Medical and Research Publications
International Open Access

Research Article **Journal of MAR Oncology (Volume 4 Issue 4)**

An Unexpected Cause of Death and Risk Factors for COVID-19 in Cancer Patients with Comorbidities

Tazhibaeva Karlygash Nartbaevna[1,2], MD, Ph.D, Sadykova Assel Dauletbaevna[1] PhD, Ormanov Almas Nurgalievich[2] MD, Kaldygozova Galiya[2] MD, Daurenov Bolat [2] MD, Kuliev Alizada [2] MD, Mussina Aiman [3] MD

1. Al-Farabi Kazakh National University, Republic of Kazakhstan, Almaty.

2. Khoja Akhmet Yassawi International Kazakh-Turkish University

3.Astana medical university", Department of Preventive Medicine and Nutrition.

Corresponding Author: Tazhibaeva Karlygash Nartbaevna, Shymkent City Oncological Dispensary, Republic of Kazakhstan

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Received Date: August 09, 2022

Published Date: September 01, 2022

Abstract:

We would like to further explore the importance of glucocorticosteroids in the treatment of COVID 19.

We focused on identifying risk factors for coronavirus in cancer patients with comorbidities and multiple organ dysfunction. The main dysfunction in coronavirus infection is damage to the alveoli and acute respiratory failure. It is associated with damage to other organs such as cardiovascular risk due to increased levels of hypertension, gastrointestinal dysfunction, chronic kidney disease, diabetes mellitus, liver dysfunction, lung damage, CNS risk, and eye risks, such as chemosis, conjunctivitis, and conjunctivitis. . flushing, cancer risk, venous thromboembolism, tuberculosis, aging, cardiovascular dysfunction, and reproductive risk. Cancer patients and their comorbidities, the clinical nature and severity of their course with COVID-19, have not been sufficiently studied in connection with numerous Lockdown. In this exploration, we obtained unexpected risk factors and benefits of comorbid conditions (comorbidities) in cancer patients.

And also researched the relationship between existing diseases and a possible increased risk of SARS-CoV-2 infection, as well as assessed the clinical nature and severity of their course (in patients who have had COVID-19, SARS-CoV-2, with a comorbid condition).

Introduction

Since the spread of COVID-19 around the world in early 2020, cancer patients have been identified as a particularly vulnerable subpopulation. Cancer patients are reported to be at increased risk of SARS-CoV-2 infection and more severe illness, with a significant proportion of people requiring high-level intensive care, faster disease progression, and increased risk of death [1]. The researchers identified people at "high risk" using the latest data. Adults over 60 years of age and young adults 18 to 59 years of age have a history of cardiovascular disease, chronic obstructive pulmonary disease, and diabetes mellitus according to the American Heart Association [2]. Many residents of the South Kazakhstan regions have high blood pressure, which is an additional risk factor. Most of these patients live in large industrial cities and metropolitan areas, the proportion of which ranges from 31 to 51%. In cities and regions, COVID-19 affects adults at a high risk of 40%, 37%, and 40%, respectively [3-4].

In the treatment of COVID-19 in cancer patients, more attention should be paid to comorbidities. In the literature, COVID-19 is characterized by symptoms of viral pneumonia such as fever, fatigue, dry cough, and lymphopenia. Many elderly patients in serious conditions have signs of an underlying disease, such as cardiovascular disease, liver disease, kidney disease, or malignant tumors. [4] These patients often die from comorbidities; therefore, we decided to accurately assess all baseline comorbidities in people with COVID-19. In addition to the risk of group transmission of infectious disease, special attention should be paid to the individual management of comorbidities in the treatment of pneumonia, especially in elderly patients with severe comorbidities. In addition to pneumonia, COVID-19 can affect other organs such as the heart, liver, and kidneys, as well as organ systems such as the blood and the immune system.3,4,5 Patients eventually die from multiple organ failure, shock, acute respiratory distress syndrome, heart failure, arrhythmia and renal failure.5,6 Therefore, in the treatment of COVID-19, we must pay attention to the potential for multiple organ damage, as well as their protection and prevention [4].

