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RESEARCH ARTICLE

Prevalence, Survival, and Outcomes of 1,143 Cancer Patients with COVID-19 at Babol University of Medical Sciences: A Prospective Follow-up Cohort Study

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Abstract

Introduction: COVID-19 infection is caused by SARS-CoV-2, a coronavirus that imposed a great burden on many countries. To date, the virus still takes lives in numbers, although the original pandemic is long gone. Cancer patients are among the most susceptible patients to COVID-19, either because of the virus itself or forced deviations in detection and treatment. Having no background data on long term survival, this study aims to investigate the 5-year survival of cancer patients based on their COVID-19 infection status. **Materials and Methods:** In this single-center prospective follow-up cohort study from Babol Oncology Center, 1143 patients were evaluated for COVID-19 status and survival. The primary outcome was 5-year survival. The secondary outcomes were mortality by cancer type, year post-infection, and sex. COVID-19 status was tested with a polymerase chain reaction (PCR) assay and/or a CT scan. **Results:** Of 1143 patients analyzed, 60% were female, and the mean age was 57.2 years old. Breast cancer was the most prevalent cancer. 10.8% of cases were COVID-19 positive, with a case fatality rate of 48/1000. Brain cancer showed the highest COVID-19–related case fatality rate. Adjusted for age and cancer type, COVID-19–negative patients showed a higher risk of death compared to COVID-19–positive patients (adjusted HR 1.78, 95% CI 1.15–2.73). **Conclusion:** The observed survival differences are likely influenced by residual confounding, selection bias, and limitations in exposure ascertainment rather than a protective effect of COVID-19 infection.

Keywords: COVID-19- Neoplasms- Survival

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Introduction

The COVID-19 pandemic was a major health and epidemiological challenge. As of February 2024, over 7 million deaths are attributed to COVID-19 based on the WHO database [1]. One of the major problems with the spread of the disease was the management of cancer patients. They require more follow-up and multiple clinic visits for diagnosis and treatment than other patients. At this time, many cancer patients missed the opportunity for early tumor detection [2], many of whom delayed treatment or at least missed part of it, if not all of it [3]. Data also show that the rate of seroconversion in this group of patients is lower than in others [4].

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Given that cancer patients expect a lower survival than the general population and other patients, late diagnosis and interrupted treatment can result in an even worse prognosis for this group. According to the report of a large cohort study of Britain, COVID-19-positive cancer patients had a higher case fatality rate compared to non-cancer matched patients during a 21-day post-infection period (22.2% vs. 15.6%). Also, cancer patients with positive COVID status had 7.76 times more risk of dying than COVID-negative patients[5]. Another larger cohort in Korea reported an Odd Ratio of 1.94 for death in COVID patients with cancer compared to non-cancer controls [6]. Underlying disease is another risk factor that is associated with diminished survival [7].

Most of the existing literature deals with survival during the early post-infection period. But one of the main questions for epidemic survivors is how this virus may affect their later life; does it lead to lower survival? Another question to be answered is how it will affect different cancer types and genders; maybe some types of cancers are more "resistant" to the virus, or maybe the virus triggers the immune system to "discover" the tumor cells [8].

The COVID-19 infection maybe leads to lymphopenia and immune exhaustion, which could potentially hamper anti-tumor responses [9]. Other observations have shown that cancer patients with either high or low humoral responses to the COVID-19 vaccine have poor cellular immunity function, which is the cornerstone in fighting tumors [10, 11]. These hypotheses require more information about the survival of cancer patients after the pandemic, but data on the survival of these patients overall and by cancer type are scarce. Given the existing information gap, this study aimed to obtain more information about the effects of viral infection on cancer patients. In this study, we followed a group of cancer patients who were diagnosed at the beginning of the pandemic.

Materials and Methods

Study design and setting

This is a single-center prospective follow-up cohort study from Babol Oncology Center in northern Iran. The original study was a 1294 cancer patient cohort, in which the COVID-19 and survival status of patients were followed during a 5 year period [12]. In this study, recruitment was conducted between February 2019 and September 2020. Ethics committee approval code was: IR.MUBABOL.REC.1400.051. Written informed consent was taken from participants, which included the consent to register and publish follow-up survival data.

