Original Article

Morbidity and mortality after elective cancer surgery—How does recent Covid-19 infection impact outcome: A prospective, comparative study

Manisha Hemrajani, Pooja Mongia[1], Pushplata Gupta, Anjum K. Joad

Department of Anaesthesiology and Palliative Medicine, Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan, [1]Department of Anaesthesiology and Palliative Medicine, Mahatama Gandhi Hospital and Research Centre, Jaipur, Rajasthan, India

Abstract

Background and Aims: Post-Covid-19 cancer patients are likely to have poor postoperative outcomes following cancer surgeries. This is mainly because of the coexisting risk factors unique to cancer patients like immunosuppression, chemotherapy, and radiotherapy-induced risk of infection and malnutrition. The purpose of this study was to compare the postoperative morbidity in cancer patients with and without a history of Covid infection.

Material and Methods: This was a prospective observational study. Subjects were divided into post-Covid 19 (PC) and non-Covid 19 (NC) groups based on the history of SARS CoV2. Preoperative data including details of past Covid infection, chemotherapy, radiotherapy, comorbidity index, Portsmouth-Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (P-POSSUM) score, and nutritional indices were recorded for patients undergoing elective cancer surgery. Thirty-day postoperative morbidity, mortality was recorded.

Results: Of the total patients (n = 414), 109 had postoperative complications (26.33%), reported to be higher in the PC group (33.87%) than the NC (25%) (P value: 0.19). Pulmonary complications were commonest with higher incidence in PC (25.8%) group (P value: 0.001). It was 40% in 2–4 weeks after Covid 19 diagnosis reducing to 18% and 25% in 4–8 weeks and 8–12 weeks, respectively. The overall mortality rate was 0.72%. P-POSSUM morbidity score was similar between the two groups. (PC: 38.30 ± 19.4; Covid negative 37.8 ± 16.7 P value 0.84). Old age, hypothyroidism, and low Prognostic nutritional index were associated with a higher incidence of complications.

Conclusions: Cancer patients with a history of Covid infection undergoing elective surgery are at a higher risk of postoperative pulmonary complications.

Keywords: Cancer, Covid-19, elective surgery, morbidity, postoperative morbidity

Introduction

There has been a resurgence of Covid-19 infection across the world, including India. While mortality is low, many patients with a history of Covid-19 infection will present for elective and emergency surgery in the future.

Increased pulmonary and thrombo-embolic complications and mortality have been observed in cancer patients with perioperative Covid-19 infection.[1-3] The complex interplay between cancer, impaired immunity due to treatment, SARS CoV2 infection, and postoperative morbidity is poorly understood. There is a paucity of literature on postoperative

Address for correspondence: Dr. Manisha Hemrajani, Department of Anaesthesiology and Palliative Medicine, Bhagwan Mahaveer Cancer Hospital and Research Centre, JLN Marg, Jaipur - 302 017, Rajasthan, India.
E-mail: satyenmanisha@yahoo.com

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_232_23

How to cite this article: Hemrajani M, Mongia P, Gupta P, Joad AK. Morbidity and mortality after elective cancer surgery—How does recent Covid-19 infection impact outcome: A prospective, comparative study. J Anaesthesiol Clin Pharmacol 2024;40:645-52.

Submitted: 23-May-2023 **Revised:** 18-Jun-2023
Accepted: 17-Jul-2023 **Published:** 27-Jun-2024

outcomes in elective cancer surgeries after SARS-CoV-2 infection. The Covidsurg collaborative group in a multicentric trial found the postoperative pulmonary complication rate to be 18.5% in cancer patients operated on within the first 2 weeks of Covid diagnosis.[4] Therefore, perioperative morbidity needs to be studied for accurate stratification of risk. Bearing in mind the time sensitive nature of cancer surgery, the optimal period after an infection also needs to be defined.

Portsmouth-Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (P-POSSUM) score[5] is a validated comprehensive surgical risk tool that incorporates preoperative and intraoperative variables and estimates the morbidity and mortality. It has not been used extensively in cancer surgeries in Indian patients.[6] At our center, this has been routinely incorporated as a risk assessment tool for all patients.

