Mortality and morbidity of curative and palliative anticancer treatments during the COVID-19 pandemic: A multicenter population-based retrospective study

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Abstract. Administration of effective anticancer treatments should continue during pandemics. However, the outcomes of curative and palliative anticancer treatments during the coronavirus disease (COVID-19) pandemic remain unclear. The present retrospective observational study aimed to determine the 30-day mortality and morbidity of curative and palliative anticancer treatments during the COVID-19 pandemic. Between March 1 and June 30, 2020, all adults (n=2,504) with solid and hematological malignancies irrespective of cancer stage and type of anticancer treatments at five large comprehensive cancer centers in Saudi Arabia were included. The 30-day mortality was 5.1% (n=127) for all patients receiving anticancer treatment, 1.8% (n=24) for curative intent, 8.6% (n=103) for palliative intent and 13.4% (n=12) for COVID-19 cases. The 30-day morbidity was 28.2% (n=705) for all patients, 17.9% (n=234) for curative intent, 39.3% (n=470) for palliative intent and 75% (n=77) for COVID-19 cases. The 30-day mortality was significantly increased with male sex [odds ratio (OR), 2.011; 95% confidence interval (CI), 1.141-3.546; P=0.016], body mass index (BMI) <25 (OR, 1.997; 95% CI, 1.292-3.087; P=0.002), hormone therapy (OR, 6.315; 95% CI, 0.074-2.068; P=0.001) and number of cycles (OR, 2.110; 95% CI, 0.830-0.948; P=0.001), but decreased with Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-1 (OR, 0.157; 95% CI, 0.098-0.256; P=0.001), stage I-II cancer (OR, 0.254; 95% CI, 0.069-0.934; P=0.039) and curative intent (OR, 0.217; 95% CI, 0.106-0.443; P=0.001). Furthermore, the 30-day morbidity significantly increased with age >65 years (OR, 1.420; 95% CI, 1.075-1.877; P=0.014), BMI <25 (OR, 1.484; 95% CI, 1.194-1.845; P=0.001), chemotherapy (OR, 1.397; 95% CI, 1.089-5.438; P=0.032), hormone therapy (OR, 1.527; 95% CI, 0.211-1.322; P=0.038) and immunotherapy (OR, 1.859; 95% CI, 0.648-4.287; P=0.038), but decreased with ECOG-PS of 0-1 (OR, 0.502; 95% CI, 0.399-0.632; P=0.001), breast cancer (OR, 0.569; 95% CI, 0.387-0.836; P=0.004) and curative intent (OR, 0.410; 95% CI, 0.296-0.586; P=0.001). The mortality risk was lowest with curative treatments. Therefore, such treatments should not be delayed. The morbidity risk doubled with palliative treatments and was highest among COVID-19 cases. Mortality appeared to be driven by male sex, BMI <25, hormonal therapy and number of cycles, while morbidity increased with age >65 years, BMI <25, chemotherapy, hormonal therapy and immunotherapy. Therefore, oncologists should select the most effective anticancer treatments based on the aforementioned factors.

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Abbreviations: COVID-19, coronavirus disease; BMI, body mass index; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; EHRs, electronic health records; OR, odds ratio

Key words: COVID-19, cancer, chemotherapy, mortality, morbidity

Introduction

Over the past decades, the number of chemotherapy agents has increased, and evidence has shown that chemotherapy

improves survival and cancer-related symptoms (1-3). Caring for cancer patients is challenging, and oncologists need to weigh the risks and benefits of anticancer treatments and identify factors that could predict mortality or morbidity to improve clinical decision-making. There are no universally agreed-upon benchmark figures for early mortality due to anticancer treatments. However, preliminarily establishing a mortality rate of 3-9% with a mean of 5% as a reference has allowed comparisons between different institutions (4).

Globally, as of September 12, 2020, the coronavirus disease (COVID-19) has caused >28.5 million confirmed cases and 916,000 confirmed deaths and affected 216 countries (5). Patients with cancer are susceptible to COVID-19 infections because of the immunosuppressive effect of cancer and anticancer treatments (6). Moreover, it is assumed that receiving anticancer treatments will increase the mortality risk from COVID-19. Hence, many concerns have been raised regarding the management of this specific population during the pandemic. Resource utilization and allocation during the COVID-19 pandemic have been modified by implementing strategies and creating frameworks for prioritizing anticancer treatments. For instance, in Italy, high priority was given to patients receiving curative anticancer treatment to minimize treatment interruption (7). Hanna *et al* (8) proposed a conceptual framework for prioritizing anticancer treatments, wherein palliative chemotherapy was considered a low priority compared to curative chemotherapy. Another suggestion was to change the route to oral anticancer therapy without compromising oncological outcomes (9). Studies have also shown that delayed adjuvant treatment is associated with inferior survival in colon cancer (10) and breast cancer (11).

