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RESEARCH ARTICLE

Mortality Rate and Effects of COVID-19 in Cancer Patients *versus* Non-cancer Patients: A Propensity Score Matching Study

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Abstract:

Background and Aim:

Coronavirus is still a life-threatening disease around the world. In patients with this disease, having an underlying disease reduces the effectiveness of treatment and increases mortality. This study aimed to examine the effect of cancer history on mortality rates in patients with COVID-19.

Materials and Methods:

This study was a case-control study involving 60 cancer patients with COVID-19 as the case group and 180 non-cancer patients with COVID-19 as the control group. A matching method based on propensity score was used to select patients in the control group. The effect of treatment on the outcome (recovery death) was studied with logistic regression, and the factors affecting patient survival were analyzed with Cox models. R software was used to analyze the data.

Results:

The mean (SD) age of patients in the case and control groups was 61.37 (13.47) and 63.19 (13.95) years, respectively. In the case group, 37 patients (61.7%), and in the control group, 114 patients (63.3%) were male. 23 cancer patients (38.3%) and 26 non-cancer patients (14.4%) died. The results of logistic regression as well as the Cox model showed the variables of age, blood oxygen level (SpO2), admission to the intensive care unit, and cancer history as significant for patient death ($P < 0.05$).

Conclusion:

To study the effect of demographic, clinical, and laboratory results on the risk of death among COVID-19 patients with and without a cancer history, control group in this study was selected by PSM method. The results of this study have indicated cancer history to be one of the factors affecting the mortality of patients with COVID-19 in addition to age variables, blood oxygen levels (SpO2), and admission to the intensive care unit (ICU).

Keywords: Cancer, COVID-19, Logistic regression, Cox proportional hazards, Matching, Propensity score.

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1. INTRODUCTION

Since the report of its first case in Wuhan, China, in December 2019, coronavirus (COVID-19) caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide. According to the Center for Systems Science and Engineering (CSSE) at Johns Hop Keynes University, COVID-19 has infected more than 25 million people in more than 200 countries and has left more than 840,000 dead as of August 31, 2020 [1, 2].

The risk of death among patients with chronic underlying diseases, especially incurable diseases, who are prone to coronary heart disease due to immune suppression, should be evaluated and compared [3]. In patients with COVID-19 who

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have underlying diseases, such as cancer, the severity of the disease and the risk of death are both high [4 - 6]. Patients with cancer are typically at high risk for viral pneumonia, with an increased risk of severe infection and also more fatal outcomes than non-cancer patients [7]. The most common symptoms are fever (6.98%), dry cough (4.59%), and shortness of breath, as well as other symptoms, such as fatigue (6.69%), muscle ache, diarrhea, sore throat, loss of olfactory and taste, and abdominal pain. At-risk groups include the elderly, pregnant women, and people with underlying medical conditions, such as chronic bronchitis, emphysema, heart disease, cancer, or diabetes [8]. While no study has yet examined the immune response of patients with malignancy to a co-infection with SARS-CoV-2, it is unclear whether the immunosuppressive status of patients with malignancy predisposes them to a more severe course of COVID-19.

It has been suggested that cancer patients with COVID-19 are at increased risk for a more severe course of the disease and a poorer outcome of treatment than non-cancer patients with COVID-19. However, the studies and patient groups have been mainly composed of patients with solid tumors due to the small number of samples [9 - 12]. Wang *et al.* showed the severity of complications to be more severe in patients with malignant diseases [13]. Based on the findings of Dai *et al.*'s study, cancer patients are significantly more likely to require ICU admission, have severe disease symptoms, or die [9]. In their study, Deng *et al.* [14] found the risk of mortality in cancer patients to be higher than in patients without cancer, while Brar *et al.* [15] found patients with COVID-19 and cancer to have similar outcomes to those without cancer.

This study was a case-control study in which the control group using the propensity score matching (PSM) method was matched with the case group since there have only been a limited number of studies comparing mortality and thefactors playing a role in it in patients with a history of cancer. We evaluated the effect of cancer history on patient mortality in the presence of demographic, clinical, and laboratory characteristics, as well as the effect of variables on patient survival.

2. MATERIALS AND METHODS

In this case-control study, 60 hospitalized cancer patients with concomitant SARS-CoV-2 infection confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) assay were included. The frequency of types of cancer is presented in Flowchart 1. For the control group, 180 patients with similar age, sex, smoking, and other underlying diseases, including hypertension, diabetes, lung and heart disease, selected among 2160 hospitalized patients with confirmed COVID-19 using the PSM method from the same time span without a cancer diagnosis, were recruited. In this study, all demographic and clinical variables were matched to increase the validity of the analysis and results. All demographic characteristics, clinical data, underlying diseases, and disease symptoms were extracted from patients' medical records. Moreover, laboratory tests were performed during hospitalization. In this study, two outcomes were considered, including a binary clinical outcome (death or recovery) and survival time. Survival time was considered as the time from admission to the hospital to death or discharge from the hospital (in days).