We hypothesized that patients who had SARS-CoV-2 infection in the past are at increased risk of postoperative complications. Our primary objective was to study the impact of SARS-CoV-2 infection by comparing the postoperative morbidity and mortality in elective cancer surgery in patients with and without a history of Covid infection. There were four secondary objectives: to compare the length of ICU and hospital stay, to correlate the holding period with postoperative morbidity, to compare observed and predicted morbidity and mortality by P-POSSUM in this population, and to explore other patient factors associated with poor postoperative outcome.

Material and Methods

This was a prospective observational study conducted at a tertiary referral cancer center. The study was approved by the Institutional Ethics Committee (BMH/2021-22/2078) in accordance with good clinical research practices. All adult cancer patients who underwent surgery from November 1 were screened for inclusion. Exclusion criteria were emergencies, endoscopies, all-day care surgeries, and minor surgical procedures like port insertion brachytherapy. Written informed consent was taken from the study subjects. As per institutional protocol, all patients were tested for Covid-19 infection by reverse transcriptase polymerase chain reaction (RT-PCR) and high-resolution CT (HRCT) chest. Subjects with a positive RT PCR or diagnostic HRCT scan were considered Covid-19 positive. The surgery was postponed for all Covid-19 positive patients for two weeks. For patients with a history of moderate to severe SARS-CoV-2 infection, the surgery was planned after 3 weeks from the date of a positive report or an extended period subject to optimization of cardiopulmonary conditions. The distribution of study subjects into two groups, i.e. post-Covid 19 (PC) and non-Covid 19 (NC) is shown in Figure 1 The recruitment process was over by the end of March 2022.

The recorded data included demographics, comorbidities, prior chemotherapy/radiotherapy, nutritional parameters (Prognostic nutritional index {(PNI) Body mass index (BMI) serum albumin}, and Charlson index. The incidence of postoperative complications was recorded as per originally used for P POSSUM prediction scores earlier.[7] The P-POSSUM scores were calculated. Severity of Covid-19 infection was documented as per WHO Clinical Progression Scale along with interval between SARS-CoV-2 positive report and surgical intervention.[8] Postoperative 30-day morbidity and mortality, length of ICU, and hospital stay were recorded. The primary end point was 30-day postoperative morbidity and mortality. The secondary end points were ICU and hospital length of stay; postoperative morbidity with respect to holding period after SARS-CoV-2 and patient-related factors; and observed and expected ratios of P-POSSUM predicted morbidity and mortality.

The sample size was calculated based on a previous study by Francesco *et al.*[9] in which postoperative pulmonary complications in post-Covid-19 and control group were 44% and 2.5%, respectively. As per this study, the expected difference in pulmonary complication rate in the two groups is 40%, indicating a huge impact on postoperative outcome. The sample size was calculated at an alpha error 0.05 and study power 90%, the for testing the hypothesis for two independent population proportion was a minimum of 286 subjects. Considering 10% attrition rate, sample size was increased and rounded off to 400 subjects.

Nominal/categorical variables were summarized as frequency and percentage and analyzed using Chi-square test. Continuous variables were summarized as mean and standard deviation and analyzed using independent sample *t* test. A P value ≤ 0.05 was taken as statistically significant.

Statistical analysis were done using Epi info version 7.2.1.0 statistical software.

Results

Of the total 414 patients included in the study, 62 were under the PC group and 352 under the NC group. Asymptomatic and mild infection rate was 27.4%, and 9.6% respectively. None had severe Covid-19 infection [Figure 1].

On comparing the two groups, there was no statistically significant difference in the baseline characteristics, including

