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Thoracic surgery during the coronavirus disease 2019 (COVID-19) pandemic in Madrid, Spain: single-centre report

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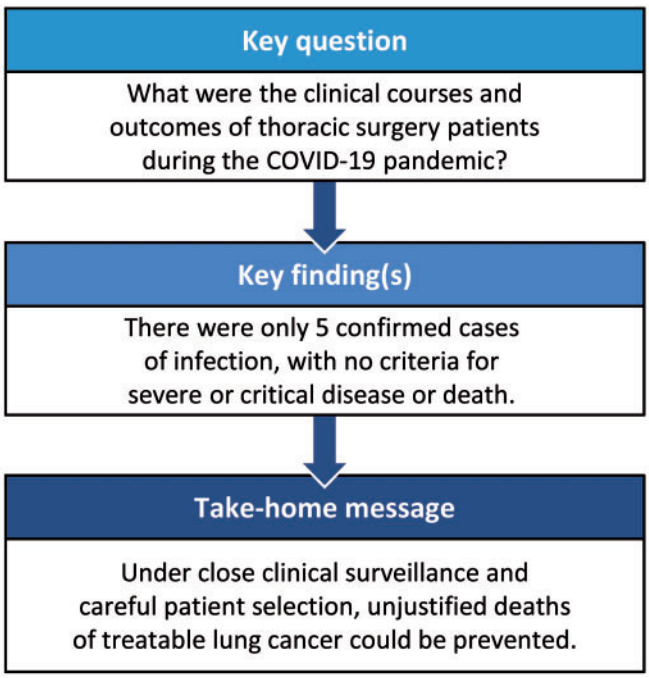

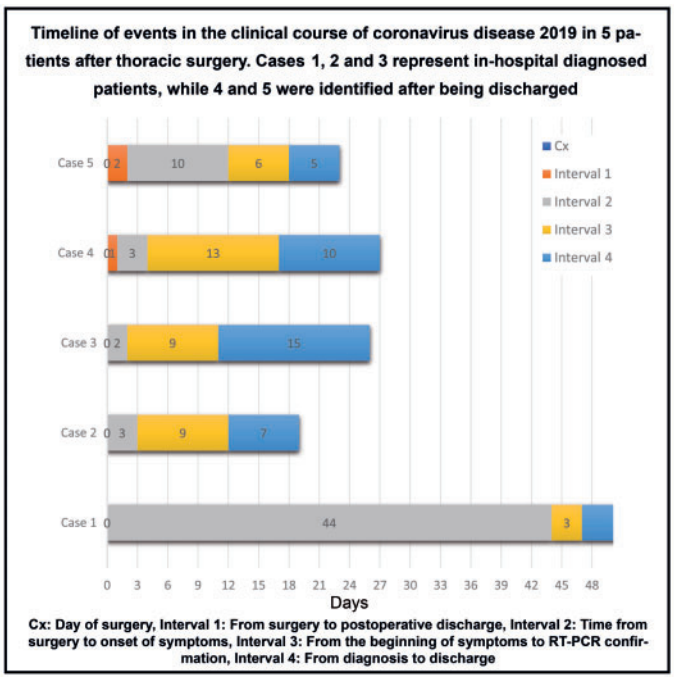

Abstract

OBJECTIVES: We reviewed the incidence of coronavirus disease 2019 cases and the postoperative outcomes of patients who had thoracic surgery during the beginning and at the highest point of transmission in our community.

METHODS: We retrospectively reviewed patients who had undergone elective thoracic surgery from 12 February 2020 to 30 April 2020 and were symptomatic or tested positive for severe acute respiratory syndrome coronavirus 2 infection within 14 days after surgery, with a focus on their complications and potential deaths.

RESULTS: Out of 101 surgical procedures, including 57 primary oncological resections, 6 lung transplants and 18 emergency procedures, only 5 cases of coronavirus disease 2019 were identified, 3 in the immediate postoperative period and 2 as outpatients. All 5 patients had cancer; the median age was 64 years. The main virus-related symptom was fever (80%), and the median onset of coronavirus disease 2019

was 3 days. Although 80% of the patients who had positive test results for severe acute respiratory syndrome coronavirus 2 required in-hospital care, none of them were considered severe or critical and none died.

CONCLUSIONS: These results indicate that, in properly selected cases, with short preoperative in-hospital stays, strict isolation and infection control protocols, managed by a dedicated multidisciplinary team, a surgical procedure could be performed with a relatively low risk for the patient.