Ohe *et al* (12) retrospectively studied the risk factors for mortality in lung cancer and found that 2.3% of patients died from chemotherapy-related toxicity. Similarly, in small-cell lung cancer, the mortality associated with sepsis was 5%, as reported by Radford *et al* (13). Stephens *et al* (14) found that the mortality was 10% within 3 weeks of chemotherapy. Another study found that the mortality was 13% in patients with non-Hodgkin's lymphoma (15).

A proportion of patients dying within 30 days of receiving anticancer treatments may be linked to poor clinical decisions. This study aimed to determine the 30-day mortality and morbidity of curative and palliative anticancer treatments during the COVID-19 pandemic and examine possible risk factors for mortality and morbidity.

Materials and methods

Study design and population. From March 1 to June 30, 2020 we retrospectively collected data of the target population: Adults aged ≥18 years who were histologically diagnosed with cancer, irrespective of the cancer stage and class of anticancer treatment received in five large comprehensive cancer centers in Saudi Arabia, namely, King Abdullah Medical City in Makkah, King Fahad Medical City in Riyadh, King Abdulaziz University in Jeddah, Princess Nora Cancer Center in Jeddah, and King Saud University Oncology Center in Riyadh. The convenience sampling method was used. The study protocol was approved by the Institutional Research Ethics Boards of the above participating centers (IRB number 20-616, April 23, 2020). Pharmacy administration provided the list of patients who received at least one cycle of anticancer treatment in the outpatient setting; a total of 2,504 patients were identified and were eligible in the study.

The inclusion criteria were adult patients with solid or hematological tumors who were receiving anticancer treatments in the outpatient setting during the study period. Both routes of anticancer treatments, oral and parenteral, were included. Patients were followed up until July 30, 2020 to assess treatment outcomes. Patients were excluded if they were on regular follow-up or surveillance; received other treatment modalities such as curative surgeries, radiation treatments alone, and best supportive care; or were under treatment with bone-modifying agents such as bisphosphonate or denosumab. The number of patients with missing variables or lost to follow-up was <1%; they were included in the analysis when appropriate.

Study procedures. Electronic health records (EHRs) were reviewed by senior oncology physicians to identify patients who met inclusion criteria and to collect the data. Each data entry was assigned a code number to ensure data anonymity. Other than the serial code number, patient characteristics comprised age, sex, and body mass index (BMI). Clinical characteristics included the presence of comorbidities, Eastern Cooperative Oncology Group performance status (ECOG-PS), cancer type, and cancer stage. Treatment characteristics included the protocol name, type (chemotherapy, immunotherapy, hormone therapy, or targeted therapy), route (intravenous, subcutaneous, or oral), intent of treatment (curative or palliative), type of curative treatment (neoadjuvant or adjuvant), line of palliative treatment (first-line, second-line, third-line, or fourth-line and beyond), and number of cycles.

The primary outcome was 30-day mortality after administration of curative and palliative anticancer treatments during the COVID-19 pandemic, which was defined as death within 30 days of the last anticancer treatment cycle (excluding road traffic accident and trauma as the cause of death). The secondary outcome was 30-day morbidity, defined as morbidity within 30 days of the last anticancer treatment cycle, which included any of the following: Hospitalizations, emergency room visits, intensive care unit admissions, delay in chemotherapy or dose reduction, COVID-19 incidence, and associations between the outcome and potential prognostic variables.

We calculated the national 30-day mortality rate by dividing the number of patients who received anticancer treatment within 30 days of their death by the total number of patients who received anticancer treatment during the study period. If a patient received multiple cycles of anticancer treatment during the study period, 30-day mortality was computed using the most recent cycle. Patients receiving multiple treatments in this period were counted only once in the dataset. Data were transferred securely to be analyzed and stored in a secure place.

Statistical analysis. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25. Descriptive statistics (percentage, mean, and standard deviation) were calculated for continuous variables, and frequencies for categorical variables. The chi-squared test for categorical variables and independent t-test for continuous variables

were conducted to determine any associations between demographic, clinical, tumor, and anticancer treatment characteristics. We used logistic regression analyses to assess any associations of the explanatory variables with 30-day mortality and 30-day morbidity (dependent variables) and with all other variables (independent variables). As none of the variables had a missing rate of >10%, all were included in the analysis. The results of the logistic regression analyses are presented as odds ratios (ORs) and 95% confidence intervals (CIs) that reflect the effect of each variable in our regression model. A P-value of <0.05 was considered statistically significant.

Results

Characteristics of the cancer patients and their outcome. Table I shows the characteristics of the cancer patients. Overall, 2,504 patients received anticancer treatments from March 1 to June 30, 2020. Among them, 1,305 were treated with curative intent and 1,195 were treated with palliative intent. In total, 2,069 (83%) were ≤65 years old, 1,743 (70%) were female, 945 (37.8%) had comorbidities, 1,832 (73%) had an ECOG-PS of 0-1, 1,266 (51.2%) had stage IV cancer, and 1,175 (46.9%) had breast cancer, which was the most common diagnosis.

