Back to normal: 1 year of early experience of surgical management of cancer patients during the coronavirus disease 2019 pandemic, a multi-institutional study in a developing country

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Background

During the coronavirus disease 2019 pandemic, the surgical practice has been severely affected, and many nonemergency surgeries were postponed and rescheduled. This is considered to be harmful for cancer patients awaiting their definitive surgical treatment. To date, there is a shortage of large evidence-based studies providing clear guidelines for resuming routine management of these specific types of patients.

Patients and methods

A clinical multi-institutional prospective study was carried out on 1446 adult cancer patients operated with the intention of achieving a cure in the centers participating in this study in the past year under the unusual circumstances imposed by this widespread pandemic, aiming to share our experience in resuming surgical management of these special types of patients, with a focus on the short-term outcomes.

Results

The patients were allocated into two groups: the control group included 1178 patients and the task group included 252 patients. Due to the recent SARS-COV-2 infection, the most common type of surgery performed was breast cancer surgery (32.6, 30.2%) in both groups. The 30-day postoperative morbidity and mortality were comparable in both groups, but slightly higher in the task group (25.4, 3.2%). Patients more than 60 years, patients with two or more comorbidities, patients with American Society of Anesthesiologists score 3, and patients undergoing major surgery were more susceptible to developing postoperative complications.

Conclusion

Surgery for cancer patients can be safely resumed during the coronavirus disease 2019 pandemic, with caution in selected patients.

Keywords:
cancer surgery, coronavirus disease 2019, pandemic, short-term outcomes

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Introduction

At the end of 2019, the world faced one of the most deleterious novel viral infections, known as SARS-CoV-2, which emerged from China. The WHO declared this viral outbreak 'a Public Health Emergency of International Concern' on January 30, 2020 [1].

This virus belongs to the coronavirus family, a group of viruses from which the well-known severe acute respiratory disease (SARA) and Middle Eastern respiratory syndrome (MERS) are also derived. The WHO officially named this new virus coronavirus disease 2019 (COVID-19), and it is believed that, similar to the aforementioned viruses, its ecological origin lies within the bat species [2].

The available data suggest that COVID-19 is mainly transmitted through respiratory droplets and contact routes, but it has also been isolated in blood, feces, urine, and peritoneal fluid. Airborne transmission of the virus has also been recognized in some patients [1,3].

Since the identification of the first infection of COVID-19 in Egypt and Africa on 14th February, the Egyptian government has allocated several hospitals to receive infected cases (isolation hospitals), but the number of infections continued to increase, as the number of confirmed cases in Egypt reached 112 676 on 22nd November [4].

Given that healthcare systems (e.g. hospitals) are the first line of defense to face this pandemic, the negative effects of COVID-19 led to unprecedented challenges for the systems and posed a direct threat to its workers [5,6], especially in developing countries like Egypt, where there is a lack of resources, shortage of equipment and protective devices, and decreased number of intensive care beds and ventilators. Therefore, there is a need to mobilize resources to meet the short-term challenges related to the physical and mental exhaustion faced by the work force of isolation hospitals (physicians and nursing teams) as well as the weak hospital infrastructure and accumulation of large numbers of elective healthcare procedures.

Furthermore, there was a long-term challenge of how these resource-limited systems can reconfigure and improve their capabilities to deal with a large-scale health crises such as COVID-19 and to maintain the sustainability of routine health resources [7].

Based on the understanding of these issues and with the rapid escalation of cases worldwide, and to slow the disease spread, the Egyptian Ministry of Health (MOH) implemented a vast spectrum of measures that had a massive impact on the medical practice and on the university teaching hospitals. The government enforced a complete lockdown of international flights and a daytime curfew [8]. As part of these measures, large numbers of elective surgical procedures were postponed, including many elective cancer surgeries.

In the early weeks of the pandemic, we faced two major dilemmas: cancer patients present a state of systemic immune-suppression (derived from the underlying neoplastic process and administered neoadjuvant chemotherapy in some patients), and thus have higher susceptibility to develop infections, with higher morbidity and mortality rates [9,10]. The second dilemma involved the limited resources and protective equipment in the early phase of the pandemic; these were assigned to more critical patients and areas.

After this early shock stage, which lasted for about 6 weeks, we began to resume and increase our routine elective cancer surgeries. The long-term effect of these measures on cancer patients was unknown. The aim of this study was to share our experience of the surgical management of cancer patients and the short-term outcomes of these patients in two large oncology centers in the previous year from March 2020 till March 2021 under the unusual circumstances imposed by this widespread pandemic.

