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MORTALITY AMONG CANCER PATIENTS RECEIVING ANTICANCER TREATMENT DURING THE COVID-19 PANDEMIC: A SINGLE TERTIARY CENTER EXPERIENCE

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ABSTRACT

Since the beginning of 2020, the emergence of the COVID-19 pandemic has limited many aspects of health care delivery. These limitations have affected cancer patients in various ways, raising concerns about worsening morbidity and mortality among this special population. No studies have assessed the impact of the pandemic on the short-term morbidity and mortality among cancer patients**.** This study aimed to determine the effect of the pandemic on the early clinical outcomes in cancer patients receiving anticancer treatment in Saudi Arabia during the pandemic period. This included adult patients with solid or hematological tumors undergoing anticancer therapy. We collected data on patient demographics, health status, type of treatment, and morbidity and mortality outcomes. We performed univariate and multivariate analyses to identify possible associations with each variable, including the COVID-19 test results. The mean age of the patients was 52.32 years, and 69.9% of the population were women. Of the patients, 64.1% were administered curative therapy. The 30-day morbidity and mortality rates were 19.2% and 5.1%, respectively. Ten patients (2.5%) developed COVID-19 during the study period, of whom three died. The mortality rate was 30% and 4.4% in cancer patients with and without COVID-19, respectively. The Eastern Cooperative Oncology Group performance status was associated with higher 30-day morbidity (odds ratio: 8.48, $P < .001$) and mortality (odds ratio: 3.86, $P < .001$). The mortality rate in cancer patients receiving anticancer treatment during the COVID-19 pandemic was similar to that reported in the literature preceding the pandemic.

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Introduction

By the end of 2019, a novel coronavirus led to a cluster of cases of severe acute respiratory syndrome in southern China [1]. In January 2020, the WHO declared the COVID-19 outbreak a public emergency, and in March 2020, many countries implemented quarantine and national lockdown to control the spread of the disease [2-4]. The dynamics of providing health care for cancer patients were affected by their vulnerability to COVID-19, obstacles limiting their access to optimal care, and their hesitation in seeking medical care [5, 6]. Many health authorities, cancer societies, and patient advocates published guidelines and new policies and procedures to maintain cancer care during this difficult period. This included changes in treatment protocols, scheduling treatment cycles, and implementing virtual care [3, 7].

The proportion of cancer patients who were diagnosed with COVID-19 has been reported to range between 1% and 8% [8]. At the same time, the proportion of COVID-19 patients with a history of cancer has been reported to range between 1% and 3.9%. In addition, cancer patients with COVID-19 have high case fatality rates, which have been reported to range between 11% and 35%, with an odds ratio for mortality of 2.25 [8, 9]. Lee *et al.*, reported similar mortality rates in COVID-19-positive cancer patients who have received different types of cancer treatments in the month prior to the COVID-19 diagnosis [10]. The mortality rates were related to their underlying comorbidities rather than the cancer treatment provided.

In Saudi Arabia, the implementation of social distancing started in March 2020, and a 24-h curfew was implemented in the following month. However, patients requiring health care were exempted [11]. To the best of our knowledge, studies assessing the impact of the pandemic on the morbidity among cancer patients are very limited. Further, mortality in cancer

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patients during the early phase of the pandemic has not been previously assessed. This study aimed at determining the 30-day morbidity and mortality among cancer patients receiving anticancer treatment during the pandemic period from March 2020 to June 2020.

Materials and Methods

Study Design and Population

We retrospectively reviewed electronic health records of all adult patients with a cancer diagnosis who received any class of anticancer treatment at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between March 1, 2020, and June 30, 2020. The study was approved by the King Abdulaziz University Hospital Institutional Research Ethics Board, and the requirement for informed consent was waived.

In this study, we included all adult patients (aged ≥ 16 years) diagnosed with solid or hematological tumors who received anticancer treatment during the 3 months between March 1, 2020, and June 30, 2020, orally or parenterally in the outpatient or inpatient setting. Patients were followed up until July 31, 2020, to determine the treatment outcomes. We excluded cancer patients who were undergoing regular follow-up or surveillance and were not on anticancer treatment. Patients undergoing treatment with other modalities such as radiotherapy, surgery, and supportive care were excluded. Patients who received bone modifying agents without any other type of anticancer treatment were also excluded.

The data collected included the following variables: sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), type of cancer, stage, treatment class, (chemotherapy, immunotherapy, hormonal therapy, or targeted therapy), route of administration (intravenous, subcutaneous, or oral), the intent of treatment (palliative or curative), type of curative treatment (neoadjuvant or adjuvant), line of anticancer treatment (first-, second-, third-, or fourth-line, and beyond), and the number of cycles of therapy administered within the study period. Comorbidities included in the data were diabetes mellitus, hypertension, stroke, chronic kidney disease, and chronic heart or lung disorders. The patients' COVID-19 nasopharyngeal swab test results were also collected. Per hospital policy, COVID-19 testing was performed in cancer patients only if clinically, and not empirically, indicated.