With regard to curative anticancer treatment characteristics, most of the patients received chemotherapy (740 patients, 48.2%), the most common route was intravenous (831 patients, 48.3%), the most common type of treatment was adjuvant (805 patients, 63%), and patients received four cycles of treatment on average. As with palliative treatment, most of the patients received chemotherapy (796 patients, 51.8%), the most common route was intravenous (890 patients, 51.7%), the majority of patients were on first-line treatment (608 patients, 50.9%), and patients received eight cycles of treatment on average.

Table II summarizes the outcomes of interest. In total, 127 (5.1%) patients died within 30 days of receiving anticancer treatments, 24 (1.8%) of whom received curative anticancer treatments, while 103 (8.6%) received palliative treatments. Among the 24 patients who received curative anticancer treatments, sepsis was the most common cause of death (11 patients, 40.7%), whereas among the 103 patients who received palliative treatments, disease progression was the most common cause of death (61 patients, 88.4%). Meanwhile, morbidity was evident in 705 (28.2%) patients within 30 days of receiving anticancer treatments. Among these patients, 234 (17.9%) had curable anticancer treatments, while 470 (39.3%) had palliative anticancer treatments.

In patients who tested positive for COVID-19, the 30-day mortality was 13.4% (n=12), and the 30-day morbidity was 75% (n=77).

Factors associated with mortality and morbidity. Table III displays the results of the multivariate regression analysis of factors associated with mortality. Thirty-day mortality significantly increased with male sex (OR 2.011, 95% CI 1.141-3.546; P=0.016), BMI <25 (OR 1.997, 95% CI 1.292-3.087; P=0.002), hormone therapy compared to targeted therapy (OR 6.315, 95% CI 0.074-2.068; P=0.001), and a greater number of cycles (OR 2.110, CI 0.830-0.948; P=0.001). However, 30-day mortality significantly decreased in patients with an ECOG-PS of 0-1 (OR 0.157, 95% CI 0.098-0.256; P=0.001), stage I-II cancer (OR 0.254, 95% CI 0.069-0.934; P=0.039), and curative treatment (OR 0.217, CI 0.106-0.443; P=0.001).

Table IV shows the results of the multivariate regression analysis of factors associated with morbidity. Thirty-day morbidity significantly increased with age >65 years (OR 1.420, 95% CI 1.075-1.877; P=0.014), BMI <25 (OR 1.484, 95% CI 1.194-1.845; P=0.001), chemotherapy (OR 1.397, 1.089-5.438; P=0.032), hormone therapy (OR 1.527, 95% CI 0.211-1.322; P=0.038), and immunotherapy (OR 1.859, 95% CI 0.648-4.287; P=0.038). However, 30-day morbidity significantly decreased with an ECOG-PS of 0-1 (OR 0.502, 95% CI 0.399-0.632; P=0.001), breast cancer (OR 0.569, 95% CI 0.387-0.836; P=0.004), urologic cancer (OR 0.505, 95% CI 0.255-0.999; P=0.050), a greater number of cycles (OR 0.964, CI 0.848-0.980; P=0.001), and curative intent (OR 0.410, CI 0.296-0.586; P=0.001).

Anti-cancer drugs used. Table V presents the anticancer drugs used in the study population. The most common drug was hormone in 463 (18.5%), followed by alkylating agents in 361 (14.4%), Her 2-based drugs in 253 (10.1%), taxanes in 218 (8.7%) and antimetabolites in 214 (8.6%). Multi-mechanism drugs comprised 179 (7.2%) and included protocols such as (fluorouracil, carboplatin, trastuzumab), (fluorouracil, cyclophosphamide, docetaxel), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), AVD (doxorubicin, vinblastine, dacarbazine), (bortezomib, pomalidomide, dexamethasone), (carboplatin, paclitaxel, bevacizumab), (carboplatin, paclitaxel, gemcitabine), (carboplatin, paclitaxel, pembrolizumab), RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), CVD (cyclophosphamide, vincristine, dacarbazine), CVP (cyclophosphamide, vincristine, prednisone), CYBORD (cyclophosphamide, bortezomib, dexamethasone), (cyclophosphamide, methotrexate, fluorouracil), (vincristine, doxorubicin, cytarabine), DA-R-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab), (dasatinib, dexamethasone, vincristine), DFCP (Dana Farber Consortium Protocol), DRD (daratumumab, lenalidomide, dexamethasone), FEC (fluorouracil, epirubucin, cyclophosphamide), FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin and irinotecan), GDP (gemcitabine, dexamethasone, cisplatin), HIDAC (high-dose Ara-C), VAC-IE (vincristine, adriamycin, cyclophosphamide, ifosfamide and etoposide), (methotrexate, dactinomycine, etoposide), THP (docetaxel, trastuzumab, pertuzumab), TPF (cisplatin, fluorouracil, docetaxel), (vincristine, doxorubicin, cytarabine), and VIP. Additional protocols included ATRA (all-trans retinoic acid), IVIG (intravenous immune globulin), mesna, octreotide, and zoledronic acid.