Patients and methods

A clinical multi-institutional prospective study was carried out on 1446 adult cancer patients (<18 years) operated with the intention of achieving a cure in the centers participating in this study from March 2020 to March 2021. Patients who required emergency or palliative surgical procedures and patients undergoing diagnostic surgical procedures were excluded from the study (i.e. lymph node biopsy, diagnostic laparoscopy, etc.).

The study was registered at the ethical committee of each participating center, and informed written consent was obtained from all patients enrolled in this study. Detailed careful triage was performed for all patients in terms of the symptoms and manifestations of SARS-CoV-2 infection, history of close contact with confirmed cases, and history of travel to highly affected regions.

Recent SARS-CoV-2 infection was confirmed before surgery by one or more of the following methods; (a) positive RT-PCR nasopharyngeal swab, (b) positive rapid antigen test, (c) chest computed tomographic (CT) scan showing changes consistent with pulmonary changes secondary to SARS-CoV-2 infection, or (d) positive preoperative immunoglobulin G or immunoglobulin M antibody test.

According to the history and the previous investigations, the patients were allocated to two groups: group A (control group) included patients who were confirmed not to have recent SARS-CoV-2 infection and group B (task group) included patients with recent SARS-CoV-2 infection.

The patients in the task group were scheduled for surgery 4 weeks after complete resolution of respiratory and nonrespiratory symptoms of SARS-CoV-2 infection. All patients underwent a chest CT scan and RT-PCR nasopharyngeal swab 48 h before admission.

Demographic data of the studied patients [age, sex, comorbidities, American Society of Anesthesiologists (ASA) physical status], all laboratory investigations [routine investigations and inflammatory mediators: C-reactive protein (CRP), serum lactate dehydrogenase (LDH), serum ferritin, and D-dimer protein for task group], surgical details (type of operation, operative time, blood loss), the time interval between diagnosis and surgery, and 30-day postoperative mortality and morbidity were collected and recorded.

The primary end point of this study was the 30-day postoperative morbidity and mortality in the task group in comparison with the control group, and the factors affecting these morbidities.

The secondary end point was the time interval between the diagnosis and surgical management in both groups under the unusual circumstances created by the community spread of this worldwide pandemic.

Statistical analysis

Results were statistically analyzed using SPSS version 22 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as the mean±SD or *n* and %. The significance of the association between the two groups for qualitative variables was determined using Pearson's χ^2 test. The independent *t* test was used to compare two means of normally distributed data. The Mann–Whitney test was used for non-normally distributed data. Odds ratio (OR) was used to detect the risk factors where OR=1ànil, more than 1à risky, and less than 1àprotective. A *P* value was considered significant if less than 0.05.

Results

During the period of 1 year (from March 2020 to March 2021), 1446 adult patients were scheduled for elective surgical oncology operations in two oncology centers in the mid-Nile delta of Egypt. Sixteen patients (from the control group) were excluded from the study due to confirmed SARS-CoV-2 infection in the 30-day postoperative period of follow-up. The remaining 1430 patients were allocated into two groups: the control group (1178 patients) of patients who did not have recent SARS-CoV-2 infection and the task group (252 patients) of patients who had recent SARS-CoV-2 infection.

The distribution of the studied task and control groups with respect to the type and grade of surgery is reported in Table 1, with no significant difference between these groups in this item. The most common surgery performed in both groups was breast cancer surgery (32.6, 30.2%), followed by surgery for colorectal cancer (23.9, 24.2%). Major surgery was required for 97% of the participants in the control group versus 95.6% of the patients in the task group.

Both groups were homogeneous in terms of age, sex, presence of comorbidities and their number, and ASA physical status classification. About two thirds of our patients were males (62.5, 56%), and younger than 60 years of age (58.7, 60.3%), and slightly more than the half of them had one or more comorbidities (51.4, 54.7%). Most of the patients in both groups were ASA 2 (62.1, 64.8%). The most commonly encountered comorbidities in both groups were cardiovascular diseases (24.3, 27%), followed by endocrine diseases (15.9, 17.8%) (Table 2).