SARS-CoV - impact on the cardiovascular system: With regard to the cardiovascular system, infection with the etiologic virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can present acutely and persist during and possibly beyond the recovery period.1 Clinical outcome is worse in patients with COVID- 19 with cardiovascular disease. diseases and risk factors (eg, hypertension, diabetes, and obesity). Acute heart injury, as evidenced by elevated cTn (cardiac troponin), is reported by 8% to 62% of patients hospitalized with COVID-19 and is associated with greater disease severity, including the need for mechanical ventilation and death.2–6 [5].

SARS-CoV - and diabetes: Infected diabetes associated with SARS-CoV-2 has a higher rate of hospitalization, severe pneumonia, and mortality compared with infection with diabetes associated with SARS-CoV-22, 3. Diabetes was an adverse impact factor associated with COVID- 197 [6].

One of the mysteries of COVID-19 is why an infection can cause extreme reactions such as a life-threatening inflammatory reaction, high fever, and breathing problems in some people, while others show little or no symptoms [7].

Part of this attention is focused on a worrying trend as intensive care physicians and endocrinologists look for clues and answers to why some people with COVID-19 suddenly develop type 1 and type 2 diabetes [8].

Initially, when the pandemic broke out in 2020, doctors noticed that a large percentage of patients with COVID-19 were diabetic," Mikhail Zilbermint, MD, Associate Professor, Department of Clinical Medicine, Department of Endocrinology, Diabetes, and Metabolism, Johns Hopkins School of Medicine. in Baltimore. "This was first seen in China because that was the majority of the patients who were initially hospitalized," he says [9].

Diabetes was originally thought to only increase the risk of getting sick or getting more severe with COVID-19, but now it seems there might be some kind of bidirectional relationship between diabetes and COVID-19, says Dr Silbermint. . . "We're still not sure what's going on because it's all-new," [10].

Angiotensin-converting enzyme-2 (ACE2) is the main receptor for SARS-CoV-2 in the human host. Differential expression of ACE2 in the lungs of diabetic patients makes them more susceptible to COVID-19. In addition, acute or chronic hyperglycemia puts people into an immunosuppressive state with impaired innate and adaptive immune function, which also contributes to the severity of COVID-19 infection among diabetic patients. Other factors contributing to the more severe course of COVID-19 include the coexistence of obesity in T2DM and endothelial inflammation caused by SARS-CoV-2 infection, which exacerbates endothelial dysfunction seen in both T1DM and T2DM, and hypercoagulability seen in T2DM. COVID-19 infection increases the tendency to thrombosis in DM [11].

Aim: to identify risk factors leading to the death of COVID-19 in patients with oncological pathology with concomitant diseases (diabetes mellitus and obesity).

Research goals:

1. Determine the prevalence of COVID19 (delta) in cancer patients with comorbidities (diabetes mellitus and obesity) by age.

2. To identify the causes of death of COVID19 (delta) in cancer patients with concomitant diseases (diabetes mellitus and obesity).

3. Determine the risk factors for the development of COVID19 (delta) in cancer patients with concomitant diseases (diabetes mellitus and obesity)

Material and method

Study Design and Eligibility Criteria

We conducted a retrospective observational study conducted on the medical records of patients diagnosed with COVID-19 hospitalized from June to August 2020 at the City Oncology Center in Shymkent, Kazakhstan. In 2020, quarantine in the Republic of Kazakhstan was announced in mid-March, and the peak of morbidity and mortality occurred in June-August. In this regard, 1000 confirmed cancer patients with COVID-19 were randomly included in the study over the specified period of time.

The present study was approved by the Committee on Medical Ethics of the Faculty of Health and Medicine of the International Kazakh-Turkish University named after Kozha Ahmet Yasawi (authorization letter No. 18). Informed consent was not required due to the study design.

Patient Selection: This study reviewed the medical records of all patients with suspected COVID-19 admitted to the center from June to September 2020. Later, patients were identified who were diagnosed with COVID-19 using a PCR test, which is 1000 patients.

Using Raosoft's online sample size calculator, 278 patient data were selected as sample size using a 95% confidence interval and 5% error. SARS-CoV-2 disease was diagnosed using real-time reverse transcription PCR based on WHO interim guidance.

Depending on age, the patients included in this study were divided into five categories.

The object of study: Cancer patients with COVID-19, SARS-CoV-2 with a laboratory-confirmed oncological diagnosis and a history of comorbidities: diabetes mellitus, obesity, cardiovascular disease, in the age group from 18 to 72 years.