Participants

All eligible patients who were referred to Babol Oncology Center for cancer treatment were included. Inclusion criteria allowed any newly diagnosed cancer patient to enter the study. Patients with a cancer diagnosis for more than 6 months before enrollment were excluded; therefore, all included patients were newly diagnosed cases at study entry. Patients were followed weekly during their treatment course. The initial report of this cohort comprised 1294 cancer patients. We excluded 151 cancer patients with insufficient records who were considered lost to follow-up (11,7 %).

Variables

The primary outcome of the present study is 5-year survival. The secondary outcomes are mortality by cancer type. In the original study, age, sex, comorbidities, performance status, cancer characteristics (i.e., type, stage, treatment intent, and modality), season of COVID-19 infection diagnosis, duration between cancer diagnosis and COVID-19 infection, admission type (ward, ICU), and COVID-19 infection symptoms were recorded. COVID-19 status was tested with a polymerase chain reaction (PCR) assay and/or a CT scan.

Data sources and measurements

Survival and mortality were defined as the time from cancer diagnosis to death by any cause. Survival status was checked by direct phone calls. Baseline characteristics were recorded from an in-person interview. Details on other variables measurement are published here.

Statistical analysis: categorical variables were depicted by numbers and percentages and were analyzed using Pearson's Chi-square test. Survival status was reported by two methods: as a categorical variable (alive/dead) and as a time-to-event variable. In the latter setting, survival in the whole cohort and subgroups (cancer type, sex, death year) was reported by hazard ratio (HR) of death using the Cox regression model. COVID-19 history was analyzed as a binary exposure (ever vs never) and not as a time-dependent covariate. All analyses were performed using STATA version 14.0 (StataCorp, College Station, Texas). The statistical significance level was set to 0.05. Patients with missing primary data and those who were lost to follow-up were excluded from the final analysis.

COVID-19 exposure was analyzed as a historical (ever/never) variable and not as a time-dependent covariate; therefore, the survival analyses are descriptive and subject to immortal time and competing-risks bias.

Results

Of all subjects (1143), 60% were female (686), the mean±SD age cohort was 57.2± 15.10 (min 3, max95). Fortunately, 69.8% of patients were alive at the end of the study. The goal of treatment intention was curative in 91% of patients. The highest and lowest number of patients were in the Breast (n=446) and Esophagus (n=42) cancer groups (Table 1).

Based on the PCR test, 10.8% of all patients (n= 124) had a history of COVID-19 disease. The highest and lowest rate of COVID-19 disease was seen in Hematologic (26%) and Head & Neck (0.3%) cancer patients. The overall death rate from COVID-19 (PCR test positive) in this cohort was approximately 5.3 per 1,000 people (Table 2).

Table 1. Gender and Type of Treatment According to Type of Cancer in Babol Cancer Cohort

Type of cancer	n (%)	Gender		P-value	Treatment intention		P-value
		Male	Female	<0.001	Curative	Palliative	0.225
		n (%)	n (%)		n (%)	n (%)	
Brain	68 (5.9)	42 (61.8)	26 (38.2)		35 (85.4)	6 (14.6)	
Breast	446 (39.0)	16 (3.6)	430 (96.4)		360 (93.3)	26 (6.7)	
Gastrointestinal	185 (16.2)	118 (63.8)	67 (36.2)		72 (87.8)	10 (12.2)	
Esophagus	42 (3.7)	30 (71.4)	12 (28.6)		6 (100)	0	
Hematologic	131 (11.5)	95 (72.5)	36 (27.5)		72 (85.7)	12 (14.3)	
Head & Neck	61 (5.3)	47 (77.0)	14 (23.0)		38 (90.5)	4 (9.5)	
Skin	94 (8.2)	52 (55.3)	42 (44.7)		61 (93.8)	4 (6.2)	
Genitourinary	116 (10.1)	57 (49.1)	59 (50.9)		68 (889.5)	8 (10.5)	
Total	1143 (100)	450 (40)	686 (60)		712 (91.0)	70 (9.0)	

Table 2. History and outcome of COVID-19 in the Babol Cancer Cohort. Death due to COVID-19 refers to death occurring during the acute phase of PCR-confirmed SARS-CoV-2 infection and recorded as COVID-19–related in clinical records. Precise attribution between COVID-19 and underlying cancer progression was not always possible.