Incidence of COVID-19. Table VI presents the incidence of COVID-19 in the study population. A total of 89 (3.6%) patients developed COVID-19 after receiving anticancer treatments. Among them, 12 (9.5%) patients died with within 30 days of receiving anticancer treatments, and morbidity was evident in 67 (9.7%) patients.

Characteristics of COVID-19 patients. Table VII presents the characteristics of COVID-19 patients in the study population.

Table I. Demographic, clinical, tumor and anticancer treatment characteristics.

Patient characteristics	All patients (n=2,504)	Curative intent (n=1,305; 52%)	Palliative intent (n=1,195; 48%)	P-value
Age, n (%)				<0.05
>65 years	435 (17.3)	181 (41.7)	253 (58.3)	
≤65 years	2,069 (82.7)	1,124 (54.4)	942 (45.6)	
Sex, n (%)				<0.05
Male	751 (30.0)	307 (41.0)	441 (59.0)	
Female	1,753 (70.0)	998 (57.0)	754 (43.0)	
BMI, n (%)				<0.05
<25	854 (34.1)	367 (43.0)	486 (57.0)	
≥25	1,648 (65.8)	937 (96.9)	709 (43.1)	
Comorbidities, n (%)				
Yes	945 (37.8)	426 (48.0)	462 (59.0)	
No	1,556 (62.2)	772 (53.7)	666 (41.0)	
Cause of comorbidity, n (%)				<0.05
DM	329 (35.0)	155 (47.1)	174 (52.9)	
HTN	239 (25.5)	128 (53.6)	111 (46.4)	
IHD	53 (5.6)	27 (50.9)	26 (49.1)	
DVT	29 (2.9)	15 (55.6)	12 (44.6)	
CKD	22 (2.3)	9 (40.9)	13 (59.1)	
ECOG-PS, n (%)				<0.05
0-1	1,832 (73.3)	1,113 (60.8)	717 (39.2)	
>1	668 (26.7)	191 (28.6)	476 (71.4)	
Cancer stage, n (%)				<0.05
I-II	548 (22.2)	501 (91.4)	47 (8.6)	
III	659 (26.6)	577 (87.7)	81 (12.3)	
IV	1,266 (51.2)	200 (15.8)	1,064 (84.2)	
Cancer diagnosis, n (%)				<0.05
Breast	1,175 (46.9)	768 (65.4)	407 (34.6)	
Gastrointestinal	499 (19.9)	146 (29.3)	353 (70.7)	
Hematological	252 (10.1)	208 (82.9)	43 (17.1)	
Gynecological	173 (6.9)	65 (37.8)	107 (62.2)	
Lung	86 (3.4)	11 (12.8)	75 (87.2)	
Urological	66 (2.6)	10 (15.4)	55 (84.6)	
Other	253 (10.1)	97 (38.5)	155 (61.5)	
Type of therapy, n (%)				<0.05
Chemotherapy	1,538 (61.4)	740 (48.2)	796 (51.8)	
Hormone therapy	458 (18.3)	363 (79.3)	95 (20.7)	
Targeted therapy	362 (14.5)	147 (40.6)	215 (59.4)	
Immunotherapy	85 (3.4)	9 (10.7)	75 (89.3)	
Route, n (%)				<0.05
IV	1,723 (68.8)	831 (48.3)	890 (51.7)	
Oral	688 (27.5)	417 (60.7)	270 (39.3)	
SC	91 (3.6)	56 (61.5)	35 (38.5)	
Type of curative treatment, n (%)				
Neoadjuvant	-	259 (20.3)	-	-
Adjuvant	-	805 (63.0)	-	-
Not applicable	-	214 (16.7)	-	-
Line of palliative treatment, n (%)				
First-line	-	-	608 (50.9)	-
Second-line	-	-	372 (31.1)	-
Third-line	-	-	139 (11.6)	-
Fourth-line and beyond	-	-	76 (6.4)	-

Table I. Continued.

Patient characteristics	All patients (n=2,504)	Curative intent (n=1,305; 52%)	Palliative intent (n=1,195; 48%)	P-value
Number of cycles, mean ± SD	5.91±9.10	4.46±5.12	7.50±11.85	<0.05

Data were analyzed using a t-test or a χ^2 test, as appropriate, and expressed as mean ± SD or n (%). Due to rounding of values, some variables may not add up to 100%. BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; DVT, deep vein thrombosis; CKD, chronic kidney disease; ECOG-PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; SC, subcutaneous; SD, standard deviation.

Table II. Summary of 30-day mortality and morbidity rates and causes.