Keywords: Coronavirus disease 2019 • Severe acute respiratory syndrome coronavirus 2 • Thoracic surgery • Postoperative • Incubation period

ABBREVIATIONS

COVID-19	Coronavirus disease 2019
HCW	Health care worker
ICU	Intensive care unit
RT-PCR	Real-time reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

Since the outbreak of the novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China [1], over 4.9 million cases have been diagnosed around the world [2]. With no known treatment or effective vaccine available in the near future, health care providers have been forced to manage growing surgical waiting lists, especially for oncology patients. The risk of tumours progression due to the delay of definitive surgery cannot be ignored [3].

As of 10 March 2020, there have been more than 235 000 cases of COVID-19 confirmed in Spain and more than 28 000 deaths [4]. On 26 February, the first case of COVID-19 infection was diagnosed in our centre. After that first case, the figures escalated substantially, as occurred elsewhere in the city; the hospital was crowded with patients with positive test results, and intensive care units (ICUs) were fully occupied by patients on ventilators. Nevertheless, our surgical team and hospital managers were able to keep a SARS-CoV-2-free circuit and provided surgical procedures for selected cases based on necessity. Currently, the clinical characteristics and outcomes of patients undergoing surgery, particularly thoracic surgery, are scarce. Lei *et al.* [5] were the first to report a postoperative series of 34 cases. However, only 3 of those were thoracic patients, with extremely high mortality. We thought that COVID-19 might complicate the perioperative course with diagnostic challenges and a high impact on survival, given that surgery itself provokes an immediate impairment of cell-mediated immunity, one of the primary mechanisms that brings the viral infection under control [3, 6–8]. Additionally, according to preliminary data from China and Italy, cancer, along with other comorbidities, occurs frequently in thoracic surgery patients and may increase deaths of COVID-19.

Our goal was to describe the clinical presentations and outcomes of patients who had elective thoracic surgical procedures performed during the SARS-CoV-2 outbreak in a single centre in Madrid, Spain.

MATERIALS AND METHODS

We retrospectively reviewed patients who had undergone elective thoracic surgery from 12 February 2020 to 30 April 2020, the early stage of the COVID-19 epidemic in Madrid, Spain. Postoperative clinical, laboratory and radiological records and timelines of clinical courses were summarized. Potential prognostic factors were evaluated.

For accuracy, 3 researchers independently recorded data using a standardized data collection form.

Consent from the COVID-19 patients analysed in this report was waived due to its retrospective nature and because the data would be de-identified at publication.

The study population included all patients admitted for thoracic surgery procedures to the department of thoracic surgery of the Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain, between 12 February and 30 April.

Patients were included, considering the time frame of 14 days before the first confirmed case was admitted to our centre. Follow-up was performed within 14 days after discharge from hospital, based on published incubation and asymptomatic carrier time frames [9]. For postoperative patients about to be discharged from the hospital, oropharyngeal swabs were used to test for SARS-CoV-2 using a real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay if the patient had suggestive symptoms or epidemiological risk factors. In contrast, patients who were already discharged were called and their electronic medical records checked for the presence of coronavirus symptoms, hospital admission related to a possible infection, or confirmation of COVID-19 based on the results of the RT-PCR test.

Patients were defined as 'critical' if they met any of the following criteria: respiratory failure requiring mechanical ventilation, septic shock or multiple organ dysfunction in the ICU. Patients were defined as 'severe' if they had dyspnoea with a respiratory rate $\geq$30/min, a PaO_2/FiO_2 ratio <300 mmHg or blood oxygen saturation $\leq$93% or lung $\leq$ infiltrates >50% within 24–48 h.

A descriptive analysis was performed using the absolute and relative frequencies for categorical variables and mean (standard deviation) or median (percentiles 25 and 75) for numerical variables. Univariable analysis was done with the Mann–Whitney *U*-test. The significance level was established at 0.05. We used Stata/IC v.16 (Stata Statistical Software: Release 16: 2019) (StataCorp LLC, College Station, TX, USA).

RESULTS

A total of 101 interventions were performed in our centre during this period, represented by 81 individual patients, including 57

oncological surgical procedures, 6 lung transplants and 18 emergency procedures (Table 1). The median age was 61 years (17–82 years), 45% women and 55% men, with a median in-hospital stay of 3 days for non-transplant patients.