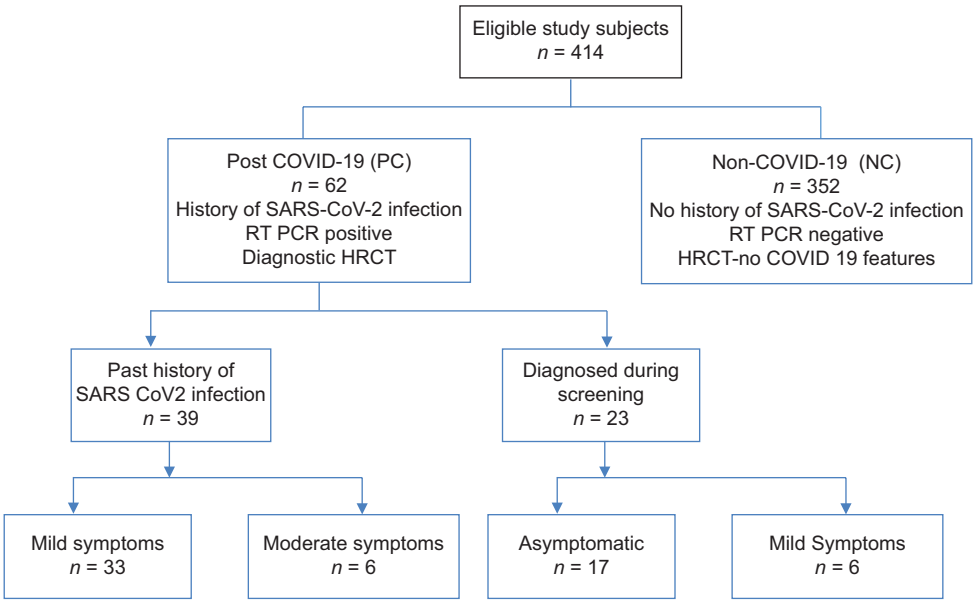

Figure 1: Distribution of study subjects

comorbidities, nutritional status, thereby eliminating confounding factors that could influence the postoperative outcome. The overall morbidity risk profile was also comparable as suggested by similar P POSSUM scores. [Table 1] (PC: 38.30 ± 19.4; NC: 37.8 ± 16.7; *P* value 0.84) Among all the surgeries, 222 were head and neck procedures (53.62%), 57 were genitourinary procedures (13.77%), and 46 were breast surgeries (11.35%) [Figure 2].

Postoperative complications within 30 days occurred in 109 patients (26.33%). The occurrence of complications was found to be 33.8% in the PC group as compared to 25% in the NC group, but the difference was not statistically significant (*P* value: 0.192) [Table 2]. Similarly, respiratory complications observed were higher in the PC group than in the NC group, but the difference was statistically significant (PC: 24.19%, NC: 7.7%; *P* value: 0.001) [Table 3]. Three patients died (0.72%). Of these three patients, two patients were of the PC group.

Re-exploration was the most frequent local complication in both groups and was required in 29 patients within 30 days after surgery (NC: 6.5%, PC: 7.1%; *P* value 0.93) [Table 4].

The mean ICU length of stay was significantly higher in the PC group than in the NC group (2.70 days vs 1.99 days *P* value = 0.036), while the hospital length of stay did not differ. (6.63 days vs 6.52 days; *P* value 0.85) [Table 5].

Considering the factors associated with postoperative complications, patients who were older than 60 and were hypothyroid had a significantly higher number of

Table 1: Preoperative baseline characteristics of participants and POSSUM scores

	PC (*n*=62)	NC (*n*=352)	*P*
Age in years (mean±SD)	52.68±13.31	50.64±13.46	0.271
Gender			
Male	33 (53.2%)	211 (59.9%)	0.257
Female	29 (46.7%)	141 (40.1%)	
Hypertension	24 (38.7%)	101 (28.7%)	0.152
Coronary artery disease	2 (3.2%)	9 (2.6%)	0.900
Diabetes	14 (22.6%)	51 (14.5%)	0.154
Hypothyroidism	11 (17.7%)	43 (12.2%)	0.324
Post chemotherapy	18 (29%)	75 (21.3%)	0.238
Post radiation	8 (12.9%)	34 (9.7%)	0.581
Redo surgery	1 (1.6%)	23 (6.5%)	0.217
Albumin (mg/dl)	4.21±0.49	4.39±2.52	0.581
PNI	52.15±6.58	51.84±7.33	0.766
BMI <18.5	2 (3.2%)	37 (4.8%)	0.621
Charlson comorbidity index	4.17±1.96	3.87±1.59	0.190
Possum morbidity score	38.30±19.4	37.8±16.7	0.848
Possum mortality score	2.65±3.15	2.56±3.62	0.865