Research methods used: To solve the task set, a retrospective observational study will be conducted on people with a positive result for COVID-19 and SARS-CoV-2, located in the City Cancer Center, Shymkent, Kazakhstan.

Inclusion Criteria: Persons with COVID-19, SARS-CoV-2 with a laboratory-confirmed cancer diagnosis and a history of comorbidities: diabetes, obesity and cardiovascular disease, in the age group from 18 to 72 years.

Exclusion criteria: patients with primary immunodeficiency, patients with tuberculosis, patients with HIV.

Control group: persons without concomitant chronic diseases from 18 to 72 years.

Type of medical study: retrospective prospective, direct observation.

Complaints and anamnesis (disease card, medical history) were collected and analyzed from the moment the first clinical manifestations appeared, in the dynamics of the disease.

Intended scope of the study: patients with a history of mild, moderate, severe and very severe cancer diagnosed with a positive result for SARSCov2 - COVID 19, comorbidities: diabetes mellitus, obesity.

As a tool for collecting information from respondents, a validated questionnaire will be compiled to conduct a survey among the study group of individuals based on the required international standards and criteria.

Statistical research methods.

The construction of survival curves and two-dimensional analysis will be carried out on the basis of the Kaplan-Meier analysis. For the statistical calculation of survival, taking into account the existing isolated or combined pathology, the Cox proportional hazards method will be used. Data visualization. In the course of the analysis, a new correction will be made for the influence of the main recorded confounding factors - the subject's age at baseline, gender, BMI levels, smoking, and alcohol consumption. All

parameters will be included in the model by forced input [17, 18]. The analysis will be performed using unadjusted and adjusted values or its 95% confidence interval.

A total of 76 deceased patients and 83 living patients were included in this study, which was divided into two sex groups: male and female, as shown in Table 1 below.

Options			**Abs**	**%**
Gender	Men		36	47,36
	Women		40	52,63
Age	<30		2	2,63
	30-34		1	1,31
	35-39		0	0
	40-44		4	5,26
	45-49		8	10,53
	50-54		9	11,84
	55-59		14	18,42
	60-64		6	7,89
	65-69		8	10,53
	70-74		7	9,21
	75-79		7	9,21
	80-84		5	6,58
	85-89		4	5,26
Total:			76	100

Table 1 Sex groups male and female

The results of our study showed that the leading causes of death in cancer patients with Covid-19 were ARDS, heart failure, cancer intoxication, multiple organ failure, and pulmonary embolism, as shown in Fig 1.