Meanwhile, all of the lung transplants were performed between the first and the third week of the study period. During the highest point of hospital occupancy due to patients with COVID-19, between the 5th and the 10th weeks, our surgical activity was further reduced to 44% compared with the same period the year before.

The main postoperative complications were prolonged air leak in 9 cases, followed by bacterial pneumonia in 4 cases and by 1 case each of haemothorax and atrial fibrillation.

In the postoperative period, only 5 patients (5%) were diagnosed with COVID-19. All 5 patients with positive test results had cancer: 4 had non-small-lung cancer, 2 of whom had open resections (lobectomy and right pneumonectomy) and 2 of whom had video-assisted thoracoscopic surgical resections and 1 had a rebiopsy for a lymphoma (Table 2). There were no severe and no critical cases of SARS-CoV-2 among our patients. However, there was 1 recorded death of an 82-year-old man with a massive pleural effusion and metastatic disease, who 8 days after a pleural biopsy and insertion of an indwelling pleural catheter, developed dyspnoea and died under at-home care, without an autopsy or RT-PCR confirmation. Hence, he was not included in this case-series due to the uncertainty of the cause of death.

The most predominant symptom was a low-grade fever in 4 patients (80%), followed by dyspnoea and cough (25%). The onset of symptoms after surgery ranged from 2 to 10 days with a median of 3 days, whereas the diagnosis occurred between 5 and 15 days (mean 12.5 days). One patient had postoperative decompensation of severe aortic stenosis after an open lobectomy; while remaining in hospital care, he developed COVID-19 symptoms 44 days postoperatively. Three days later, RT-PCR test results were positive; he was discharged from the hospital 57 days after the initial oncological surgery (Table 2).

Only 3 patients were diagnosed with COVID-19 while in the hospital; the remaining 2 patients were diagnosed after discharge. A total of 80% of our patients infected with SARS-CoV-2 required hospitalization after diagnosis, for a median of 5 days. Nevertheless, COVID-19 infection does not represent a statistically significant factor for a prolonged postoperative in-hospital stay in our series ($P = 0.13$).

All patients had normal complete blood counts and clinical biochemical values preoperatively. Two patients (40%) experienced reductions in the white blood count at the beginning of the infection in concurrence with a low lymphocyte count. D-dimer levels were remarkably higher in those infected close to the time of the operation (patients 2, 3) (Fig. 1). Finally, the most significant changes in liver enzymes were seen in the oldest patient in the series, although they were not related to any other severity criteria.

All patients received hydroxychloroquine and azithromycin, whereas only 2 patients received additional treatment with lopinavir/ritonavir. Prophylactic fractioned heparin during convalescences was also prescribed as recommended [10, 11].

Table 1: Operations performed during the pandemic

Operations	Number
Lobectomy	25[a]
Sleeve resection	2
Pneumonectomy	1
Sublobar resection	19[b]
Mediastinal tumour	7
Pleural tumour	6
Chest tumour	2
Mediastinoscopy	15
Lung transplant	6 (bilateral)
Urgent surgery	18
Total	101

[a]88% VATS procedure.
[b]90% VATS procedure.
VATS: video-assisted thoracoscopic surgery.

Table 2: Summary of clinical characteristics of the 5 patients with positive test results for coronavirus disease 2019

Patient	1	2	3	4	5
Age (years)	77	68	25	34	70
Sex	Male	Female	Female	Male	Male
Smoking history	Yes	No	No	No	Yes
Comorbidity	HT DM	CC	No	NHL	HT, DM
Tumour location	LUL	LUL	RLL	Mediastinum	RUL
Operation	Lobectomy	Lobectomy	Pneumonectomy	Mediastinoscopy	Lobectomy
Approach	Open	VATS	Open	No	VATS
Histological type	SSC	Adeno	Blastoma	NHL	SCC
Tumour stage	pTaN0M0	pT1bN0M0	T4N0		ypT1bN0
Main symptom	Fever	Fever	Fever	Fever	Dyspnoea
Onset of symptoms	44	3	2	3	10
RT-PCR, positive results	47	12	9	13	16
Neg/pos ratio, RT-PCR	0:1	0:1	1:1	2:1	0:1
Severity	Mild	Mild	Mild	Mild	Mild
Discharged day of surgery	75	19	24	1	3
Discharged day post COVID	10	7	15	10	5

CC: cancer; DM: diabetes mellitus; HT: hypertension, LUL: left upper lobe; neg/pos ratio: number of negative RT-PCR test results before a positive result; NHL: non-Hodgkin lymphoma; RLL: right lower lobe; RT-PCR: real-time reverse transcriptase polymerase chain reaction; RUL: right upper lobe; SSC: squamous cell carcinoma; VATS: video-assisted thoracoscopic surgery.