Variables	All patients, n (%) (n=2,504)	Curative intent, n (%) (n=1,305)	Palliative intent, n (%) (n=1,195)	COVID-19-positive, n (%) (n=89)
30-day mortality rate	127 (5.1)	24 (1.8)	103 (8.6)	12 (13.4)
Cause of 30-day mortality				
Disease progression	69 (60.0)	8 (11.6)	61 (88.4)	1 (8.3)
Sepsis	27 (23.5)	11 (40.7)	16 (59.3)	5 (41.7)
Pneumonia	7 (6.1)	0 (0.0)	7 (100.0)	3 (25)
Other	6 (5.2)	1 (16.7)	5 (83.3)	2 (16.7)
Febrile neutropenia	2 (1.7)	1 (50.0)	1 (50.0)	1 (8.3)
Stroke	2 (1.7)	0 (0.0)	2 (100.0)	0 (0.0)
30-day morbidity rate	705 (28.2)	234 (17.9)	470 (39.3)	67 (75.0)
Cause of 30-day morbidity				
ER visits	407 (29.7)	136 (33.5)	270 (66.5)	54 (13.5)
Hospitalizations	367 (26.8)	115 (31.4)	251 (68.6)	54 (15.0)
Delay in chemotherapy	327 (23.9)	97 (29.8)	229 (70.2)	47 (14.7)
Dose reduction	211 (15.4)	54 (25.6)	157 (74.4)	11 (5.3)
ICU admission	58 (4.2)	23 (39.7)	35 (60.3)	8 (14.3)

Due to rounding of values, some variables may not add up to 100%. COVID-19, coronavirus disease; ER, emergency room; ICU, intensive care unit.

A total of 79 (88.8%) patients were older than 65 years, 62 (69.7%) were female, 53 (59.6%) had BMI ≥25, and 60 (67.4%) had ECOG-PS 0-1. Stage IV was the most common in 54 (63.6%), and breast and gastrointestinal were the most frequent cancers in 32 (36%) and 25 (28.1%), respectively. Palliative intent was the aim in 53 (59.6%), intravenous route was the most common in 72 (81%), chemotherapy drugs were used in 72 (81%), and alkylating agents, multi-mechanism, and oxaliplatin-based drugs were used in 16 (18%), 14 (15.7%), and 12 (13.5%), respectively.

Discussion

To our knowledge, this is the first study to investigate the outcomes of curative and palliative anticancer treatments during the COVID-19 pandemic. The data were collected from large comprehensive cancer centers to support the assumption of the risks of mortality and morbidity associated with anticancer treatments during pandemics.

Our population-based study demonstrated that 30-day mortality for all patients who received anticancer treatments was 5.1%, of which 1.8% accounted for curative intent, 8.6% for palliative intent, and 13.4% for COVID-19-positive cases. The 30-day mortality rate of 5.1% in this study could be established as a benchmark at the national level and is comparable to those reported in Australia, UK, and New Zealand (5.6, 4 and 5.17%, respectively) (16-19). For curative and palliative intent, we examined all patients with different cancers-unlike other studies that focused only on certain types of tumors, such as the Systemic Anti-Cancer Therapy Dataset collated by Public Health England, which reported 30-day mortality rates of 3 and 10% for curative and palliative chemotherapy, respectively, for patients with lung cancer. For breast cancer, the 30-day mortality rates were 1 and 7% for curative and palliative chemotherapy, respectively (20). Moreover, the Royal Marsden Hospital reported 30-day mortality rates of 0.5 and 1.5% for curative chemotherapy in breast cancers and for curative chemotherapy in gastrointestinal malignancies, respectively (21).

Table III. Regression analysis of potential prognostic variables associated with 30-day mortality.

Variable	OR	P-value	95% CI for OR
Age (≤65 years)	Reference group		
Age (>65 years)	1.053	0.840	0.636-1.745
Sex (female)	Reference group		
Sex (male)	2.011	0.016	1.141-3.546
BMI (≥25)	Reference group		
BMI (<25)	1.997	0.002	1.292-3.087
ECOG-PS (>1)	Reference group		
ECOG-PS (0-1)	0.157	0.001	0.098-0.253
Stage IV	Reference group		
Stage I-II	0.254	0.039	0.069-0.934
Stage III	1.129	0.700	0.610-2.090
Diagnosis (others)	Reference group		
Breast cancer	1.614	0.056	0.725-3.594
Hematologic cancer	2.375	0.926	0.977-5.774
Gynecologic cancer	1.033	0.499	0.523-2.041
Gastrointestinal cancer	1.405	0.858	0.524-3.764
Lung cancer	1.091	0.186	0.421-2.829
Urologic cancer	0.392	0.241	0.098-1.569
Type (targeted therapy)	Reference group		
Type (chemotherapy)	2.110	0.062	0.250-3.485
Type (hormone therapy)	6.315	0.001	0.074-2.068
Type (immunotherapy)	1.239	0.774	0.262-5.253
Number of cycles	2.110	0.001	0.830-0.948
Route (SC)	Reference group		
Route (IV)	1.412	0.596	0.395-5.043
Route (oral)	0.470	0.282	0.119-1.861
Intention (curative)	0.217	0.001	0.106-0.443

OR, odds ratio; CI, confidence interval; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status; SC, subcutaneous; IV, intravenous.