Table 1 Distribution of the studied groups in terms of type of surgery

	Type of surgery [*n* (%)]		
	Controls (*N*=1178)	Task group (*N*=252)	Groups
Breast surgery	MRM	205 (17.4)	38 (15.1)
	Conservative	179 (15.2)	38 (15.1)
Head and neck	Thyroidectomy	75 (6.4)	9 (3.6)
	Salivary	15 (1.3)	4 (1.6)
	Oral cavity	9 (0.8)	3 (1.2)
	Neck dissection	12 (1.0)	3 (1.2)
GIT	Colorectal	279 (23.9)	61 (24.2)
	Gastrectomy	42 (3.6)	10 (4.0)
	Pancreatectomy	13 (1.1)	4 (1.6)
	Hepatic resection	9 (0.8)	3 (1.2)
	Splenectomy	34 (2.9)	9 (3.6)
Gynecological	Ovarian	86 (7.3)	18 (7.1)
	Endometrial and cervix	75 (6.3)	15 (6.0)
	Vulva	8 (0.6)	0
Urological	Nephrectomy	52 (4.4)	9 (3.6)
	Cystectomy	31 (2.6)	9 (3.6)
	Adrenalectomy	28 (2.4)	5 (2.0)
Grade of surgery	Minor	35 (3.0)	11 (4.4)
	Major	1143 (97.0)	241 (95.6)

Laboratory inflammatory marker tests among the task group revealed that lymphopenia occurred in 70.6%, high D-dimer in 31.7%, CRP elevation in 83.3%, elevated LDH in 41.7%, and severe chest affection (>50% affection by CT scan) in 15.1% of the patients in the studied task group (Fig. 1).

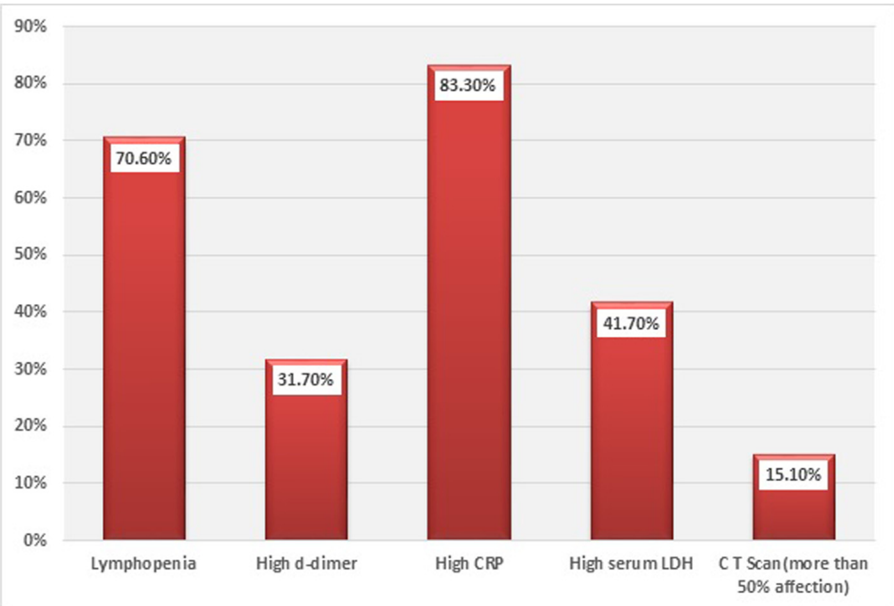
In terms of the timing and perioperative outcomes of the planned surgery, the mean time elapsed from

Table 2 Characteristics of the studied groups

	Groups [*n* (%)]		
	Controls (*N*=1178)	Task group (*N*=252)	*P* value
Age			
<60	692 (58.7)	152 (60.3)	0.644
≥60	486 (41.3)	100 (39.7)	
Sex			
Male	736 (62.5)	141 (56.0)	0.053
Female	442 (38.5)	111 (44.0)	
Comorbidity			
Yes	606 (51.4)	138 (54.7)	0.338
No	572 (48.6)	114 (45.3)	
Type of comorbidity			
Respiratory disease	112 (9.5)	32 (12.7)	0.156
Cardiovascular disease	286 (24.3)	68 (27.0)	0.411
Endocrine disorder	187 (15.9)	45 (17.8)	0.516
Hepatic disease	73 (6.2)	21 (8.3)	0.279
Renal disease	19 (1.6)	8 (3.2)	0.149
Neurologic disease	11 (1.9)	5 (1.9)	0.799
Number of comorbidities			
One	474 (40.1)	104 (43.3)	
Two	95 (8.2)	27 (10.7)	0.507
More than two	37 (3.2)	7 (2.7)	
ASA			
1	388 (32.9)	70 (27.7)	
2	731 (62.1)	163 (64.8)	0.111
3	59 (5.0)	19 (7.5)	

ASA, American Society of Anesthesiologists. *Significant as no value is not less than .05.

