. After the adjustment of demographics and other pre-existing chronic diseases, the significant associations were remained. However, the risk ratio didn't show statistically significant difference between Blacks and Whites.

	Total Number	Death Rate	Risk Ratio*	P value	Risk Ratio [§]	P value
No Cancer	20,915	3.69%	1		1	
Respiratory Cancers	284	23.94%	6.49 (5.21, 8.07)	<0.001	1.89 (1.31, 2.73)	0.001
Oral Cancer	71	14.09%	3.82 (2.14, 6.81)	<0.001	1.00 (0.44, 2.25)	1
Digestive Tract Cancer	366	14.75%	4.00 (3.10, 5.16)	<0.001	1.59 (1.06, 2.38)	0.023
Breast Cancer	366	5.74%	1.55 (1.02, 2.37)	0.04	1.05 (0.58, 1.90)	0.872
Female genital Cancer	153	6.54%	1.77 (0.97, 3.24)	0.064	1.00 (0.43, 2.33)	1
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Female genital Cancer	153	6.54%	1.77 (0.97, 3.24)	0.064	1.00 (0.43, 2.33)	1

*. Univariate Analysis.

§. Adjusted by Age, Gender, Race, Obesity, Diabetes, Hypertension, Heart Disease, Asthma, COPD, and CKD.

Table 2: Association between Selected Cancers and COVID-19 Related Death among COVID-19 Patients.

	Number	Death	risk ratio*	P value	risk ratio [#]	P value	Risk ratio [§]	P value
<i>By race</i>								
White	826	79	1		1		1	
Black	2,346	241	1.08 (0.85, 1.37)	0.536	1.18 (0.88, 1.59)	0.2754	1.06 (0.79, 1.42)	0.68
<i>By gender</i>								
Female	1,968	137	1		1		1	
Male	1,651	203	1.77 (1.44, 2.17)	<0.001	1.59 (1.28, 1.97)	<0.0001	1.41 (1.12, 1.78)	0.003

*. Univariate Analysis.

#. Adjusted by Age, Gender, And Race.

\$. Adjusted by Age, Gender, Race, Obesity, Diabetes, Hypertension, Heart Disease, Asthma, COPD, and CKD.

Table 3: Associations between Death with Race and Gender Among Cancer Patients Contracting COVID-19.

Discussion and Conclusion

In the study, we reported the significant increased COVID-19 related death among cancer survivors. The elevated risk was particularly evident among those who had cancers in respiratory, digestive tract, and blood. As expected, the most significant cancer site was respiratory cancer, which includes cancers of the lung, larynx, trachea, and bronchus. Respiratory failure in COVID-19 contraction is a common feature in fatal cases and has been considered as a failure of the immune system to control the virus. Additionally, we found that male cancer survivors contracting COVID-19 were found to have higher risk of death than female cancer survivors.

Delayed treatment, COVID-19 related comorbidities, and reduced immunocompetence of cancer patients may play roles in the increased COVID-19-related death among cancer patients. COVID-19 related comorbidities and older age are related to worse prognosis among COVID-19 patients [2]. Hypertension, cardiovascular disease, and diabetes were the most common comorbidity in patients death due to COVID-19. However, significant increased COVID-19 related death among cancer survivors persist even we adjust these covariates in the analysis. Cancer care has frequently been delayed or altered due to system- and patient-level factors related to the COVID-19 pandemic [5]. For example, recent data showed that half of European breast centers altered systemic treatments and one-fifth of breast cancer patients experienced delay in radiation therapy during the pandemic. Additionally, recent study confirms that immunocompromised patients more likely to die if hospitalized with COVID-19 [6]. Immune system of cancer patients can be compromised through multiple means, including immune suppression by the tumor and by therapies such as chemotherapy and radiation. Studies also showed that impairment of immune system after cancer treatment can last a long time. Further investigation in the

factors contributing to the increased COVID-19-related death among cancer patients, is needed. The strengths of this study included the large COVID-19 patient population around the U.S., and the utilization of real-time data. This study has some limitations. No individual level data and advanced data analysis tools were available at TriNetx. Nevertheless, findings from this study shed light on the importance of previous cancer diagnosis in the determination of COVID-19 related death. Additional research, particularly addressing the limitations mentioned above, is warranted to validate our findings, and further clarify the increased risk of COVID-19 related death among cancer survivors.

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