Our study highlights that important subgroups may be at higher risk of mortality, such as male patients, those with BMI <25, and those receiving hormone therapy. The number of cycles also significantly increased the risk of mortality. We also found that ECOG-PS 0-1, cancer stages I and II, and curative intent significantly decreased the mortality risk. For COVID-19 cases, similar to the results of the TERAVOLT registry (22), our study showed that receiving chemotherapy was associated with an increased mortality risk. However, the patients enrolled in the TERAVOLT registry were older, had lung cancer only, and were COVID-19-positive; this differs from our study where we included patients regardless of the cancer type and the majority of patients were aged <65 years. Likewise, similar to data from the CCC19 database (23), male sex and having an ECOG-PS of ≥2 in this study were associated with increased 30-day mortality. Our study included all patients on active anticancer treatments, in contrast to the CCC19 database where only 39% of patients were on active anticancer treatment. Our observed mortality rate for COVID-19 was 13.4%, which is comparable to that reported in China (14%) (24), the CCC19 database (13%) (23), and the Mount Sinai Health System (11%) (25). However, contrary to international reports, we had a lower incidence of COVID-19 in our cohort, and this needs to be explored in future studies.

Thus far, no studies have described the 30-day morbidity associated with all types of anticancer treatments. Our study results showed that the 30-day morbidity was 28.2% for all patients receiving anticancer treatments, of which 17.9% accounted for curative intent, 39.3% for palliative intent, and 75% for COVID-19 cases. The factors significantly associated with an increased risk of morbidity were age >65 years, BMI <25, chemotherapy, hormone therapy, and immunotherapy. We also found that a significant decrease in morbidity was associated with an ECOG-PS of 0-1, breast cancer, urologic cancer, and curative intent of treatment. The significant increase in the 30-day morbidity of anticancer treatments suggests that oncologists should carefully consider selecting the best regimen, dose, schedule, route, and follow-up for patients receiving anticancer treatments. This must be coupled

Table IV. Regression analysis of potential prognostic variables associated with 30-day morbidity.

Variable	OR	P-value	95% CI for OR
Age (≤65 years)	Reference group		
Age (>65 years)	1.420	0.014	1.075-1.877
Sex (female)	Reference group		
Sex (male)	0.963	0.787	0.730-1.270
BMI (≥25)	Reference group		
BMI (<25)	1.484	0.001	1.194-1.845
ECOG-PS (>1)	Reference group		
ECOG-PS (0-1)	0.502	0.001	0.399-0.632
Stage IV	Reference group		
Stage I-II	0.778	0.195	0.533-1.137
Stage III	1.058	0.734	0.765-1.461
Diagnosis (others)	Reference group		
Breast cancer	0.569	0.004	0.387-0.836
Hematologic cancer	1.046	0.845	0.667-1.639
Gynecologic cancer	1.170	0.376	0.826-1.658
Gastrointestinal cancer	0.866	0.560	0.534-1.405
Lung cancer	0.763	0.341	0.438-1.331
Urologic cancer	0.505	0.050	0.255-0.999
Type (targeted therapy)	Reference group		
Type (chemotherapy)	1.397	0.032	1.089-5.438
Type (hormone therapy)	1.527	0.038	0.211-1.322
Type (immunotherapy)	1.859	0.038	0.648-4.287
Number of cycles	0.964	0.001	0.948-0.980
Route (SC)	Reference group		
Route (IV)	1.424	0.251	0.779-2.602
Route (oral)	0.779	0.437	0.415-1.462
Intention (curative)	0.410	0.001	0.296-0.568

OR, odds ratio; CI, confidence interval; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status; SC, subcutaneous; IV, intravenous.

with an appropriate healthcare system and quality indicators to identify patients who need continuous support (e.g., day care, home care visit, or telemedicine), along with supportive medications to avoid potential harm.

Anti-cancer drugs show promising potential and could be useful as antiviral tools against COVID-19. Nitulescu *et al* (26) reviewed potential treatments and mechanistic characteristics of drugs that may suppress transmission or ameliorate COVID-19. They found that due to the diversity of clinical studies, using a repurposing strategy for drugs is a rapid response solution. Drug repurposing is the use of approved drugs in an off-label use, which may reduce the cost of drug development and identify potential targetable pathways. Moreover, El Bairi *et al* (27) highlighted 20 anticancer drugs that have the potential and are currently being tested such as Janus kinase (JAK) pathways, monoclonal antibodies that targets vascular endothelial growth factor (VEGF), antiprotease that targets multiple receptors, inhibition of viral cellular transcription with antibiotics that have anticancer activity, immune check point inhibitors (antiprogrammed cell death), and kinase inhibitors to inhibit the cell cycle and viral life cycle. Whether a single drug or combined treatment may exhibit synergistic action against COVID-19 remains unknown and is an active area of investigation. Similar to the aforementioned studies, many of our patients have been exposed to anticancer drugs with antiviral activity against COVID-19. Further, our multicenter observational study demonstrates lower rates of COVID-19 cases; this may be attributed to the type of anticancer drugs that have antiviral activity and therefore, these could be future drugs to treat COVID-19. Nonetheless, this hypothesis needs to be tested in larger, controlled, prospective studies. Additionally, because of the lower rates of COVID-19, involvement in adaptive clinical trials is encouraged to enrich the field with an international collaborative group to accelerate drug repurposing and development.