Type of cancer n (%)		COVID-19 history n (%)		Death due to COVID-19
		No	Yes	
Brain	68 (100)	64 (94.1)	4 (5.9)	2 (50)
Breast	446 (100)	401 (89.9)	45 (10.1)	2 (4.4)
Gastrointestinal	185 (100)	175 (94.6)	10 (5.4)	-
Esophagus	42 (100)	40 (95.2)	2 (4.8)	-
Hematologic	131 (100)	97 (74.0)	34 (26.0)	2 (5.9)
Head & Neck	61 (100)	59 (96.7)	2 (3.3)	-
Skin	94 (100)	81 (86.2)	13 (13.8)	-
Genitourinary	116 (100)	102 (87.9)	14 (12.1)	-
Total	1143 (100)	1019 (89.2)	124 (10.8)	6 (0.5)

In this study, 1143 subjects were followed (51181 person-month at risk). The median of follow-up was 44 months (minimum 1, maximum 144), and 345 (30.2%) deaths occurred (mortality rate 301 per 1000). The most and least deaths occurred in patients with esophageal (85.7%) and breast (10.9%) cancers, respectively. Median follow-up according to type of cancer is depicted in Table 3.

Results of the multivariable Cox regression analysis are reported in Table 4. COVID-19 history was analyzed as a binary exposure (ever vs never) and not as a time-dependent covariate. Death risk in gastrointestinal, esophagus, and brain cancer patients was 5.54, 4.73, and 4 times more than breast cancer, adjusted for sex, age, and covid19 history. The risk of death was 1.7 times higher in Cancer patient without a history of covid19, adjusted for age and type of cancer.

Discussion/Limitations

This study has several important limitations. Formal TNM staging, time-dependent treatment status, and reliable cause-specific mortality data were not uniformly available across cancer types, precluding cancer-specific or COVID-19–specific survival analyses and formal competing-risks modeling. COVID-19 exposure was analyzed as a historical (ever/never) variable rather than a time-varying covariate, which may introduce immortal time and survivor bias. Limited access to diagnostic testing during the early phases of the pandemic likely resulted in under-ascertainment and misclassification of COVID-19 infection. In addition, baseline characteristics were not fully balanced between COVID-19–positive and negative groups, and residual confounding is likely.

Breast cancer patients comprised a substantial proportion of the cohort and generally have a superior prognosis, which may influence overall survival estimates despite adjustment for cancer type. Finally, wide confidence intervals observed in some cancer subgroups likely reflect limited sample sizes, and these findings should be interpreted as exploratory rather than definitive. Accordingly, the observed associations should be interpreted cautiously and do not support causal inferences regarding a protective or harmful effect of COVID-19 on cancer survival.

Of 1143 patients in this cohort, 60% were female and breast cancer was the most prevalent tumor (39% of all tumors). 91% of patients were treated with a curative intent. With only 10.9% death rate, the breast cancer patients experienced the least mortality during the 5-year follow-up period, while the esophageal cancer patients had the most (85.7%). Case-fatality rate (CFR), i.e., mortality that can be directly attributed to COVID-19

Table 3. Median Follow-up According to Type of Cancer

Type of cancer n (%)	Person-month at risk	Deaths n (%)	Median (lower, upper) months	P-value
Brain (n=68)	2929	28 (41.2)	42 (6, 74)	<0.001*
Breast (n=446)	20421	49 (10.9)	45 (3. 118)	
Gastrointestinal (n=185)	7600	103 (55.6)	42 (2, 67)	
Esophagus (n=42)	1857	36 (85.7)	46.5 (1, 60)	
Hematologic (n=131)	5877	44 (33.6)	44 (2, 96)	
Head & Neck (n=61)	2954	19 (31.1)	42 (3,144)	
Skin (n=94)	4048	28 (29.8)	42 (5, 63)	
Genitourinary (n=116)	5495	38 (32.8)	44 (5, 132)	