2.1. Statistical Analysis

Demographic and clinical characteristics were described as mean and standard deviation (SD) for continuous variables, and categorical variables have been presented as frequency (percentage). To compare the categorical variables, Pearson's chi-square test was used, and to compare the continuous variables, t-test was used.

A propensity score matching was performed to estimate the effect of cancer by accounting for the covariates statistically significant in the multivariable model. For each cancer patient, three comparable patients were selected in the non-cancer population (1:3 ratio) [16].

The possible factors identified with univariable logistic regression were entered into the multivariable logistic regression to determine independent predictors of patient outcome. Univariable and multivariable logistic regression was used to estimate the odds ratio (OR) of patients' death and to explore the risk factors of death from COVID-19 among patients with cancer. Stepwise regression using the backward selection (Wald) method was also utilized to conduct variable selection. The final model only included the variables that contributed significantly to the model.

The univariable and multivariable Cox models, and their 95% confidence intervals (CI) were also used to compare patient survival time and the hazard ratio (HR). Kaplan–Meier curves were plotted for the time from admission to death (in days) for patients who died.

Statistical analysis was performed using SPSS software version 27 and the R package. A P-value less than 0.05 was considered statistically significant. The "MatchIt" package was used for PSM. The "GLM", "survival" and "survminer" package was used to fit the logistic and Cox proportional hazard regression model.

3. RESULTS

The steps of selecting control group patients using PSM are shown in Flowchart 1. Flowchart 2 shows the frequency of types of cancer and the patients affected by active cancer or in treatment. A mean (SD) age of 61.37(13.47) in the case group and 63.19 (13.95) in the control group years was found, and 61% of patients in the case group and 63% of patients in the control group were male. Tables **1** and **2** show the laboratory parameters, demographic and clinical characteristics of patients in the case and control groups. On the other hand, the results of Table **1** show no statistically significant differences in the other laboratory characteristics between cancer and non-cancer groups of patients with COVID-19, except for NUT and lymphocyte variables. The table shows 23 deaths among 60 cancer patients (38%) and 26 deaths among 180 non-cancer patients (14%). There was no Statistically significant difference in the variables of age, gender, smoking and use of tobacco, and underlying diseases, such as hypertension, heart disease, diabetes, lung disease, renal failure, in the two groups, and they

were minimized by comparison based on the skewed score between the two groups, and the relative risk of death (HR) and mortality (OR) in the two cancerous groups (case group) and non-cancerous (control group) were completely matched. Table **3** shows the results of univariable logistic regression used to compare mortality rates among patients. The multivariable model was applied to all variables with a value of less than 0.1, and then the most appropriate variables were selected by stepwise and regression methods and tested; the results are shown in Table **4**. This resulted in a modified logistic regression model. The variables of age, blood oxygen level, admission to the intensive care unit, and cancer history, were found to affect the risk of death in patients (P <0.05). According to the results of Table **4**, with one year of age increase or one unit of decreased blood oxygen level, the risk of death of patients increased by 4%. It was estimated that patients admitted to the intensive care unit had a 6.57-fold higher chance of dying than other patients, and that patients with a history of cancer had a 5.03-fold higher chance of dying.

Additionally, the Cox proportional hazards model was used to examine the effect of cancer history on the survival of patients with COVID-19 (Table **5**). As with the logistic regression model, all variables were entered into the multivariable model with a value of less than 0.01. The results of the multivariable Cox hazard model are shown in Table **6**. The results showed the variables of age, blood oxygen level, admission to the intensive care unit, and cancer history to affect the survival of patients with COVID-19 (P <0.05). An increase of one year in age or a decrease of one unit in blood oxygen level increased the hazard of death for patients by 2%. Intensive care unit patients had a 5.10 times higher hazard of death than other patients, and cancer patients had a 2.43 times higher hazard of death. Figs. (**1** - **5**) display the survival rate, as well as the half-life of patients from admission to death or discharge (days) using the Kaplan-Meyer method. The median duration of hospitalization in cancer patients was 14 days, and in non-cancer patients, it was 17 days.