Our cancer centers have adopted the international and national guidelines for management of cancer patients during the COVID-19 pandemic (28-30). Cancer care prioritization should include the following: Providing curative and palliative intent based on the risks/benefits assessment, minimizing

Table V. Characteristics of anticancer drugs.

Class of anti-cancer drugs	N (%)	Curative intent (n=1,307; 52%)			Palliative intent (n=1,195; 48%)			Schedule of administration	Interval of doses
		IV	Oral	SC	IV	Oral	SC		
Hormone	463 (18.5)	5	348	3	12	83	12	Daily	4 weeks, 8 weeks, 12 weeks
Alkylating agents	361 (14.4)	169	11	0	169	12	0	Once	Weekly, 3 weeks, 4 weeks
Her-2 based group	253 (10.1)	84	3	33	111	8	14	Once	3 weeks
Taxanes	218 (8.7)	129	5	1	82	1	0	Once or daily	Weekly, 3 weeks
Antimetabolites	214 (8.6)	37	46	3	43	82	3	Once or 5 days	2 weeks, 3 weeks, 4 weeks
Oxaliplatin based drugs	204 (8.2)	102	0	0	101	1	0	Once	2 weeks, 3 weeks
Multi-mechanism	179 (7.2)	134	0	0	44	1	0	Variable	Variable
Other	118 (4.7)	72	1	8	23	10	4	Variable	Variable
Irinotecan based drugs	110 (4.4)	6	0	0	104	0	0	Once or 5 days	2 weeks, 3 weeks
Check point inhibitors	107 (4.3)	19	0	0	86	1	1	Once	2 weeks,3 weeks
Monoclonal antibodies	85 (3.4)	46	0	8	29	1	1	Once or daily	Weekly, 2 weeks, 3 weeks, 4 weeks, 8 weeks
Gemcitabine based drugs	80 (3.2)	11	1	0	67	1	0	Once	1 week, 3 weeks
CDK inhibitors	46 (1.8)	0	2	0	3	41	0	Daily	4 weeks
Anthracyclines	35 (1.4)	19	0	0	16	0	0	Once	3 weeks
Kinase inhibitors	29 (1.2)	0	1	0	0	28	0	Daily	2 weeks, 3 weeks, 4 weeks

Due to rounding of values, some variables may not add up to 100%. IV, intravenous; SC, subcutaneous; CDK, cyclin-dependent kinase.

Table VI. Incidence of COVID-19 and association with 30-day mortality and morbidity.

Variable	COVID-19, n (%)		P-value
	Yes	No	
30-day mortality			
Yes	12 (9.5)	114 (90.5)	<0.05
No	77 (3.3)	2,256 (96.7)	
30-day morbidity			
Yes	67 (9.7)	622 (90.3)	<0.05
No	22 (1.2)	1,748 (98.8)	
Total	89 (3.6)	2,370 (96.4)	

Data were analyzed using a χ^2 test. COVID-19, coronavirus disease.

interruptions or delays, providing COVID-19 testing for cancer patients, expanding use of granulocyte colony-stimulating factor (GCSF) and low molecular weight heparin (LMWH) prophylaxes, switching intravenous anticancer treatment to acceptable alternative oral drugs, increasing intervals between doses, and modifying the schedule and clinic visits using telemedicine. Patients who recover completely from COVID-19 infection will gradually be able to resume full anticancer treatments.

Similar to the CCC19 database (23), the majority of COVID-19 patients in our study exhibited the following characteristics: Older than 65 years, obese, breast cancer as the most common malignancy, and chemotherapy as the most commonly prescribed anticancer drug. Moreover, palliative intravenous chemotherapy drugs were alkylating agents, multi-mechanism drugs and oxaliplatin based drugs were the most common classes used. These are possible factors contributing to COVID-19 infection and mortality.

This study has several strengths. First, we described the 30-day mortality and morbidity of curative and palliative anticancer treatments in the outpatient setting during the COVID-19 pandemic, which have not been reported previously. Second, our population was diverse in terms of age distribution, stage and type of cancer, curative and palliative intent, and presence of solid versus hematological malignancies. Lastly, we included all types of anticancer treatments such as chemotherapy, immunotherapy, targeted therapy, and hormone therapy as well as the most common routes of treatment such as intravenous, subcutaneous, and oral.