PNI – Prognostic nutritional index, BMI – Body mass index

Table 2: Postoperative outcome in post Covid-19 (PC) and non-Covid-19 (NC) groups

	PC	NC	*P*
30 day postoperative morbidity *n* (%)	21 (33.87%)	88 (25%)	0.192
Local, n (%)	7 (11.3%)	41 (11.6%)	0.893
Systemic, n (%)	17 (27.4%)	63 (17.9%)	0.115

complications (*P* value 0.002, 0.037, respectively). Among the nutritional indices, mean PNI values were significantly lower in patients who had complications as compared to patients without postoperative complications (49.95 ± 8.20, 55.69 ± 53.12, respectively; *P* value = 0.001) [Table 6].

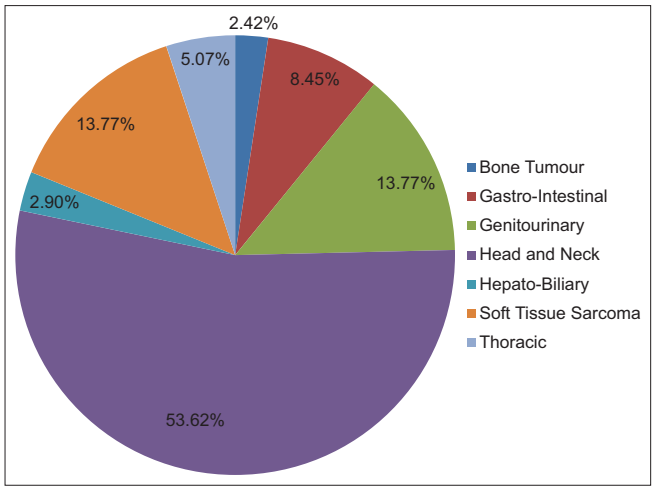

Figure 2: Distribution of patients according to the site of malignancy

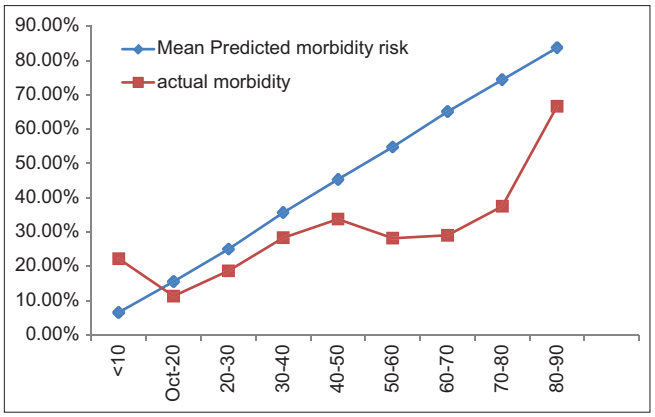

Figure 3: Graphical representation of the relationship between actual and predicted (by P- POSSUM) morbidity of study participants

Within the PC group, 25 patients were operated within 2–4 weeks after a positive RT-PCR test, 11 patients within 4–8 weeks, 8 patients between 8 and 12 weeks, and 18 patients after 12 weeks. The incidence of respiratory complications was 40% in the first group, 18.2% and 25% in 4–8 weeks and 8–12 weeks, respectively, and 5.6% in >12-week group [Table 7].

The incidence of "any complication" in patients with P-POSSUM predicted morbidity ranging between 10 and 50 percent (n = 81) matched with the predicted outcome. The actual incidence of complications in patients with a POSSUM score less than 10% was greater than predicted, while it was less than expected in patients with POSSUM predicted morbidity greater than 50% [Table 8] [Figure 3].