Figure 1



Laboratory investigations of the task group.

diagnosis to surgery in the task group (21.01±4.29 days) was significantly longer than that that in the control group (15.50±4.64) (*P*<0.001); the estimated median of blood loss in task group (median=450; interquartile range: 250–700) was found to be significantly higher than that in the control group (median=300, interquartile range: 200–450) (*P*<0.001). Also, there was no significant difference between the two groups in the operative time (120 and 110 min, respectively) (Table 3).

Thirty-day postoperative morbidity occurred in 64 (25.4%) patients. In the task group, 16 (6.3%) patients developed serious complications (according to the Clavien–Dindo classification 3–5), while 268 (22.8%) patients developed postoperative complications in the same period in the control group; among them, 48 (4.1%) patients developed serious complications. The 30-day mortality rate was found to be insignificantly higher in the task group (eight patients, 3.2%) than in the control group (18patients, 1.5%) (Table 3).

By studying the risk factors associated with 30-day morbidity between the task and control groups, age more than or equal to 60 years old [OR=1.98, confidence interval (CI): 1.08–3.64, *P*=0.024), ASA 3 (OR=2.21, 95% CI: 1.04–4.67), having two or more comorbidities (OR=1.92, 95% CI: 1.02–3.61, *P*=0.042), and undergoing major surgery (OR=3.46, 95% CI: 1.03–11.59, *P*=0.032) were significantly associated with 30-day morbidity (Table 4).

On studying the risk factors associated with 30-day morbidity in the task group, elevated D-dimer (OR=10.28, 95% CI: 5.40–19.57, *P*<0.001) and severe chest affection (OR=91.0, 95% CI: 33.79–245.08, *P*<0.001) were found to be significantly associated with 30-day morbidity in the task group (Table 5).

Table 3 Distribution of the studied groups in terms of the timing and perioperative outcome of surgery

	Groups		
	Controls (*N*=1178)	Task group (*N*=252)	*P* value
Time from diagnosis to surgery (days) (mean±SD)	15.50±4.64	21.01±4.29	<0.001*
Estimated blood loss (ml) [median (IQR)]	300 (200–450)	450 (250–700)	<0.001*
Operative time (min) [median (IQR)]	120 (90–150)	110 (90–155)	0.360
Number of serious complications [*n* (%)]	48 (4.1)	16 (6.3)	0.172
30-day mortality [*n* (%)]	18 (1.5)	8 (3.2)	0.113
30-day morbidity [*n* (%)]	268 (22.8)	64 (25.4)	0.421

IQR, interquartile range. *Significant.

Table 4 Factors associated with postoperative morbidity between the task group and the control group

	30-day morbidity [*n* (%)]			
Type of surgery	Controls (*N*=268)	Task group (*N*=64)	*P* value	OR (95% CI)
Age				
<60	112 (41.8)	17 (26.6)	0.024*	1.0
≥60	156 (58.2)	47 (73,4)		1.98 (1.08–3.64)
Sex				
Female	119 (44.4)	28 (43.8)	0.924	1.0
Male	149 (55.6)	36 (56.2)		1.03 (0.59–1.78)
ASA				
1–2	239 (90.7)	52 (81.3)	0.035*	1.0
3	25 (9.3)	12 (18.7)		2.21 (1.04–4.67)
Comorbidity				
No	61 (22.8)	16 (25.0)	0.703	1.0
Yes	207 (77.2)	48 (75.0)		0.88 (0.47–1.67)
Number of comorbidities				
One	136 (65.7)	24 (50.0)	0.042*	1.0
Two or more than two	71 (34.3)	24 (50.0)		1.92 (1.02–3.61)
Grade of surgery				
Minor	39 (14.6)	3 (4.7)	0.032*	1.0
Major	229 (85.4)	61 (95.3)		3.46 (1.03–11.59)

ASA, American Society of Anesthesiologists; CI, confidence interval; OR, odds ratio. *Significant.