The outcome events were calculated from the beginning of the last treatment cycle before the event. The last follow-up was defined as the date of the last visit mentioned in the records. Morbidity included any illness requiring admission to the hospital including complications of therapy, or complications of cancer itself.

Statistical Analyses

A descriptive analysis of all the demographic and outcome variables was performed. Data were analyzed using Stata SE version 16.1 (StataCorp LLC, College Station, TX, USA). The main outcome of this study was 30-day morbidity and mortality among patients receiving anticancer treatment. We performed a simple logistic regression analysis and then incorporated all variables in a multivariate analysis to establish the odds ratio (OR) for each variable. The following variables were included in the multivariate analysis: age, gender, BMI, class of therapy, the intention of treatment, comorbidity status, type of cancer, stage, and COVID-19 positive status. We also used a stepwise modeling approach, excluding variables with $P > .2$, to identify the variables that are significantly associated with the main outcome. We only reported the results of the univariate model and the final multivariate model determined using the stepwise approach. A P-value < .05 was considered significant.

Results and Discussion

During the study period, 395 patients received anticancer treatment and met the inclusion criteria. Their mean age was 52.3 years and 267 (69.9%) were women. They were mainly overweight with a mean BMI of 28.4 kg/m^2 and their mean ECOG performance status was fair at 0.79; most patients (69.6%) had no comorbidities. However, 46.4% were at an advanced stage of cancer (Stage IV). Most patients had breast cancer (43.8%). **Tables 1 and 2** present the baseline clinical and demographic characteristics of the study patients.

Table 1. Baseline clinical and demographic characteristics of the study patients

Variable	**Mean (95% CI)** **N (%)**
Age	52.32 (50.96-53.69)
BMI	28.44 (27.78-29.11)
ECOG	0.79 (0.69-0.89)
Gender	
Female	276 (69.9%)
Male	119 (30.1%)
Class of therapy	
Chemotherapy	282 (71.4%)

Hormonal therapy	42 (10.6%)
Immunotherapy	1 (0.3%)
Targeted therapy	70 (17.7%)
Route	
IV	357 (90.4%)
Intrathecal	1 (0.25%)
Oral	1 (0.25%)
SC	36 (9.1%)
Intention	
Curative	253 (64.1%)
Palliative	142 (35.9%)
Line of therapy	
1st line	319 (82.9%)
2nd line	45 (11.7%)
3rd line	15 (3.9%)
4th line & beyond	6 (1.5%)
Co-morbidity	
No	275 (69.6%)
Yes	120 (30.4%)
Stage	
Stage I	19 (5.7%)
Stage II	47 (14.0%)
Stage III	114 (33.9%)
Stage IV	156 (46.4%)

Table 2. Types of malignancies presented for care during the study period

Variable	**N (%)**
Diagnosis	
Breast	173 (43.8%)
CNS	3 (0.8%)
Colorectal	57 (14.4%)
Gastro-esophageal	10 (2.5%)
Gynecological	41 (10.4%)
Head and neck	17 (4.3%)
Leukemia	16 (4.0%)
Lung	12 (3.0%)
Lymphoma	25 (6.3%)
Multiple Myeloma	13 (3.3%)
Neuroendocrine	1 (0.3%)
Pancreatic-biliary	9 (2.3%)
Prostate	3 (0.8%)
Sarcoma	6 (1.5%)
Testis	2 (0.5%)
Thyroid	2 (0.5%)
Other	5 (1.3%)

The 30-day morbidity and 30-day mortality rates were 19.2% and 5.1%, respectively. Ten patients during the study period were diagnosed with COVID-19. **Table 3** illustrates the different adverse outcomes experienced by patients during the study period. Twenty patients died at the end of the study period, and three of them had COVID-19. Overall, the mortality rate was 30% and 4.4% in cancer patients with and without COVID-19, respectively.

Table 3. Adverse outcomes for cancer patients at the end of the study period.

Variable	N=395 (%)
30-day mortality	20 (5.1%)
30-day morbidity	76 (19.2%)
Hospitalizations	75 (18.9%)
ER visits	83 (21.0%)
ICU admission	12 (3.0%)
COVID Positive	10 (2.5%)

Multivariate analyses revealed that the 30-day morbidity OR for ECOG performance status was 3.86 ($p < .001$). In addition, higher BMIs were significantly associated with marginally better 30-day morbidity. Patients who received chemotherapy had higher 30-day morbidity than those who received hormonal therapy or targeted therapy **(Table 4)**. The 30-day mortality OR for the ECOG performance status was 8.48 ($p <.001$) **(Table 5)**.