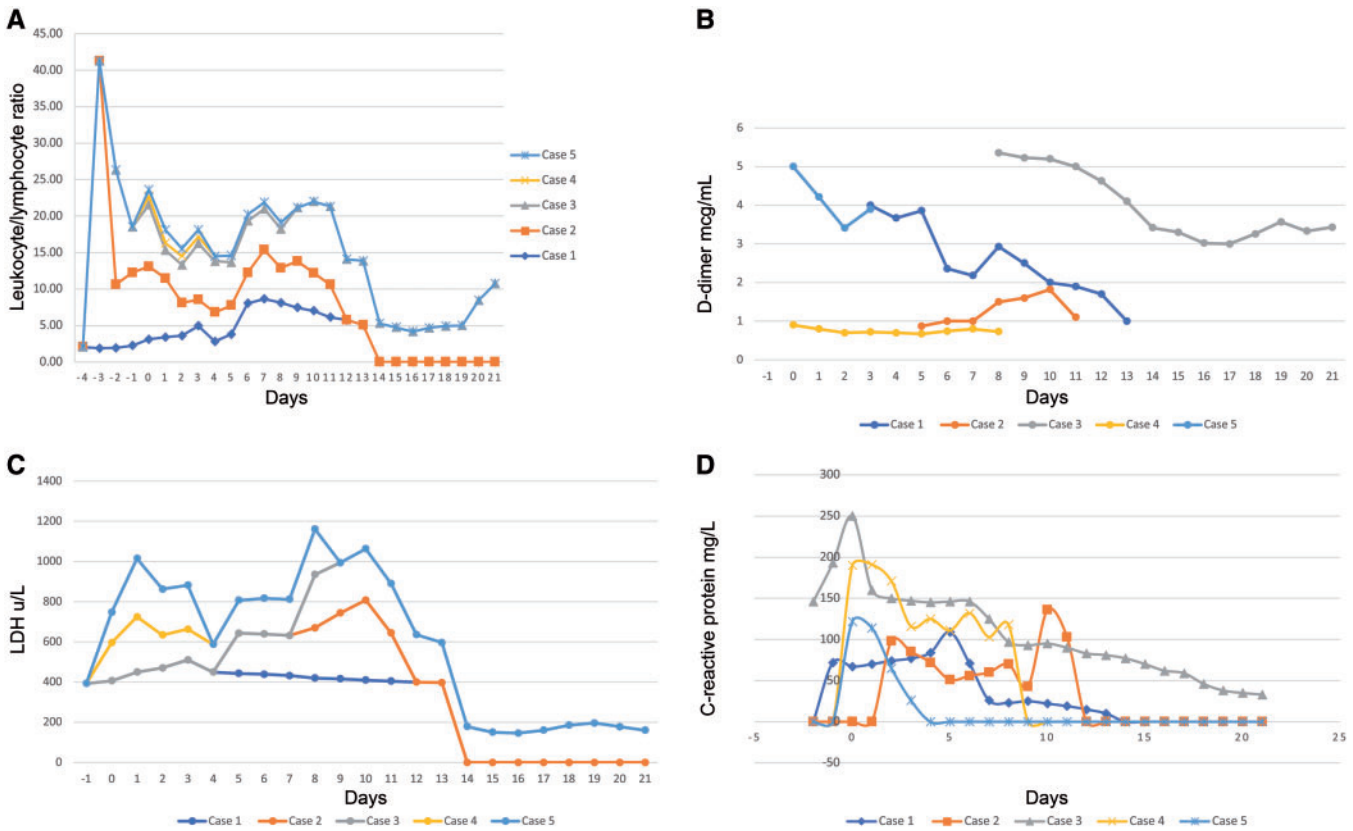

Figure 1: Laboratory findings for 5 patients with coronavirus disease 2019 during their in-hospital stays. (**A**) Leucocyte/lymphocyte ratio. (**B**) D-dimer levels. (**C**) Lactate dehydrogenase levels. (**D**) C-reactive protein levels. The 0 represents the day of onset of symptoms for the in-hospital patients (1, 2 and 3) and the day of diagnosis for the outpatients (4 and 5).