Table 5 Factors associated with postoperative morbidity in the task group

	30-day morbidity [*n* (%)]			
	No (*N*=188)	Yes (*N*=64)	*P* value	OR (95% CI)
Lymphopenia				
Yes	143 (76.1)	35 (54.7)	0.001	0.38 (0.21–0.69)
No	45 (23.9)	29 (45.3)		1.0
CRP				
Elevated	172 (91.5)	38 (59.4)	<0.001	0.14 (0.07–0.28)
Normal	16 (8.5)	26 (40.6)		1.0
D-dimer				
Elevated	34 (18.1)	46 (71.9)	<0.001*	10.28 (5.40–19.57)
Normal	152 (81.9)	20 (28.1)		1.0
Serum LDH				
Elevated	76 (40.4)	29 (45.3)	0.493	1.22 (0.69–2.16)
Normal	112 (59.6)	35 (54.7)		1.0
Severity of chest affection				
Severe	6 (3.2)	48 (75.0)	<0.001*	91.0 (33.79–245.08)
Mild	182 (96.8)	16 (25.0)		1.0

95% CI, confidence interval at 95%; LDH, lactate dehydrogenase; OR, odds ratio. *Significant.

Discussion

On February 11, 2020, the WHO named the respiratory disease related to infection COVID-19 [11]. On March 1, 2020, the WHO declared the COVID-19 outbreak a pandemic [12].

Since then, the world has changed and strict measures were taken by most governments to prevent the spread of this obscure and lethal viral infection, keeping in mind the limited resources and the lack of a safe vaccination. Moreover, a complete ban on international flights and a daytime curfew were declared by most governments. Under these circumstances, some extraordinary measures were taken to direct the available medical resources to isolate and treat patients with confirmed or suspected SARS-CoV-2; many health facilities were transformed into isolation hospitals or parts of these facilities were transformed into special isolation partitions in other hospitals.

This, by far, had affected the surgical practice and during the transmission phase of the pandemic, only emergency surgeries were allowed; most elective procedures were postponed. Cancer patients represented a special group of patients, as delay of their scheduled surgery may result in disease progression with resultant mortality; for example, the NHS (England) estimated an increase in the rate of deaths from colorectal cancer by 15–16% due to the COVID-19 pandemic [13], This means those cancer patients are in a critcal situation as delay may upstage the disease and Surgery carries the risk of infection by corona. Soon, many centers in different parts in the world resumed surgery for these groups of patients under special considerations and published their results recently.

In our study, we share our experience of resuming surgery for these groups of patients, highlighting the increased risks of morbidity and mortality among them during the early period of this outbreak.

This study was carried out at two tertiary oncology centers serving two districts of an estimated population of around 10 million people. Over the last year, the two centers continued their surgical services, but at a lower rate, especially in the early transmission phase of the pandemic which continued in Egypt from late March 2020 to the beginning of July 2020, in which the elective surgical procedures decreased to about 30% of the routine activity, and then later on, it increased to reach about 80%.

We adopt a dynamic approach in selecting and deciding the surgical approach for every case, according to the overall pandemic situation, tumor biology, clinical response to treatment, age, and physical status of the patients, and this was done by a multidisciplinary tumor board.

The priority for admission was for aggressive tumor behavior, patients who had completed their neoadjuvant protocols, young and fit patients, and patients who did not have other therapeutic modalities. This is clear in our results; most of our patients (58.7, 60.3%) were younger than 60 years of age and the majority (95, 92.5%) were ASA 1 or 2. Breast cancer surgery and colorectal cancer surgery constituted the main bulk of our cases, representing about 70% of all cases, and this is in agreement with the study carried out by Shrikhande *et al*. [14], In which 41.3% of their patients were breast cancer patients.

At the beginning of our study during this pandemic, we implemented a strict protocol of admission with our anesthesia colleagues: every patient should have undergone an RT-PCR nasopharyngeal swab, and recent CT chest 48 h before admission, and patients with a positive history of COVID-19 were not allowed to undergo an operation until they were symptom free for 4 weeks and the nasopharyngeal swab was negative. This is in agreement with the recommendation published by Cavaliere *et al*. [15] that stated that for COVID-19-positive cancer patients, surgery should always be postponed until the swab is negative.

In a recent study published by the Global Health Research Unit on Global Surgery in UK, it was recommended that elective surgery be postponed for 7 weeks after COVID-19 infection, with a resultant decrease in 30-day mortality in these patients; however, they recommend more delay if symptoms still persist in the patient [16].

This resulted in a significant increase ($P<0.001$) in the time elapsed between the diagnosis and the operation in the task group (21.01±4.29 days) in comparison to that of the controls (15.50±4.64 days). Thus, with this strict protocol, only a small number of patients (16 patients) contracted COVID-19 infection in the immediate postoperative period.