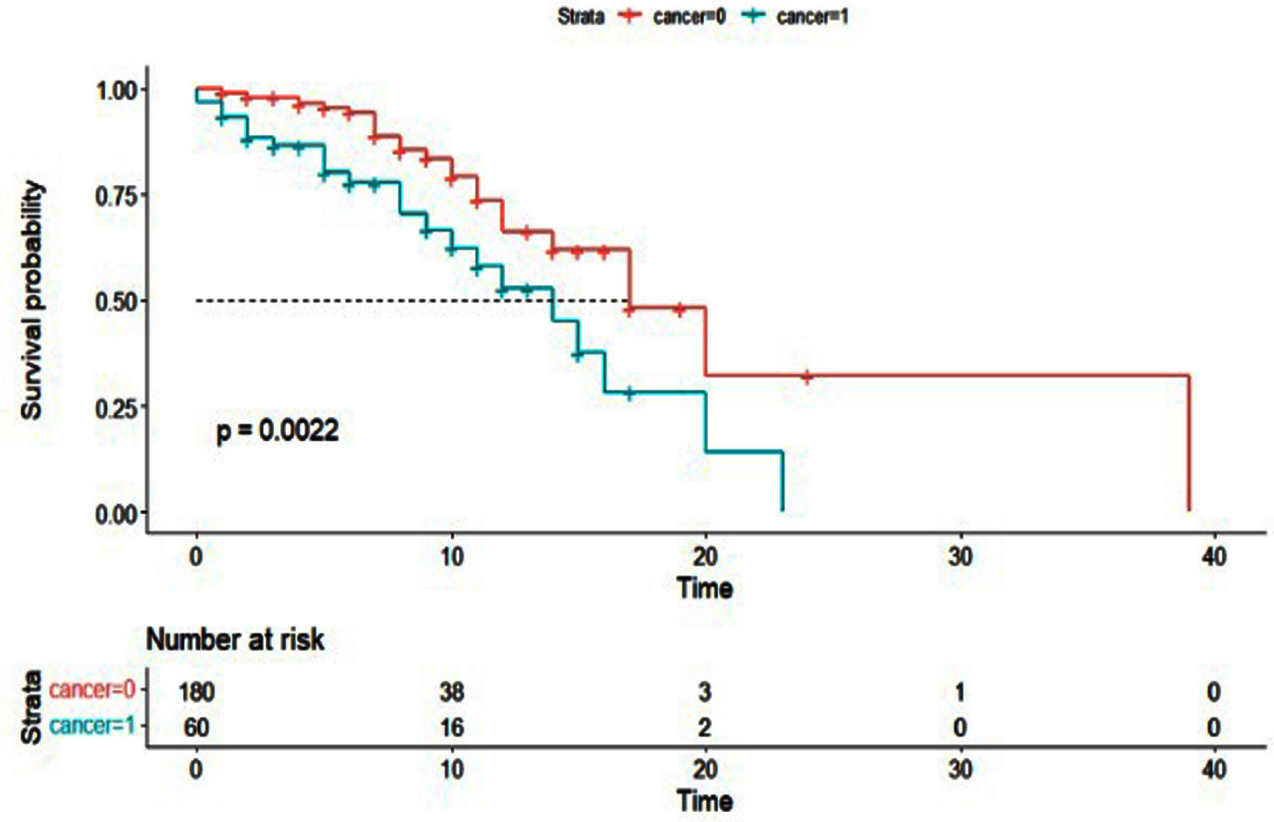

Fig. (1). Survival time (days) from admission to discharge.