DISCUSSION

This report, to the best of our knowledge, is the first retrospective cohort study to describe the clinical characteristics and outcomes of patients infected with SARS-CoV-2 after thoracic surgical procedures in Europe.

Since the first case of COVID-19 was diagnosed at our centre, the hospital general management decided to change many divisions into COVID wards, leaving some surgical services operational, including the thoracic oncology surgery division. The rationale was then, as it is now, to cancel all elective surgical procedures during the global pandemic and create a tiered system for prioritizing other surgical procedures [12, 13]. Therefore, we selected the more advanced oncological cases, which we believed could not afford a delay in the surgery. We then concentrated on well-established, clear paths of surgical cases and ward isolation during this period. These actions allowed us to provide a high standard of care during the highest rate of infection in the country, and one of the highest worldwide [2]. We had an overall reduction of 25% of operative cases in this period compared to the same period last year and a further reduction of 44% during the highest point of the wave.

In the last 2 weeks of our study, our hospital implemented a mandatory preoperative RT-PCR screening programme no more than 24 h before the procedure, for all surgical procedures. Hence, only 4 patients were tested; none of them had positive test results or developed an infection in the postoperative period. Before that, our primary screening strategy was based on clinical-epidemiological criteria. During the studied phase of 12 weeks, our infection rate after surgery was 5%, compared with 5% and 9% reported by other groups over shorter periods [14, 15]. There was no established protocol for screening patients scheduled to have a lung transplant until right after the national state of emergency was declared on 15 March. As of 15 March, every potential lung donor must be screened using an RT-PCR assay of lower airway samples at least 24 h before the donation. Although lung transplantation completely halted nationwide from the 13 of March until the middle of May, this screening protocol was followed when the transplantation activities re-started.

Whereas 3 cases of COVID-19 infections were identified during the in-hospital postoperative period, the remaining 2 cases (20%) were diagnosed 10 and 13 days after the patients were discharged. Two of the early patients with positive test results (cases 1 and 3) (Table 2) were suspected of having acquired the disease nosocomially because they occurred during the early phase of implementation of the isolation circuits and visit-restriction policies and had long in-hospital stays before the operation. Although our centre's policy for scheduling thoracic surgical procedures is to avoid hospitalization before the scheduled date, these 2 patients were in the hospital for 37 and 44 days before the surgery, which may have contributed to the increased risk of infection, as suggested by previous reports [5] with a median stay of more than 2.5 days. The third case is suspected to be due to an operation performed during the incubation period. The COVID-19 symptoms manifested 3 days after the operation, although the SARS-CoV-2 infection was suspected and laboratory-confirmed more than a week later. The time from the operation to the onset of infection was shorter than the median incubation

time of 5 days obtained from a study of patients with confirmed SARS-CoV-2 infections in Wuhan [9] and also shorter than the overall incubation time [median time, 4.0 days (interquartile range 2.0–7.0)] derived from a study of patients with COVID-19 from 552 hospitals in China [14]. It is essential to consider that the overlap between symptoms of COVID-19 and the usual thoracic postoperative clinical course may result in a delayed diagnosis. Fever and cough are common reactions after pleural manipulation [15] as are effusions and atelectasis. Although many suffer chest tightness and fatigue, loss of appetite and nausea due to postoperative analgesics, these symptoms are usually self-limiting, and dyspnoea may be secondary to lung resection and chronic obstructive pulmonary disease. Therefore, a high level of suspicion and a well-established diagnostic protocol should be considered.

In the reported cohorts of non-surgical patients with SARS-CoV-2 in China, the proportion of severe and critical disease was 2–6.1% and 13.8%, respectively [16–18], and reports of surgical patients and the subpopulation of thoracic patients were not better. A report from 4 hospitals in Wuhan published by Lei *et al.* [5] included 34 postoperative patients who were infected with SARS-CoV-2, where 44% received care in the ICU, 32% developed acute respiratory distress syndrome and 20.6% died of the disease. Surprisingly, if we look at the group of thoracic patients in this cohort, the rate of shock, acute respiratory distress syndrome was 66% each, while death was 100%. Cai *et al.* [19] analysed a selected population of patients who had lung resections. Seven patients had an incidence of disease graded as severe, critical and fatal at 57%, 42% and 42%, respectively. Meanwhile, in the latest report from Wuhan regarding the same subpopulation, including 11 positive cases, the figures were not that different, with 27.3% severe cases, 36.4% critical and 27.3% fatal [19]. Our study did not reproduce these findings: No critical or severe cases were reported for our population, nor were any patients admitted to the ICU nor was there a statistically significant prolonged hospital stay compared with the non-infected surgical population. Remarkably, in our experience, there have been no postoperative deaths for COVID-19 infection.