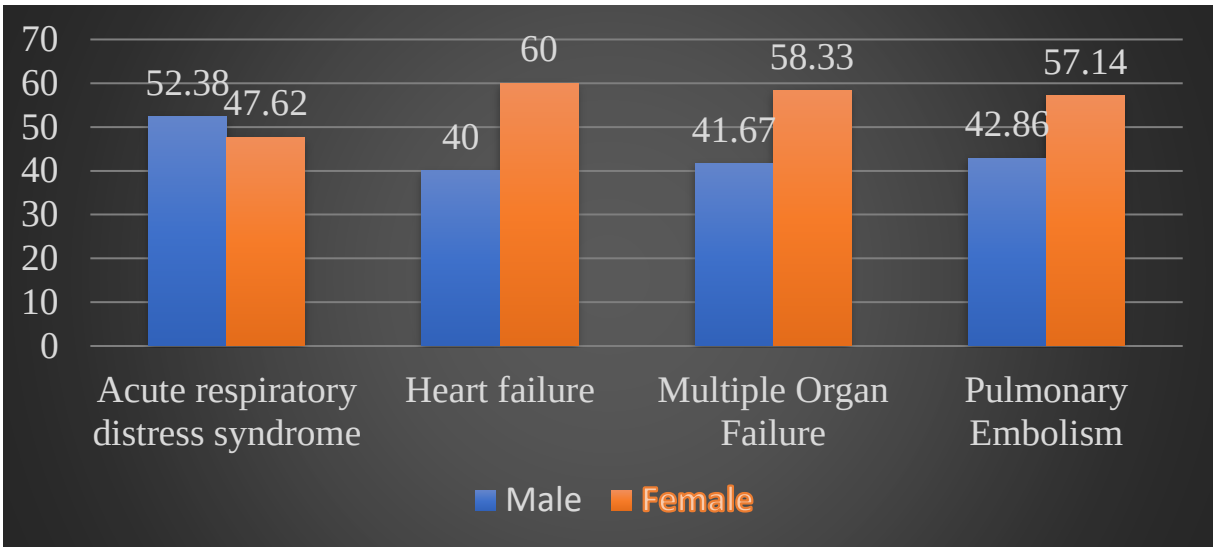

Fig. 1. leading causes of death in cancer patients with Covid-19

As can be seen in (Figure-2), most cases of the disease occur in the age group of 50-59 years, and then 60-69 years, which is 52 (27.7%) and 40 (21.3%), respectively. Thus, the largest number of patients by age falls on the age groups of 50-69 years. The smallest number of patients in the age group up to 20 years is also observed.

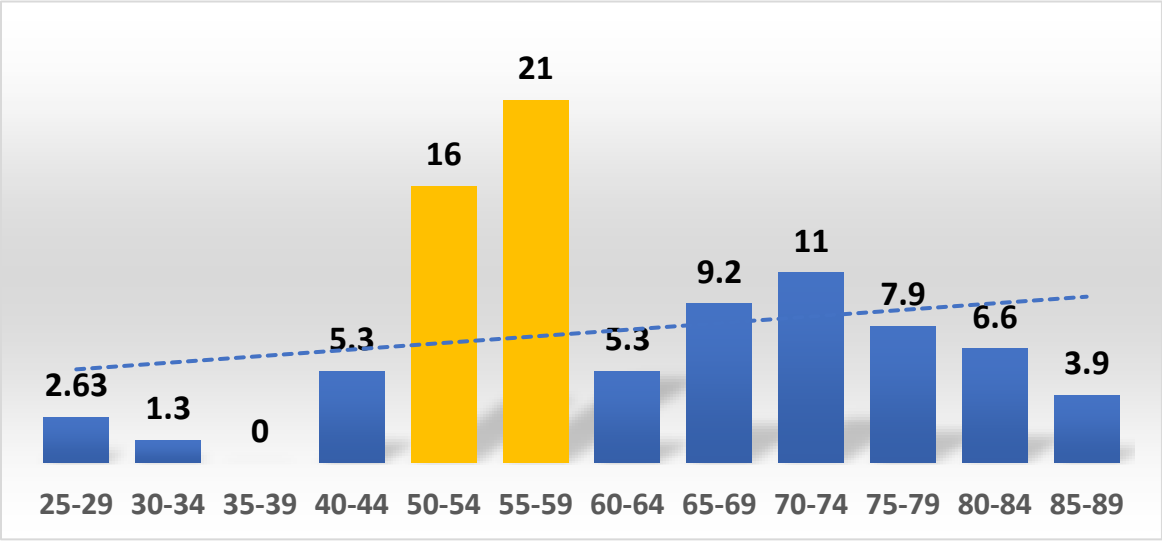

Figure 2 - Structure of causes of death of non-survivors depending on age

Causes of death by age group: In addition, we divided non-survivors (Table 2) into age groups based on causes of death such as ARDS, heart failure, cancer, intoxication, multiple organ failure, and pulmonary embolism.

Age categories / Causes		ARDS	Cancer intoxication	Multi-organ	Multi organ failure	Pulmonary embolism	Total (%)
25-29	Abs	2					
	%	4.76					2.63
30-34	Abs	1	1				
	%	2.38	2.3				1.3
35-39	Abs						
	%						
40-44	Abs	2	2	1	1		
	%	4.76	1.6	6.67	8.33		5.3
50-54	Abs	4	2	2	2	2	
	%	9.52	3.2	13.33	16.67	28.57	16
55-59	Abs	6	2	5	3	2	
	%	14.28	1.98	33.33	25	28.57	21
60-64	Abs	3	3		1	1	
	%	7.14	2.1		8.33	14.28	5.3
65-69	Abs	3	2.73	1	1	2	
	%	7.14	1	6.67	8.33	28.57	9.2
70-74	Abs	5	9.2	2	1		
	%	11.9	3	13.33	8.33		11
75-79	Abs	6	1.28	1			
	%	14.29		6.67			7.9
80-84	Abs	3		2			
	%	7.14		13.33			6.6
85-89	Abs	3					
	%	7.14					3.9

Table 2- Causes of death distribution according to age groups

Table (2) clearly shows that the majority of people are concentrated in the age category of 75-79 and 55-59 years old, who died from ARDS, respectively, 14.29% and 14.28%, also 12.1% at the age of 60-64 suffered from cancer intoxication. In the category of non-survivors with heart failure, the majority (33.33%) died at the age of 55-59 years. Of the rest, who died from multiple organ failure, the highest percentage (16.67%) of them were older, in the category of 50-54 years.