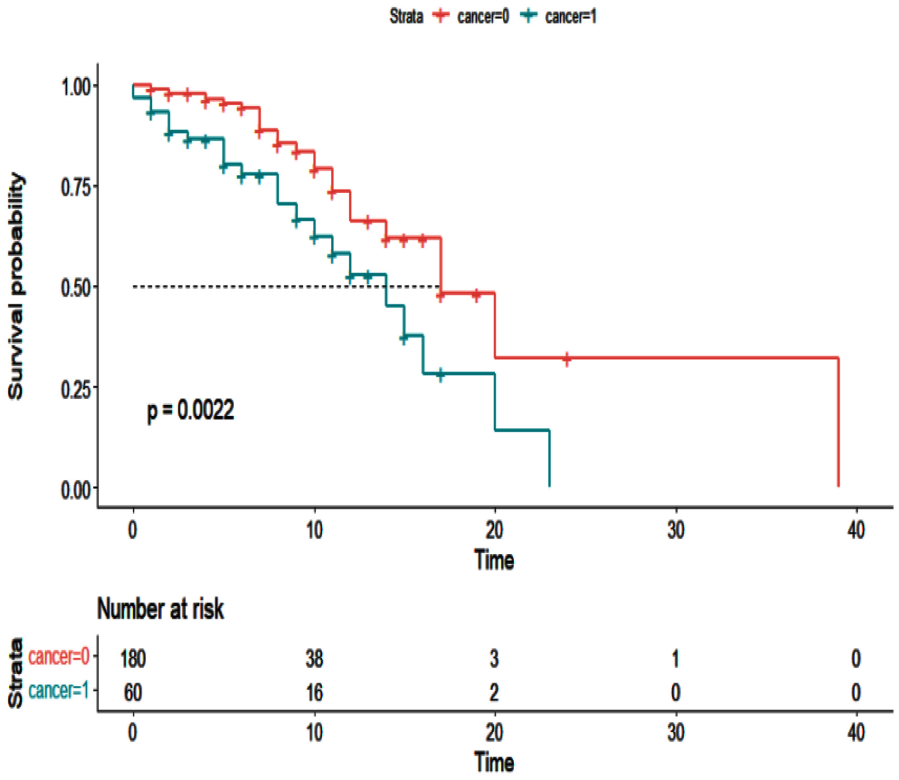

Fig. (2). Survival time (days) from admission to discharge.

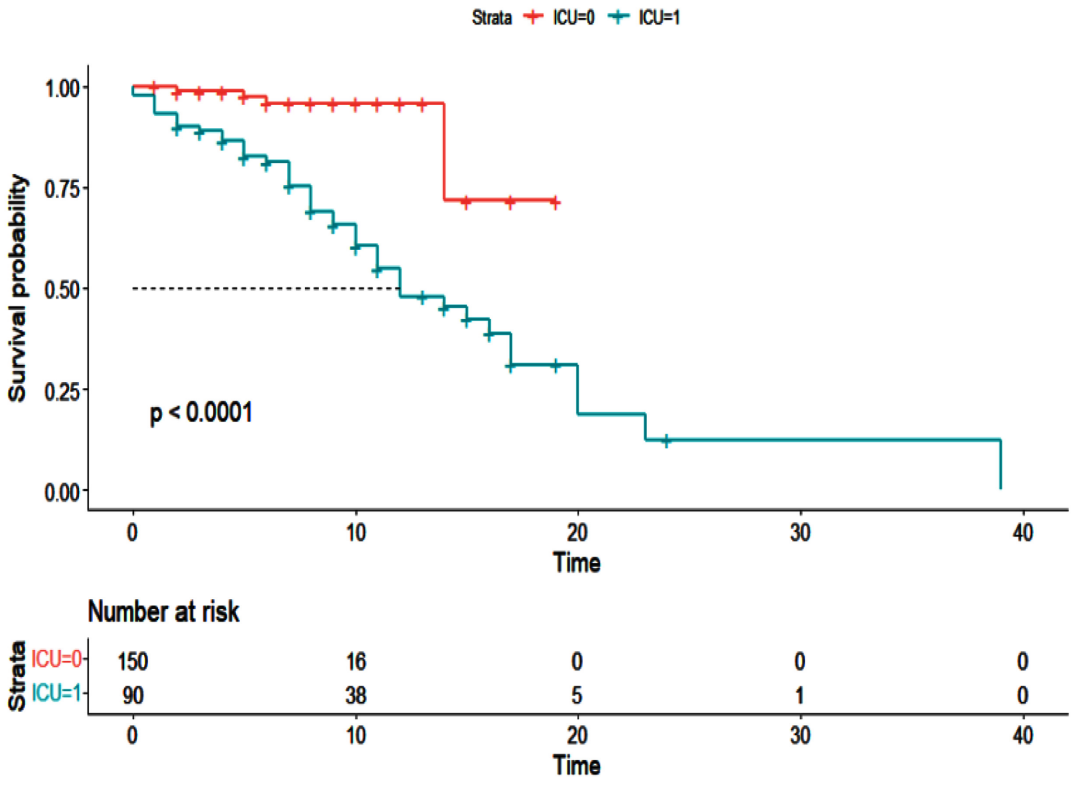

Fig. (3). Survival time (days) from admission to discharge.