*Log-rank test for equality of survivor functions

Table 4. Death Risk by Characteristics of Cancer Patients

Variable		Unadjusted HR			Adjusted HR			
		HR	Std. Err	CI 95%	HR	Std. Err	CI 95%	P-value
Type of cancer	Brain	4.56	1.08	2.86, 7.26	4	1	2.44, 6.55	<0.001
	Breast	1	-	-	1	-	-	-
	Gastrointestinal	7.94	1.39	5.63, 11.19	5.54	1.11	3.76, 8.21	<0.001
	Esophagus	7.25	1.6	4.1, 11.18	4.73	1.21	2.86, 7.2	<0.001
	Hematologic	3.18	0.66	2.11, 4.78	3.3	0.76	2.09, 5.21	<0.001
	Head & Neck	2.11	0.61	1.19, 3.71	1.44	0.45	0.78, 2.70	0.239
	Skin	3.16	0.75	1.9, 5.03	2.53	0.63	1.55, 4.15	<0.001
	Genitourinary	2.37	0.52	1.54, 3.66	1.87	0.45	1.17, 3.00	0.009
Gender	Female	1	-	-	1	-	-	-
	Male	2.22	0.25	1.78, 2.76	1.13	0.15	0.87, 1.46	0.327
Covid19 history	Yes	1	-	-	1	-	-	-
	No	1.79	0.38	1.18, 2.72	1.78	0.39	1.15, 2.73	0.009
Age		1.03	0.004	1.02, 1.04	1.02	0.004	1.01, 1.03	<0.001

acute infection, was 48 (per 1000) compared to 301 (per 1000) mortality rate in this cohort. With a large margin, the highest CFR of COVID-19 was seen in brain cancer patients (50%).

We presented a 5-year CFR of 4.8% in our cohort, while in Lee et al.'s study, it was 22% in early COVID-19 infection [5]. This vast difference could be attributed to many factors. First, that study was conducted in Britain, a country with an immense health infrastructure that allows for testing more patients, early and accurately. Contrary to this, in Iran, COVID-19 was denied until late February 2020, which could lead to many deaths in those cancer patients who are the frailest and at [5] most risk, hence leading to lower CFR documented. COVID-19 tests were not readily available in our country until summer 2020, and many of the tests led to false negative results. Also, death registration was heavily compromised in the early pandemic, as many victim families forced physicians and authorities not to attribute death to COVID-19 infection in the death certificate (because bodies were not handed to families until a full investigation was done).

Factoring out skin cancer patients, our results have shown that COVID-19 infection was more prevalent in hematologic, genitourinary, and breast cancer patients, respectively. Higher COVID-19 mortality has been observed in this order: brain tumors, hematologic malignancies, and breast cancer. Hematologic malignancy patients exhibit lower humoral response to virus antigens and are more prone to death due to either infection or multiple systemic chemotherapies, needing early and multiple vaccinations [13, 14].

One of the main hypotheses of this study was to check whether there is a clue that those infected with COVID-19 before vaccination live less or not. Adjusted for Cancer type and age, a 1.78 times higher mortality rate in COVID-19 negative patients show that the mentioned hypothesis is not consistent with reality, and there is not enough evidence that long-time survivors of COVID-19 suffer more mortality than those not infected before vaccination. The apparent survival difference in our study should not be interpreted as a survival benefit of COVID-19 infection. Collectively, in this long-term observational cohort, prior documented COVID-19 infection was not associated with worse overall survival among cancer patients. The observed survival differences are likely influenced by residual confounding, selection bias, and limitations in exposure ascertainment rather than a protective effect of COVID-19 infection.

These findings describe survival patterns in a real-world cancer cohort and do not support causal inferences

regarding the effect of COVID-19 infection on cancer outcomes.

Declarations

Funding

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Clinical trial registration

Not applicable

Conflicts of interest/Competing interests

Authors declare that they have no conflicts of interest.

Availability of data and material

The data sets used and analyzed during the current study are available from the corresponding authors per reasonable request.

Code availability

The custom code was used.

Authors' contributions

According to title page numbers: Author 1, Project development, Data collection, Manuscript writing/editing, Final Approval; Author 2: Project development, Data analysis; Author 3: Project development, Data collection, Manuscript writing/editing; Author 4: Project development, Data collection, Manuscript writing/editing; Author 5: Project development, Data collection, Manuscript writing/editing; Author 6: Data collection, Manuscript writing/editing; Author 7: Data collection, Manuscript writing/editing; Author 8: Data collection, Manuscript writing/editing; Author 9: Data collection, Manuscript writing/editing; Author 10: Project development, Data collection, Manuscript writing/editing, Final Approval.

Ethics approval

The original study was approved by the ethics committee of Babol University of Medical Sciences under the code: IR.MUBABOL.REC.1400.051.

Consent to participate

Written informed consent was obtained from all participants

Consent for publication

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Originality Declaration for Figures

All figures included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

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Declaration on generative AI and AI-assisted technologies in the writing process

The authors maintain that they have not used generative AI, nor AI-assisted technologies in the writing process.

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