Sex

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid		1	.3	.3	.3
	Female	40	13.7	13.7	14.1
	Male	36	12.4	12.4	26.5
	wife	17	5.8	5.8	32.3
	Female	111	38.1	38.1	70.4
	Husband	6	2.1	2.1	72.5
	Male	80	27.5	27.5	100.0
	Total	291	100.0	100.0	

Sex code (1 or 2)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	122	41.9	42.1	42.1
	2	168	57.7	57.9	100.0
	Total	290	99.7	100.0	
Missing	System	1	.3		
Total		291	100.0		

High patient mortality rates were associated with late hospitalization, inadequate dose of glucocorticosteroids, lack of sufficient time for laboratory and instrumental studies, lack of drugs in the hospital, and inappropriate treatment times, which are presented in Figures 3-4.

As can be seen from Figures 5-6, 38.6% of those who died during the pandemic were hospitalized late in extremely serious condition. Patients with late hospitalization had a high mortality rate of 93%. Other causes of mortality, respectively, were an inappropriate dose of glucocorticosteroids, the lack of the

possibility of laboratory and instrumental studies, the lack of drugs in the hospital and untimely started therapy.

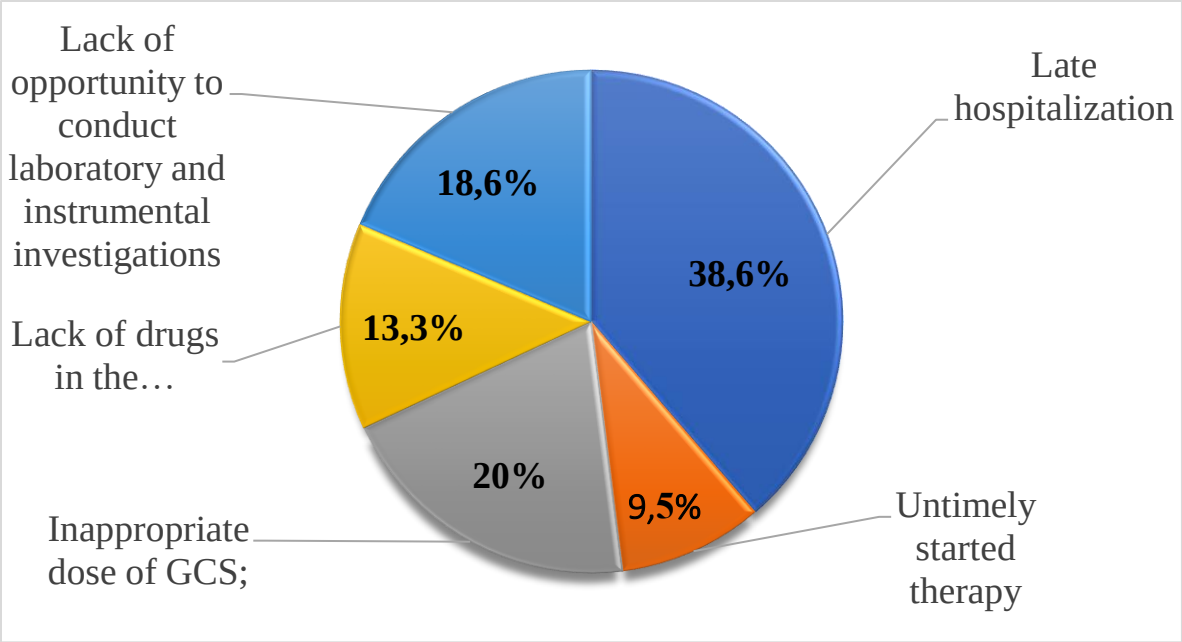

Figure 3- Causes of high mortality

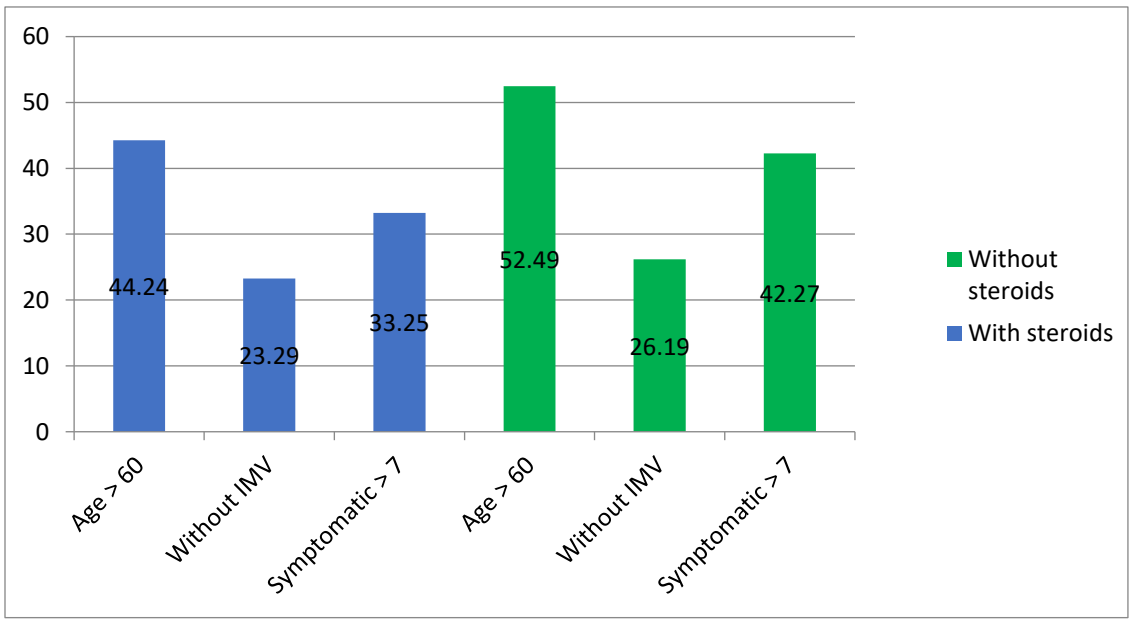

Figure 4- Mortality in different groups of patients

The figure above shows that 20% of patients did not receive a sufficient dose of drugs, including corticosteroids, which could improve their condition. According to the WHO recommendation [12], the use of corticosteroids leads to a decrease in mortality in patients who are in critical condition and do not have indications for mechanical ventilation, with the exception of patients with absolute contraindications to 7-10 days of steroid therapy.

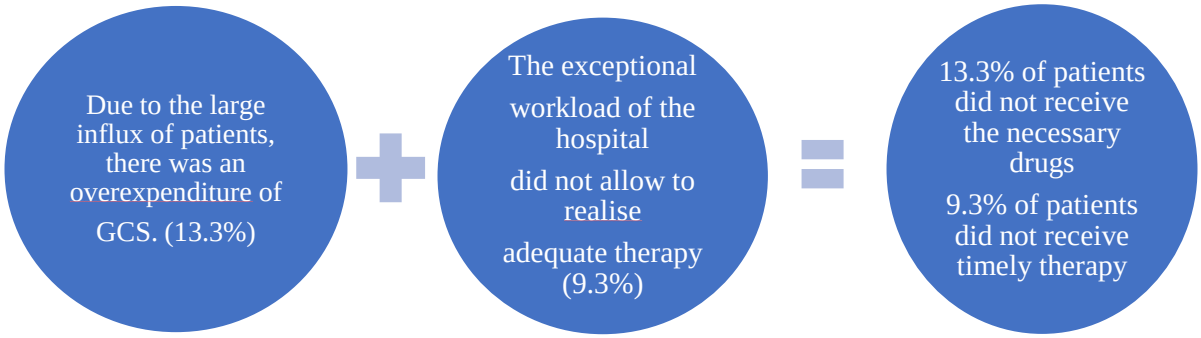

Figure 5- Lack of drugs and initiation of appropriate therapy

The patients were admitted in critical condition. At this time, the intensive care unit was extremely overcrowded, and the stocks of medicines were exhausted. Accordingly, due to the large influx of patients and the high expedition of glucocorticosteroids, about 13.3% of patients did not have access to glucocorticosteroids. Also, the high and exceptional workload of the hospital did not allow to start adequate treatment in a timely manner.