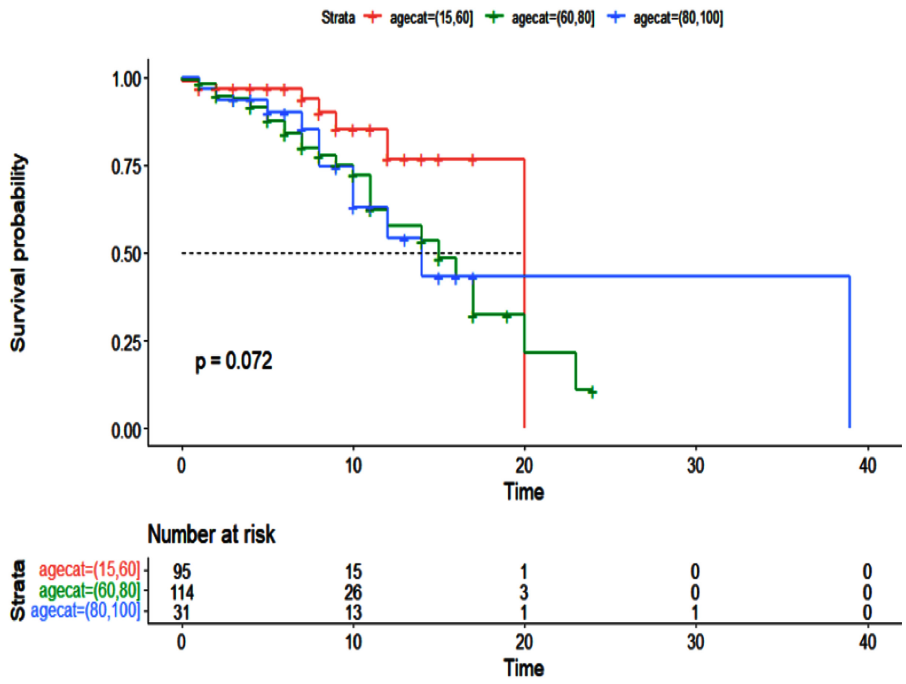

Fig. (4). Survival time (days) from admission to discharge.

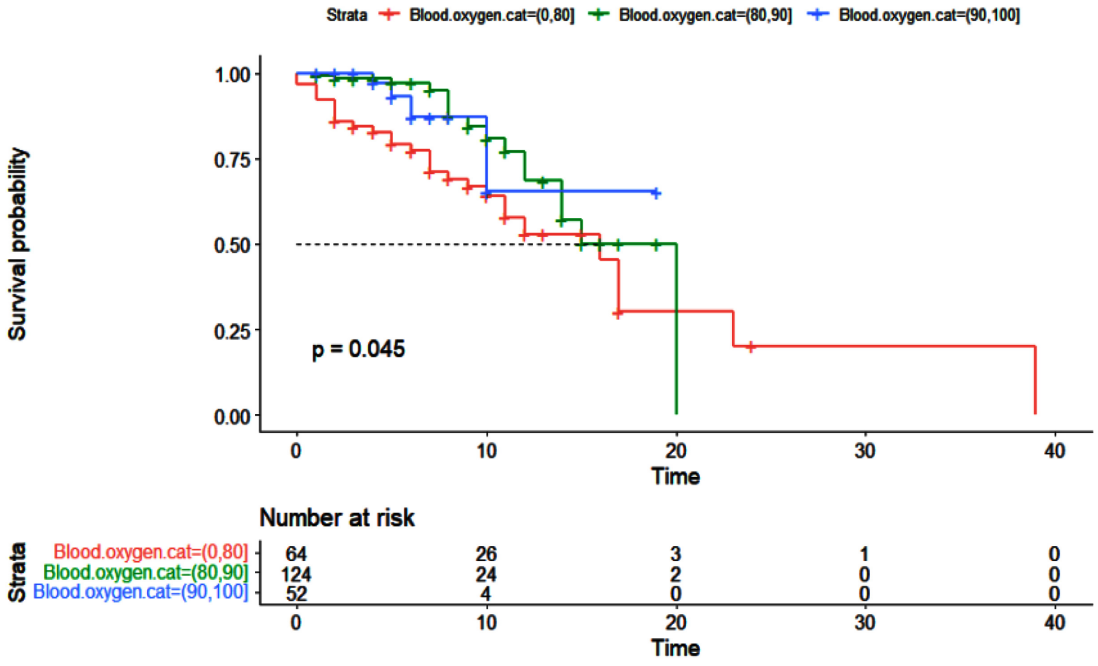

Fig. (5). Survival time (days) from admission to discharge.

Table 1. Laboratory parameters and clinical course in COVID-19-infected cancer patients and matched noncancer controls.

Variable	Case group (n=60) Mean(SD)	Control Group (n=180) Mean (SD)	p-value
Lymphocyte	23.8 (11.5)	20.1 (10.8)	0.02
Mono	3.2 (6.6)	3 (1.8)	0.82

(Table 1) contd.....