Table 4. Univariate and Multivariate Analysis for 30-Day Morbidity

	Univariate Analysis		Multivariate Analysis	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Line of therapy	1.43 (0.99-2.07)	0.060	0.64 (0.34-1.20)	0.166
BMI	0.92 (0.88-0.96)	0.000	0.92 (0.87-0.98)	0.010
ECOG	3.73 (2.63-5.29)	0.000	3.86 (2.48-6.00)	0.000
Class of therapy	0.67 (0.50-0.90)	0.007	0.56 (0.33-0.96)	0.035

Table 5. Multivariate and Univariate Analysis for 30-Day Mortality

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Age	1.00 (0.98-1.02)	0.755	0.93 (0.86-1.00)	0.084
Comorbidity	2.35 (1.40-3.93)	0.001	9.47 (0.59-152.98)	0.113
ECOG	3.73 (2.63-5.29)	0.000	8.48 (2.79-25.77)	0.000
Gender	1.57 (0.93-2.65)	0.091	11.48 (0.67-197.63)	0.093

This paper presents novel data regarding the morbidity and mortality rates among cancer patients in Saudi Arabia during the early phase of the COVID-19 pandemic. Our study shows that performance status is the strongest predictor of morbidity and mortality in patients receiving anticancer treatment.

Contrary to our study, most reports globally had focused on cancer outcomes in patients with confirmed COVID-19 or the prevalence of COVID-19 in patients with a history of cancer rather than the effect of the pandemic itself on the course of the care [8-10].

During the course of our study, most patients were female and breast cancer was the most common type of cancer, which is consistent with the data reported by the Saudi Cancer Registry [12]. In our study, most patients received curative therapy, most likely because of the consensus during the initial phase of the COVID-19 pandemic that treatment should be limited to those receiving curative therapy. The mean BMI noted in our study was higher than optimal. This finding warrants more research, especially those focused on breast cancer.

In an earlier study on the outcomes of 19 cancer patients at another center in Saudi Arabia, Jazieh *et al*., reported that the most common underlying malignancy in patients with confirmed COVID-19 was hematological cancer (47.4%) [13]. Lee *et al*. reported similar rates in COVID-19 patients with malignancy, although men were predominant (56%) and gastrointestinal malignancies were the most common type of cancer (19%) [10]. The differences in the demographics between populations could be related to the scope of clinical practice and eligibility at the treatment centers and differences in cancer epidemiology in a country or the differences in patient selection method in the mentioned studies.

This study demonstrated the general outcomes of cancer patients who received anticancer treatment during the initial phase of the COVID-19 pandemic. The 30-day mortality rate reported globally prior to the COVID-19 pandemic ranged from 2.5% to 5.12% [14-17]. Similarly, in our study, the 30-day mortality rate was 5.1%. To the best of our knowledge, no comparable study from Saudi Arabia addressing early mortality and morbidity post-chemotherapy in cancer patients is available.

Previous studies have shown that treatment with palliative therapy, stage 4 disease, and an ECOG performance status ≥ 2 were factors associated with higher mortality. The 30-day morbidity was higher in patients with stage 4 disease and in those with comorbidities. Our data showed that a higher BMI was associated with lower 30-day morbidity. This requires further investigation to determine whether being overweight leads to a better prognosis or whether cachexia is associated with

higher morbidity. Patients who received chemotherapy had higher 30-day morbidity than those who received hormonal therapy or targeted therapy, as chemotherapy is more toxic than other therapies.

Even though the rate of COVID-19 was on the rise during the study period, only a few cancer patients (2.5%) tested positive for severe acute respiratory syndrome coronavirus 2. Our results align with those initially reported from China (0.8%) and Spain (4.2%) [8]. The lower rates of infection among cancer patients in our study population could be attributed to the strict curfew rules that were applied by the Saudi Government as well as the strong health education messages that were constantly being broadcasted to the public [11]. The mortality rate among cancer patients with COVID-19 in our study (30%) is within the range of 11% to 35% that was previously reported [8, 18]. This may be because different protocols were used for treating COVID-19 in different countries.

Our study has some limitations. The most important is that this was a retrospective study. Data regarding some of the variables such as the stage of cancer, oral medications, and the intent of treatment were incomplete. The follow-up was based on the information available in patients' medical records. Another limitation is the heterogeneity with respect to the presence of different types of cancer (solid and hematogenous), stages of cancer, and the general health conditions in our study population. Moreover, COVID-19 testing was limited to patients presenting with suggestive symptoms.

The results of this study could provide more insights into the effect of COVID-19 on cancer patients and assist in creating an evidence-based management plan for cancer patients during these unprecedented times.

Conclusion

Our study showed that the mortality rate in cancer patients receiving anticancer treatment during the COVID-19 pandemic was similar to that reported in the literature preceding the pandemic. During the COVID-19 period, most patients treated received curative therapy. Similar to the pre-COVID-19 era, the performance status was the strongest predictor of morbidity and mortality in patients receiving anticancer treatment, and proper risk assessment should be conducted for this vulnerable group. Further investigations should be done to compare mortality and morbidity among cancer patients during the COVID-19 pandemic to those during the pre-COVID-19 period.

Limitations

Retrospective design and few patients had incomplete data.

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