Figure 6- Lack of opportunity to conduct laboratory and instrumental research

As a result, hospitals and the intensive care unit were extremely overcrowded with patients from severe to extremely severe conditions. There was an acute shortage of resources to provide care to patients.

The results of our study showed that the main causes of death in people with Covid-19 were ARDS, heart failure, multiple organ failure, and pulmonary embolism, as shown in (Figure-6).

Discussion

Patients with cancer have been identified as being at higher risk of a worse outcome of SARS-CoV-2 infection than those without cancer [13]. Cancer patients often have comorbidities that further increase susceptibility and risk. Cancer patients with COVID-19 typically experience symptoms similar to those in the general population, such as fever and dry cough with shortness of breath and possibly increased fatigue. Additional features such as anemia and hypoproteinemia may be found [14].

We did not find a significant increase in the risk of death from COVID-19 among cancer patients in general, but patients with comorbidities and patients with metastases had a significantly higher risk of death compared to the general population. With the combination of death and/or hospitalization due to COVID-19 as a major outcome parameter, we found a significantly increased risk of SARS-CoV-2 infection among cancer patients diagnosed less than 1,5 year after a cancer diagnosis, as well as in patients undergoing surgery. Interventions or receiving systemic chemotherapy, we associated this with a weak and depleted immune system.

Early reports from China reported that cancer patients were overrepresented among COVID-19 patients [15]. Hospitalization and return visits have been suggested as risk factors for infection, but these have been small. More recent reports on the prevalence of patients with COVID-19 cancer vary, and recent studies have shown that the proportion of patients with cancer is 0.4–8% among confirmed cases of COVID-19 [16].

This study was limited to the first months of the pandemic, and we found that the risk of contracting COVID-19 among cancer patients was the same as in the general population. Higher rates have previously been reported in male cancer patients [17] but we found a slight downward trend in male cancer patients compared to women. The trend toward decreasing incidence of COVID-19 with age in both cancer and non-cancer populations may be related to recommended interventions early in the pandemic, especially in patients with multiple risk factors and with a focus on older age [18].

Consistent with previous reports, we found that patients with comorbidities such as diabetes mellitus, cardiovascular disease, obesity along with endocrine tumors are at greater risk of contracting COVID-19 [19,20,21,22,23,24], while in our study we also found the similarity of such a risk.

Several studies have found an increased mortality rate in cancer patients with COVID-19 [25,26]. We found that the mortality rate among cancer patients was comparable and not significantly lower in both women and men compared to age-adjusted non-cancer populations. A significantly increased risk of death from COVID-19 was found in patients with concomitant diseases such as cardiovascular disease, diabetes mellitus, obesity, anemia with a mortality rate of 0.35 with a significant increase in OR by 12.4%.

Previous reports have suggested that high mortality from COVID-19 in cancer patients appears to be determined by age, gender, and comorbidities [27]. Cancer patients tend to be elderly with chronic comorbidities, and some reports do not take into account known risk factors such as age and gender when interpreting results [28]. In a multivariate model, we found that the risk of death in cancer patients with COVID-19 did not differ from the risk of death in non-cancer patients with COVID-19.

The strengths of this study include high-quality data from registries including, but not limited to, completeness of all confirmed cases of COVID-19, diagnosis of cancer with comorbidities, data on treatment, intensive care, and reliability of causes of death.

Drawbacks include the low total number of COVID-19 cases, resulting in a wide confidence interval. The number of reported cases and results will vary depending on the availability of testing and often underestimate the overall burden of COVID-19.

In conclusion, we found that cancer patients with COVID-19 did not generally have an increased risk of death compared with patients without cancer. However, we found an increased risk in patients with comorbidities.

Conclusion

Populations with cancer and comorbidities have an increased risk of contracting COVID-19 and, if infected, also have a high risk of serious complications and death as a result. Based on the data collected in a number of studies, it is necessary to take into account the various causes and risk factors that influenced the initial situation of patients could be prevented by formulating a reliable assessment of severity in the form of an algorithm for COVID-19 disease in cancer patients. In our study, there was also

a case among survivors of cancer and COVID-19 disease, they had a history of chronic lung disease and took glucocorticosteroids for a long time, and this is true evidence that hormones played an important role in the treatment of COVID 19 in cancer patients.

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