Variable	Case group (n=60) Mean(SD)	Control Group (n=180) Mean (SD)	p-value
NUT	71.9 (12.3)	75.7 (12)	0.03
CBC	6.6 (3.3)	8.2 (5.3)	0.01
LDH	578 (277.4)	662.5 (616.3)	0.19
HCT	41.9 (7)	42.9 (6.4)	0.31
Hb	13.7 (2.4)	14.2 (3.6)	0.22
K	4.2 (0.6)	4.2 (0.5)	0.36
Plat	186.6 (64.9)	196.8 (72.9)	0.29
Alp	202 (105.9)	206.6 (75.1)	0.74
PTT	32.7 (10.2)	32.9 (6.5)	0.89
SGPT	34.1 (44.1)	52.7 (117.7)	0.11
SGOT	38.7 (36.4)	79 (263.5)	0.07
CPK	261.9 (506.4)	209.3 (336.4)	0.49
ESR	39.1 (28.8)	39.5 (25.8)	0.93
BUN	20.7 (15.7)	21.3 (15.5)	0.79
BS	133.4 (58.5)	145.3 (69.1)	0.25
CR	1.3 (1.6)	1.3 (0.9)	0.72
PT	13.5 (2.8)	13.4 (1.7)	0.78

Note: * statistically significant

Table 2. Demographic and clinical characteristics of patients.

Characteristics	Case Group (n=60)	Control Group (n=180)	p-value
Age [mean (SD)]	61.37 (13.47)	63.19 (13.95)	0.37
Sex=male (%)	37 (61.7)	114 (63.3)	0.94
Resident (urban)	53 (88.3)	145 (80.1)	0.83
Temperature [mean (SD)]	37.31 (0.75)	37.47 (0.88)	0.20
Systolic BP [mean (SD)]	123.27 (17.97)	12.48 (20.8)	0.34
Diastolic BP [mean (SD)]	76.03 (12.80)	76 (11.05)	0.99
SpO2 [mean (SD)]*	84.28 (10.34)	79.85 (15.24)	0.04
LOH in ICU [mean (SD)]	6.43 (3.4)	5.27 (4.48)	0.26
Total LOH [mean (SD)] *	9.13 (16.4)	5.7 (3.9)	0.01
Oxygen therapy (yes) (%)	54 (71.2)	164 (91.1)	0.42
Admission to ICU (yes) (%)	29 (48.3)	61 (33.9)	0.06
Length of ICU stay [mean (SD)]	3.02 (4.72)	2.24 (5.05)	0.30
Mechanical ventilation (yes)*	21 (35)	31 (17.2)	0.01
Addict	4 (6.7)	15 (8.3)	0.79
Smoking (yes) (%)	3 (5)	12 (6.7)	0.77
Pulmonary disease (yes) (%)	4 (6.7)	13 (7.2)	0.99
Heart (yes) (%)	7 (11.7)	17 (9.4)	0.80
Kidney	6 (10)	11 (6.1)	0.38
Hypertension	15 (25)	41 (22.8)	0.86
Diabetes	14 (23.3)	25 (13.9)	0.13
Other	19 (31.7)	62 (34.4)	0.81
Death*	23 (38.3)	26 (14.4)	<0.01
Diarrhea (yes) (%)	4 (6.7)	13 (7.2)	0.98
Dry cough (yes) (%)*	14 (23.3)	72 (40)	0.03
Sputum cough (yes) (%)	17 (28.3)	35 (19.4)	0.20
Muscle pain (yes) (%)	20 (33.3)	80 (44.4)	0.17
Fever (yes) (%)	29 (48.3)	82 (45.5)	0.82
Chills (yes) (%)	23 (38.3)	73 (40.5)	0.88
Sore throat (yes) (%)	0	9 (5)	0.12

(Table 2) contd.....

Characteristics	Case Group (n=60)	Control Group (n=180)	p-value
Nausea (yes) (%)	12 (20)	36 (20)	0.97
Headache (yes) (%)	7 (11.7)	36 (20)	0.21
Fatigue (yes) (%)	0	7 (3.9)	0.20
Vomiting (yes) (%)	7 (11.7)	29 (6.1)	0.53
Asthma (yes) (%)	33 (55)	103 (57.2)	0.88
Runny nose (yes) (%)	0	2 (1)	0.96

Note: * statistically significant.

Table 3. The effect of covariates on clinical outcome (mortality) of patients with COVID-19 using univariable logistic regression.