However, there are limitations to be considered. First, the study has a retrospective design. Second, the study was restricted to Saudi Arabia, which limits the inferences that can be drawn from the findings. Third, the majority of patients were younger than 65 years and were female patients with breast cancer. However, we attempted to control for these factors by

Table VII. Characteristics of COVID-19 patients.

Variables	N (%)
Age, years	
>65	79 (88.8)
≤65	10 (11.2)
Sex	
Male	27 (30.3)
Female	62 (69.7)
BMI	
<25	36 (40.4)
≥25	53 (59.6)
ECOG-PS	
0-1	60 (67.4)
>1	29 (32.6)
Cancer stage	
Stage II	16 (18.8)
Stage III	15 (17.6)
Stage IV	54 (63.6)
Cancer diagnosis	
Breast	32 (36.0)
GI	25 (28.1)
Haematological malignancy	13 (14.6)
Other	9 (10.1)
Gynaecological	6 (6.7)
Lung	2 (2.2)
Neurological malignancy	2 (2.2)
Intention	
Curative	36 (40.4)
Palliative	53 (59.6)
Route	
IV	78 (87.6)
Oral	8 (9.0)
SC	3 (3.4)
Class	
Chemotherapy	72 (81.0)
Hormonal	5 (5.6)
Immunotherapy	2 (2.2)
Targeted	10 (11.2)
Class of anti-cancer drugs	
Alkylating agents	16 (18.0)
Multi-Mechanism	14 (15.7)
Oxaliplatin based drugs	12 (13.5)
Antimetabolites	8 (9.0)
Taxanes	8 (9.0)
Her 2 based drugs	6 (6.7)
Irinotecan based drugs	6 (6.7)
Hormone	4 (4.5)
Gemcitabine based drugs	3 (3.4)
Monoclonal antibodies	3 (3.4)
Check point inhibitor	2 (2.2)
CDK inhibitors	2 (2.2)
Antibiotics	1 (1.1)
Anthracyclines	1 (1.1)
Topoisomerase inhibitors	1 (1.1)
Vinca alkaloids	1 (1.1)
Proteasome inhibitor	1 (1.1)

Due to rounding of values, some variables may not add up to 100%. BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status; GI, Gastrointestinal; IV, intravenous; SC, subcutaneous. CDK, cyclin-dependent kinase.

inviting more centers to participate, which could yield a real difference in findings between our study and those of others. Finally, there was a lower incidence of COVID-19 cases in our cohort, which might be related to patients having no or mild symptoms. Prospective cancer registries for COVID-19 cases can capture more accurate data, which would be a possible avenue for future research.

In conclusion, our findings add to previous knowledge regarding the outcomes of curative and palliative anticancer treatments for solid and hematological malignancies during the COVID-19 pandemic. Our data strongly indicated that curative intent was associated with a lower 30-day mortality than was palliative intent, and COVID-19 cases had the highest risk of mortality. Additionally, mortality appeared to be driven by male sex, BMI <25, hormonal therapy, and number of cycles, while morbidity doubled with palliative treatments and reached 75% with COVID-19 cases. Morbidity was driven by age>65 years, BMI <25, chemotherapy, hormonal therapy, and immunotherapy. These data support the conclusion that curative and selected palliative anticancer treatments can be safely continued, thereby reducing the burden of accumulated delays in elective cancer surgeries. Avoiding delays in treatment could relieve pressure among oncologists and maintain good oncological outcomes among cancer patients.

Our data do not necessarily suggest that curative and palliative anticancer treatments can increase the COVID-19 infection risk, as only 3.6% (n=89) out of 96.4% (n=2,370) of patients developed COVID-19 infection. This may provide confidence to oncologists to continue administering anticancer treatments during pandemics assuming appropriate protective measures are undertaken along with tele-oncology care. Our study highlights the importance of informed decision-making between oncologists and cancer patients concerning whether to withhold or continue anticancer treatments during pandemics. This study can contribute to existing literature by providing a benchmark that can be used as a reference for comparing the mortality and morbidity rates of curative and palliative anticancer treatments.

The 30-day mortality rate after anticancer treatment might be a useful clinical indicator for most anticancer treatment protocols. Stopping or delaying anticancer treatments during pandemics can lead to adverse oncological outcomes. Hence, understanding the outcomes of curative and palliative anticancer treatments as well as the outcomes for COVID-19 is urgently needed to help in clinical decision-making.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ET and RA analyzed and interpreted the patient data. ET, MAH, MAM and RA wrote the manuscript. AAA, BB, AA and MA made substantial contributions in data analysis and interpretation. AA, FA, LH, BA, SB and NA helped in acquiring the data for the work. ET, AAA, MA, MAH and MAM conceived the concept and designed the study. ET, MAH and RA were responsible for confirming the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Research Ethics Board at King Abdullah Medical City (no. 20-616; Makkah, Saudi Arabia).

Patient consent for publication

The requirement for written informed consent from patients was waived due to the retrospective design of the study.

Competing interests

The authors declare that they have no competing interests.

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