Discussion

Four hundred and fourteen patients undergoing elective cancer surgery were followed up to 30 days to examine the impact of prior SARS CoV2 infection on the postoperative outcome by comparing two matched groups (PC vs NC) with a similar surgical risk profile. The postoperative morbidity was found to be higher in patients with a history of Covid-19 infection despite a liberal postponement strategy of a minimum two weeks. In a similar study by Ranganathan on post-Covid-19 patients undergoing cancer surgery, the morbidity reported was 17% against 33.8% in our study.[10] This huge difference could be due to the fact that major proportion of patients in their study were operated seven weeks after SARS-CoV-2 infection in contrast to short interval of 2–4 weeks in our study Kothari *et al.*,[11] in a propensity-matched cohort study found no difference in postoperative morbidity rates in cancer patients with and without a history of mild-to-moderate Covid-19 infection. Possibly, the difference in the type of surgeries could explain the observed discrepancy. Almost half of the surgeries in their study were daycare against high-risk head and neck surgeries in our study.

In an Indian study during the nationwide lockdown on cancer patients, Pai *et al.*[12] observed an overall postoperative morbidity rate of 27.7%, similar to our study and mortality

Table 3: Systemic complications in post Covid-19 and non-Covid-19 patients

Systemic complications	PC *n* (%)	NC *n* (%)	*P*
Anemia	1 (1.6)	4 (1.1)	0.354
Pulmonary	15 (24.19)	27 (7.7)	<0.001 (S)
Cardiac	4 (6.5)	18 (5.1)	0.900
Renal	2 (3.2)	4 (1.1)	0.488
Delayed extubation	0 (0)	2 (0.6)	0.690
Delirium	1 (1.6)	5 (1.4)	0.646
Septicemia	4 (6.5)	7 (2)	0.113
Dyselectrolytemia	0 (0)	3 (0.9)	0.934
Hypotension	0 (0)	1 (0.3)	0.326
Septic shock	1 (1.6)	2 (0.6)	0.394
MODS	0 (0)	1 (0.3)	0.326

MODS: Multiorgan dysfunction

Table 4: Local complications in post-Covid-19 (PC) and non-Covid-19 (NC) patients

Local complications	PC *n* (%)	NC *n* (%)	*P*
Anastomotic leak	2 (3.2)	1 (0.3)	0.088
Bleeding/hematoma	0 (0)	2 (0.6)	0.690
Infection	2 (3.2)	18 (5.1)	0.750
Fistula	1 (1.6)	0 (0)	0.326
Re-exploration	4 (6.5)	25 (7.1)	0.932

Table 5: Length of stay (LOS) of post-Covid-19 and non-Covid-19 patients

	PC	NC	*P*
ICU LOS (days)	2.70±4.02	1.99±2	0.036
Hospital LOS (days)	6.63±4.54	6.52±4.15	0.858

Table 6: Factors associated with postoperative complications

	Complications (*n*=109)	No complications (*n*=305)	*P*
Age ≥60 years	43 (40.3%)	72 (23.6%)	0.002 (S)
Male	70 (64.2%)	175 (57.4%)	0.257
Female	39 (35.8%)	130 (42.6%)	
Hypertension	34 (31.2%)	91 (29.8%)	0.886
Coronary artery disease	5 (4.6%)	6 (2%)	0.266
Diabetes mellitus	14 (12.8%)	51 (16.7%)	0.423
Hypothyroidism	21 (19.3%)	33 (10.8%)	0.037 (S)
Post chemotherapy	26 (23.9%)	67 (22%)	0.786
Post radiation therapy	15 (13.8%)	27 (8.9%)	0.203
Redo-surgery	6 (5.5%)	18 (5.9%)	0.931
Intraoperative event	13 (11.9%)	19 (6.2%)	0.089
Preoperative albumin (mg/dl)	4.09±0.66	4.47±2.69	0.157
PNI	49.97±8.16	52.58±6.73	0.001 (S)
BMI <18.5	11 (10.1%)	28 (8.2%)	1.000

Table 7: Pulmonary complications in post-Covid-19 patients

Duration from Covid-19 to surgery	Total no. of patients	Pulmonary complications *n* (%)
2–4 weeks	25	10 (40)
4–8 weeks	11	2 (18.2)
8–12 weeks	8	2 (25)
>12 weeks	18	1 (5.6)
Total	62	15 (24.19)

Chi-square=6.917 with 2 degrees of freedom; P=0.031 (S)

rate 1.6%. However, in their study, Covid was ruled out only in patients with symptoms or a history of exposure to Covid.