Characteristics ID	OR	95% CI		p-value
		Lower	Upper	
Age*	1.05	1.02	1.07	<0.01
Sex (male)	1.43	0.74	2.88	0.29
Smoking	0.26	0.01	1.36	0.20
Hypertension (yes)	1.74	0.59	2.51	0.55
Temperature	2.53	0.65	1.46	0.93
SpO2*	0.93	0.90	0.95	<0.01
Pulmonary disease (yes)	1.69	0.52	4.83	0.34
Kidney failure (yes)	1.68	0.51	4.82	0.33
Diabetes (yes)	1.43	0.62	3.11	0.38
Heart disease (yes)	1.99	0.25	1.09	0.09
Cancer (yes)*	3.68	1.89	7.19	<0.01
Other diseases (yes)	1.18	0.60	2.52	0.62
Admission to ICU (yes)*	5.74	11.31	23.83	<0.01
Oxygen therapy (yes)	-	-	-	0.98
Length of ICU stay*	1.19	1.11	1.28	<0.01
Mechanical ventilation*	72.95	31.58	403.83	<0.01
Asthma (yes)	1.14	0.60	2.18	0.69
Diarrhea (yes)	0.82	0.18	2.66	0.77
Dry cough (yes)*	0.45	0.21	0.90	0.03
Muscle pain (yes)	0.55	0.27	1.06	0.08
Fever (yes)	1.27	0.68	2.39	0.45
Chills (yes)	0.84	0.43	1.59	0.60
Sore throat (yes)	1.12	0.16	4.81	0.89
Nausea (yes)	0.74	0.30	1.62	0.47
Vomit (yes)	0.93	0.35	2.17	0.87
Fatigue (yes)	0.64	0.03	3.88	0.68
Headache (yes)	0.46	0.15	1.14	0.12
Sputum cough (yes)	1.22	0.57	2.51	0.59

Note: * statistically significant.

Table 4. The adjusted effect of covariates on treatment outcome of patients with COVID-19 using multivariable logistic regression.

p-value	95% CI		OR	Characteristics
	Upper	Lower		
0.02	1.07	1.01	1.04	Age*
<0.01	13.26	2.04	5.03	Cancer (yes)*
<0.01	0.99	0.93	0.96	SpO2*
<0.01	23.52	7.32	6.57	Admission to ICU (yes)*

Note: * statistically significant.

Table 5. The adjusted effect of covariates on clinical outcome of patients (dead, alive) with COVID-19 using the univariable cox regression model.

Characteristics ID	HR	95% CI		p-value
		Lower	Upper	
Age	1.02	0.99	1.04	0.09
Sex (male)	1.16	0.63	2.13	0.64
Smoking	0.26	0.36	1.96	0.19
Hypertension (yes)	0.88	0.46	1.70	0.71
Temperature	1.02	0.68	1.54	0.90
SpO2*	0.98	0.96	0.99	<0.01
Admission to ICU (yes)*	7.00	2.71	18.13	<0.01
Oxygen therapy (yes)	-	-	-	0.89
Length of ICU stay*	1.01	0.90	0.99	0.04
Mechanical ventilation*	3.54	10.6	111.8	<0.01
Pulmonary disease (yes)	1.38	0.54	3.52	0.49
Kidney failure (yes)	1.93	0.76	4.90	0.17
Diabetes (yes)	0.85	0.41	1.72	0.65
Heart disease (yes)	1.80	0.96	2.68	0.07
Cancer (yes)*	2.34	1.33	4.14	<0.01
Other diseases (yes)	0.82	0.45	1.50	0.53
Asthma (yes)	1.25	0.70	2.24	0.45
Diarrhea (yes)	1.06	0.33	3.46	0.92
Dry cough (yes)	0.67	0.34	1.32	0.24
Muscle pain (yes)	1.08	0.57	2.02	0.82
Fever (yes)	1.28	0.73	2.27	0.39
Chills (yes)	1.25	0.69	2.28	0.46
Sore throat (yes)	1.78	0.43	7.40	0.43
Nausea (yes)	0.89	0.41	1.92	0.77
Vomit (yes)	1.14	0.51	2.57	0.75
Fatigue (yes)	0.75	0.10	5.44	0.77
Headache (yes)	0.85	0.33	2.18	0.74
Sputum cough (yes)	1.32	0.69	2.55	0.40

Note: * statistically significant

Table 6. The adjusted effect of covariates on clinical outcome of patients (dead, alive) with COVID-19 using multivariable Cox regression model.

Characteristics ID	HR	95% CI		p-value
		Lower	Upper	
Age*	1.02	0.95	0.99	0.049
Admission to ICU (yes)*	5.10	1.93	13.44	<0.01
SpO2*	0.98	0.96	0.99	0.049
Cancer (yes)*	2.43	1.30	4.54	<0.01

Note: * statistically significant

4. DISCUSSION

By matching based on propensity scores, 60 cancer patients with COVID-19 were matched with 180 non-cancer patients with COVID-19. Moreover, none of the underlying diseases had a significant relationship with patient mortality in patients with a history of cancer. As reported by Sorouri *et al.* and Meng *et al.*, there was no significant association observed between underlying diseases and patient mortality [10, 17]. Other studies have shown that high blood pressure or ischemic heart disease can increase the risk of death among patients with COVID-19 and a history of cancer [18, 19]. In the present study, due to the modified logistic regression result and Cox model, increasing age increased the death rate of COVID-19 patients with a history of cancer, despite the fact that in this study, the age variable was matched between the treatment and control groups. Therefore, we managed to reduce the number of significant variables by matching the variables, and due to the small amount of data, this work is of particular importance. However, the only variable that remained significant after adjustment was age. In the case and control groups, the mean

age was 61 and 63 years, respectively (P = 0.37). Comparing the data and examining the patients in the two groups of patients with and without a history of cancer with the same age group, we concluded the presence of a significant relationship between a history of cancer and patient mortality. Immune function has been reported to largely reduce with aging [20]. There has been a significant correlation observed between the age and mortality of patients with COVID-19 [18, 20 - 22]. Also, studies indicate no significant correlation between age and mortality for COVID-19 patients [10, 17].