Some laboratory results are to be expected to be different postoperatively. These include leucocytosis and lymphopenia, which can occur in 22–35.6% of patients within 7 days [20, 21], in addition to the increase in inflammatory reactants such as erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase or D dimer [22]. Lymphopenia and a high level of inflammatory parameters are also standard features of SARS and SARS-CoV-2 infections [23, 24] and are even used as an indicator of complications [24, 25]. These results indicate that abnormal laboratory findings in surgical patients lack specificity and may work as a confounding factor. In this series, other than a slightly higher incidence of low lymphocyte counts, there was no other useful indicator of infection or poor prognosis (Fig. 1).

The patient's immune function is a major determinant of disease severity and mortality after infection with SARS-CoV-2 [1, 26], and surgery may not only cause immediate impairment of the immune function [27] but may also induce an early systemic inflammatory response [22], which, added to the infected lung, could increase the levels of pro-inflammatory cytokines and chemokines [28, 29]. In our experience, other than minor analytical changes (hepatic enzymes, D dimer) and X-ray findings, there was little evidence of poor prognosis or bad progression of the disease in our patients after COVID-19. Therefore, we believe there is not enough evidence to change the standard care of our patients after surgery if proper isolation protocols and infection control practices are rigorously adhered to. We agree with researchers who recommend that thoracic surgeons should increase precautions, carefully select which operations are to be performed and consider replacing postoperative chest X-rays with computed tomography scans and use COVID-19, RT-PCR or serum antibody tests if persistent fever occurs [19, 30].

During February and first week March, all health care workers (HCWs) who cared for patients in the COVID-clean area were tested if any patient had a positive test result. After that, tests were limited to symptomatic HCW only. During the entire study, no member of the staff, trainee or HCW from our team had a positive test result, not even after the first cases were diagnosed. In comparison, Cai described that after the first patient had a positive test result, 3 HCW had positive test results and 6 more patients and 5 workers followed [19]. Therefore, our procedures may have contributed to reducing the risk of nosocomial transmission among the rest of the ward.

Limitations

There are some methodological limitations in this case series. Due to the retrospective nature of this analysis, the presumed date of symptom onset from medical records and personal statements may be affected by recall bias. The different types of surgical procedures may have variable impacts on clinical course and outcomes. In addition, the baseline characteristics of the patients varied with respect to underlying comorbidities. The small sample size and the lack of severe complications linked with COVID-19 infection prevented us from identifying causality or associated risk factors. All enrolled patients acquired COVID-19 infection in the Madrid area during the beginning and highest points of the outbreak, and they were operated on in a high-volume surgical centre with plentiful resources, so generalizability may be limited to similar settings as opposed to all operating settings.

CONCLUSION

In conclusion, according to preliminary data from China and Italy, cancer and other comorbidities may increase the number of deaths of patients with COVID-19. However, much uncertainty remains because the observations may be the result of malignancy, treatment effects or both. For thoracic surgery patients, the risk of tumour progression with the delay of definitive surgery cannot be ignored. These results indicate that surgery in properly selected cases, with short preoperative in-hospital stays, strict isolation and infection control protocols and a dedicated multidisciplinary team, could be performed with relatively low risk for the patient.

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Conflict of interest: none declared.

Author contributions

Lucas Hoyos Mejia: Conceptualization; Data curation; Investigation; Methodology; Project administration; Writing—original draft; Writing—review & editing. **Alejandra Romero Román:** Data curation; Formal analysis; Investigation; Resources. **Mariana Gil Barturen:** Data curation; Formal analysis; Software; Validation. **María de Mar Córdoba Páez:** Conceptualization; Investigation; Methodology; Project administration. **José Luis Campo-Cañaveral de la Cruz:** Validation; Writing—review & editing. **José Manuel Naranjo:** Visualization; Writing—review & editing. **Silvana Crowley Carrasco:** Writing—review & editing. **Shin Tanaka:** Conceptualization; Writing—review & editing. **Alvaro Sanchez Calle:** Visualization. **Andrés Varela de Ugarte:** Writing—review & editing. **David Gómez de Antonio:** Supervision; Validation; Visualization; Writing—review & editing.

Reviewer information

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