Regarding the type of complications, re-explorations were the most common local complications, whereas pulmonary complications were the most frequently seen systemic complication. Its incidence was three times higher in the PC group than in the NC group. Resultantly, the ICU length of stay was also significantly prolonged in the PC group.

Surgery within a 2–6-week period of recovery after mild viral respiratory infection is a risk for respiratory complications.[13] In an international multicenter trial by Covidsurg collaborative group, the postoperative pulmonary complication rate was significantly higher in post-Covid-19 patients compared to control group similar to our study.[4] However, in their study, the pulmonary complication rate was the highest in the first 2 weeks, while in our study, none of the patients were operated within 2 weeks' time. Possibly, this could be the reason for a high mortality rate of 7.7% reported in the first 2 weeks in Covid-19-recovered patients in their study. The pulmonary morbidity rate in our study was 40% between 2 and 4 weeks, falling to 25% between 8 and 12 weeks. It was found to be a minimum beyond 12 weeks (5.6%). Though the number of patients who were operated beyond 12 weeks after Covid-19 were less, it can be inferred that these patients had respiratory complication rate similar to those in Covid-19 negative patients. In Deng's series it was found to be in the range of 14.6% (0–4 weeks), 5% (4–8 weeks), and 4.2% (more than 8 weeks).[14]

The observed discrepancy in morbidity rates could be due to variability in the clinical course of Covid-19 infection. The asymptomatic RT PCR positivity rate in our study was 27.4%, whereas the CovidSurg Collaborative group did not specify the Covid-19 severity andcomplexity of surgery in their study.[4] In our study, more than 40% were major head and neck resections with microvascular reconstructions. Risk factors unique to head and neck cancer surgeries are smoking, malnutrition, radiation, disrupted postoperative airway reflexes, and delayed extubation, which increases the risk of postoperative respiratory complications.[15] This could also be the possible reason for the difference in the pulmonary complication rates. Moreover, 77% of our patients scored moderate to high risk as per Charlson comorbidity index. Therefore, it is difficult to compare results given the expected differences in age, cancer stage, type, performance status, comorbidities, and clinical presentation of Covid infection.

Recently updated guidelines recommend a safe waiting period of 7–8 weeks for elective surgeries after Covid-19 infection.[16] So far, no evidence-based guidelines are available on the safe holding period for elective cancer surgeries in patients who have acquired SARS CoV2 infection.

However, cancer surgeries are time sensitive. Delays can lead to progression of cancer, more extensive surgery, and inoperability. A recent systematic review found that postponement of cancer surgery by 1 month was associated with an increased risk of mortality.[17] Decision-making requires weighing the benefit of timely surgery against the heightened risk of SARS-CoV-2-associated morbidity and mortality We,

Table 8: P Possum morbidity scores interpretation of the study population

POSSUM risk category	Mean Predicted morbidity risk	Total patients	No of predicted morbidity	No. of observed morbidity	O: E ratio	Interpretation by POSSUM
<10	6.54%	9	1	2	2.00	Under estimation
10–20	15.54%	53	8	6	0.75	over estimation
20–30	25%	75	19	14	0.74	over estimation
30–40	35.66%	113	40	32	0.80	over estimation
40–50	45.34%	77	35	26	0.74	over estimation
50–60	54.8%	39	21	11	0.52	over estimation
60–70	65.1%	31	20	9	0.45	over estimation
70–80	74.4%	8	6	3	0.50	over estimation
80–90	83.7%	9	8	6	0.75	over estimation
Total	38.12%	414	158	109	0.69	over estimation

therefore, deferred surgeries for two weeks in patients who were asymptomatic or had mild symptoms and for 3–4 weeks for optimization of patients with a history of moderate to severe symptoms in consultation with the multidisciplinary tumor board.

The CovidSurg-Cancer study (122 patients) reported that elective surgery within four weeks after infection was associated with a higher risk of pulmonary complications and mortality.[4] Kothari *et al.*[11] considered a minimum of 20 days after SARS-CoV-2 infection as the safe wait period. Another paper from the same group reported higher postoperative mortality, venous thrombo-embolism, and pneumonia for surgeries within 1–6 weeks after Covid-19.[4] Deng *et al.*[14] reported that elective surgery within 8 weeks after recovery from Covid-19 was associated with increased adverse events.