In another study published in west Scotland in 2020 on patients undergoing breast cancer surgery, patients suspected of having COVID-19 were asked to self-isolate and surgery was postponed by a minimum of 2 weeks, followed by a reassessment of the patient [17]. Similarly, Fregatti *et al*. [18] followed the same principle of a 2-week delay in a three patients suspected of having COVID-19 before breast cancer surgery.

The 30-day postoperative morbidity and mortality were acceptable in both groups, and found to be slightly higher in the patients with a recent history of SARS-COV-2 infection (22.8, 1.5%) when compared with the controls (25.4, 3.2%), and this did not reach a significant difference.

Serious life-threating complications (Clavein–Dindo stages 3–5) occurred only in 48 (4.1%) patients in the control group, and most of them (16/48) had respiratory complications in the form of pneumonia and pulmonary embolism. This was also comparable to the task group, in which 16 (6.3%) patients developed serious complications; half of them had respiratory complications (pneumonia and pulmonary embolism).

On analysis of the risk factors associated with increased postoperative morbidity between both groups, we found that patients aged more than 60 years old, patients with two or more comorbidities, patients with ASA score 3, and patients undergoing major surgery were more susceptible to developing postoperative complications.

These results were slightly different from the study carried out at Tata Memorial Centre, India, by Shrikhande *et al*. [14] on 520 cancer surgery patients (among them, 494 patients had opted for elective surgery). They reported serious complications in 29 (5.6%) patients, but they reported no mortality, and found that age of the patient did not affect the rate of postoperative complications.

Similarly, recent data reported by Lee *et al*. [19] from the UK Coronavirus Cancer Monitoring Project (UKCCMP), which included 800 cancer patients with COVID-19 infection, demonstrated no significant effect on mortality for patients who received chemotherapy, immunotherapy, hormonal, or radiotherapy within 4 weeks of their infection. Also, they reported that age (>70), male sex, and severe comorbidities were independently associated with mortality due to COVID-19 infection in these patients [19].

Also, in a large-scale international cohort study (COVID surg collective) including 294 patients with preoperative confirmed COVID-19 infection from a cohort of 1128 patients undergoing surgery and with adjusted analysis, the 30-day mortality was strongly associated with male sex, age (>70), ASA grades 3–5, malignancy, emergency, and/or major surgery [20].

The COVID-19 and Cancer Consortium (CCC19) database, which includes 928 patients with COVID-19 infection undergoing active anti-cancer treatment, revealed that 30-day all-cause mortality is independently associated with age, male sex, and number of comorbidities, among others, but not the type of anti-cancer therapy or recent surgery [21].

However, Zhang *et al*. [22] reported a high mortality rate of 28.6% in patients with COVID-19 infection in Wuhan, China, who received anti-cancer treatment within 2 weeks of infection, and this is similar to a worldwide analysis carried out by Liang *et al.* [9] based on data of 18 cancer patients among 1590 patients with COVID-19 infection.

There are many simple laboratory markers that indicate both the severity of COVID-19 infection and development of complications: presence of absolute lymphopenia, elevated D-dimer, elevated serum LDH, and elevated CRP protein.

It is established that D-dimer higher than 1000 ng is one of the poor prognostic indicators for disease progression and complications, as published by Liu *et al.* [23].

In this study, we attempted to correlate between the 30-day postoperative morbidity and mortality and these laboratory markers, and the severity of chest affection in the CT scan in the patients in the task group; we found that patients with higher D-dimer and patients who had severe chest affection during their COVID-19 infection are more at risk for development of postoperative morbidity and mortality.

Limitations of the study

There are certain limitations in this study: the patients in both groups were not homogeneous in terms of the indication for surgery, the short period of follow-up, and the possibility of the presence of asymptomatic COVID-19 patients in the control group.

This study has many strengths; it included a relatively large number of patients as compared to others in the literature, admitted over 1 year with a clear admission protocol. It represented a safe and dynamic way of resuming surgical oncology practice in developing countries with limited resources suffering during this prolonged worldwide pandemic.

Conclusion

From this encouraging low rate of morbidity obtained in our results, it is safe to resume routine surgical services for cancer patients with a clear and strict protocol and guidelines.

This is of paramount importance in developing countries like Egypt facing great difficulties with national mass vaccination programs. More studies including large numbers of patients with long follow-up periods are needed to develop clear guidelines for surgical practice amid this prolonged worldwide pandemic.

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Conflicts of interest

There are no conflicts of interest.

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