The results did not show a significant relationship between gender and mortality rate in the present study. Other studies have not found a correlation between gender and mortality in COVID-19 cancer patients [10, 17, 23]. Although, some studies have shown a relationship between gender and patient mortality [18 - 22]. It may be due to the matching of demographic variables. Our study found 87% of participants to experience shortness of breath, 76% to have fever, and 62% to have muscle pain. Sorouri *et al.*'s study reported shortness of breath and fever as the two most common symptoms [17]. In this study, shortness of breath was the most common symptom among deceased cancer patients. Sorouri *et al.*, Young *et al.*, and Lee *et al.* found shortness of breath to be significantly higher in cancer patients who died than other symptoms [17, 19, 22].

The percentage of cancer patients who died in this study was significantly higher than that of non-cancer patients (38% *vs.* 14%). The results of this study are consistent with those of Meng *et al.* 's study [10], in which the mortality rate of cancer patients *versus* non-cancer patients was reported to be 29% and 10%, respectively. Hospitalized patients' poor health may have contributed to the high mortality rate in this study. With univariable and multivariable logistic regression, the odds ratio of death in cancer patients was 3.68 and 5.03, respectively. Meng *et al.* reported a 2.98 odds ratio of a cancer patient dying [10]; Sorouri *et al.* reported a 5.4 odds ratio in the univariable and a 3.57 odds ratio in the multivariable model [17].

Additionally, in the present study, the univariable and multivariable Cox regression models were used to compare the survival rate and the relative risk of death of the patients. In the univariable model, the relative hazard of death was 2.34, and in the multivariable model, it was 2.43. In the study conducted by Cai *et al.*, cancer patients were reported with a death risk that was 1.99 times greater in univariable Cox regression and 2.02 times greater in multivariable regression than other patients [24].

Hypoxia (SpO2) was significantly associated with patient mortality in this study. The results of logistic regression and Cox showed the mortality of patients to be increased by 4% and their risk of death by 2% with each unit of reduction in blood oxygen levels. Sorouri *et al.* and Lee *et al.* showed oxygen saturation to be lower in deceased patients with a history of cancer [17, 19].

In the current study, patients admitted to the intensive care unit had a 2.43 times higher relative risk of death than other patients. In the study of Elfaituri *et al.*, the relative risk of death for patients admitted to the intensive care unit was 2.32 times higher than for other patients [23]. Safari *et al.* also found a significant relationship between intensive care unit admissions and mortality in patients with COVID-19 [25]. In other studies, patients with a history of cancer were more likely to be admitted to the intensive care unit [21, 26].

5. LIMITATION

The most important limitation of this study was the small number of cancer patients. Lack of staging of cancers and their therapies was the other limitation in our study.

CONCLUSION

A PSM method was used to select the control group in this case-control study. The effect of demographic, clinical, and laboratory characteristics on the risk of death in COVID-19 patients with and without cancer history was studied. Cancer history was found to be among the factors affecting death, in addition to age variables, blood oxygen level (SpO2), and admission to an intensive care unit. With a history of cancer, patients were at a higher risk of mortality, and they required intensive care to prevent infection with COVID-19 as well as timely treatment. In addition, cancer history was the only independent risk factor for COVID-19 disease among the common diseases, while other comorbidities may be influenced by other factors. A number of laboratory parameters also differed significantly between cancer and non-cancer patients, suggesting lower immunity and inflammatory reactions in COVID-19 cancer patients.

LIST OF ABBREVIATIONS

SpO_2	=	Blood Oxygen Levels
ICU	=	Intensive Care Unit
COVID-19	=	Coronavirus 2019
CSSE	=	Center for Systems Science and Engineering
RT-PCR	=	Reverse-transcriptase Polymerase Chain Reaction
OR	=	Odds Ratio
SD	=	Standard Deviation
CI	=	Confidence Intervals
HR	=	Hazard Ratio

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Ethic Committee of the Hamadan University of Medical Sciences, Shahid Fahmideh Ave, postal code: 6517838695, Hamadan, Iran.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee, and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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