However, other studies have indicated that surgeries performed earlier after Covid-19 diagnosis could be safe. Kane *et al.*[18] reported on six Covid positive patients who underwent elective surgery within 36 days (mean 25 days) after infection without mortality or major morbidity. Baiocchi did not find any significant difference in postoperative morbidity and mortality in asymptomatic Covid-19 recovered and Covid-negative patients.[19] Ranganathan *et al.* showed that elective cancer surgery is safe before the recommended seven-week period after mild Covid-19 infection.[9]

In our study, the mortality in the PC group was 3.2% against 0.2% in the NC group. However, the overall mortality was too low to comment on its significance on statistical grounds.

A retrospective observational analysis on a similar subset of patients during the peak of second wave reported a mortality rate of 2.5% in the Covid-positive group against 0.6% in the Covid-negative group.[20] These deaths were the patients who had tested positive on RT PCR early in the postoperative period. None of our patients tested Covid positive in the early postoperative period. This could be because we eliminated RT-PCR false negatives preoperatively by screening HRCT chest for all our patients.

We chose both RT PCR and HRCT chest as diagnostic tools because the former is highly specific, while the latter has high sensitivity and allows early detection of SARS CoV2. The expense of both tests is a deterrent but was deemed necessary because of the potential risk of aerosol transmission of undiagnosed Covid-19 during the perioperative care of intubated head and neck cancer patients. Head and neck cancer constitute a major proportion of surgical patients at our center.

In our study, patients older than 60 years had a significantly higher postoperative morbidity. Preoperative radiotherapy and chemotherapy were not associated with a higher complication rate. However, hypothyroidism, more commonly seen in postradiotherapy head and neck cancer patients, was an independent risk factor for postoperative complications.[21]

Many patients with cancer are nutritionally depleted. Numerous studies have emphasized the role of PNI as an index to measure nutrition status and predict the risk of postoperative complications in cancer.[22,23] However, the optimum cut-off value of PNI is debatable. In our study, mean PNI was statistically low in patients who had complications (P value = 0.001).

The POSSUM score of our study patients accurately predicted morbidity for scores ranging between 10% and 50%. The number of patients with a less than 10% score was too low to draw a conclusion. Above 50% the estimated morbidity was higher than the observed morbidity. [Figure 3] Similar results were obtained by Mukherjee *et al.*[24] in patients with gynecological and gastrointestinal cancer.

This study had few limitations. Since this study included only elective cancer surgical patients, the results cannot be generalized to other patient populations. The practice

of retaining the endotracheal tube or tracheostomy tube postoperatively in head and neck cancer patients, unlike other cancer surgeries, predispose this category to the added risk of respiratory complication, which can confound the results of this study. Larger studies are needed to establish the correlation between the Covid severity, holding period, and postoperative morbidity.

The strengths of our study are – the postoperative outcome was compared with a concurrent control group. We recorded 30-day morbidity, including all cancer surgeries and patients irrespective of grade of Covid-19 infection.

Our study data support the recommendation to postpone surgery whenever possible in Covid-19-recovered cancer patients. It further guides on risk stratification and counselling of patients and their families accordingly. Prehabilitation and optimization during the holding period of 2–4 weeks target nutrition, lung, and thyroid function may improve postoperative outcome. Logistic support and postoperative care of these patients can also be planned, keeping in mind the high risk of pulmonary complications and longer ICU stay. We may witness a significant surge in Covid-19 and given the large numbers of Covid affected persons in India – we will be anesthetizing many more patients with a history of Covid infection.

Conclusion

Cancer patients with a history of SARS CoV2 infection undergoing major elective surgery are at a higher risk of postoperative pulmonary events. Our results suggest a minimum four weeks holding period for asymptomatic patients for surgery. A longer waiting period would be recommended in patients recovering from symptomatic Covid-19 infection. The risk stratification based on factors: low PNI, hypothyroidism, and old age, give an insight into ways to improve the perioperative outcomes, from prehabilitation to postoperative critical care support.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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