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## Full title:

# Impact of COVID-19 lockdown on in-hospital mortality and surgical activity in elective digestive resections. A nationwide cohort analysis

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## Category:

Original article

# Abstract

## Background:

The outbreak of COVID-19 infection has led to the reorganization of hospital care in several countries. The objective was to report the postoperative mortality after elective digestive resections in a nationwide cohort during the lockdown period.

## Method:

This analytic study was performed using a national billing database (*PMSI*). Patients who underwent elective digestive resections were divided into two groups: the lockdown group defined by hospital admissions between March 17<sup>th</sup> and May 11<sup>th</sup> 2020; and the control group, defined by hospital admissions during the corresponding period in 2019. Groups were matched on propensity score, geographical region, and surgical procedure. The primary outcome was the postoperative mortality.

## Results:

The overall population included 15,217 patients, 9325 patients in the control group and 5892 in the lockdown group. The overall surgical activity was decreased by 37% during the lockdown period. The overall in-hospital mortality during the hospital stay was 2.7%. After matching and adjustment, no difference in mortality between groups was reported (OR=1.05; 95%CI: 0.83–1.34; p=0.669). An asymptomatic COVID-19 infection was a risk factor for a twofold increased mortality whereas a symptomatic COVID-19 infection was associated with a tenfold increased mortality.

## Conclusions:

Despite a considerable reduction in the surgical activity for elective digestive resections during the lockdown period, mortality remained stable on a nationwide scale in COVID-free patients. These findings support that systematic SARS-CoV-2 screening should be advocated prior to elective gastrointestinal surgery and that all efforts should be made to maintain elective surgical resection for cancer during the second wave in COVID-free patients.

# Introduction

The outbreak of COVID-19 infection has led to the reorganization of hospital care in several countries. In France, on March 12<sup>th</sup> 2020, the government imposed national restrictions to elective surgery. Several guidelines were rapidly published to help surgeons to adapt their practice to the pandemic context.(1-7)

The first reason for postponing elective surgery was optimizing manpower and healthcare resources to favour COVID-19 patients' treatment, impacting the overall activity. The COVIDSurg collaborative study estimated a worldwide decrease in elective surgery of about 70%, representing more than 28 million people during 3 months of disruption with a major effect on benign disease surgery.(8) The same trend has been estimated in France, in 14 academic hospitals, with a reduction of 50% of elective colorectal surgeries during the lockdown period.(9) Nevertheless, it has been suggested that these estimations could be biased because of a possible transfer of oncological patients from hospitals massively impacted by COVID-19 (especially public and academic hospitals) to institutions less involved in COVID-19 management (in particular, private institutions). (9)

The second reason for this strategy was the prevention of hospital-acquired COVID-19 infection for surgical candidates and the prevention of postoperative complications in COVID-19-positive patients.(5, 10, 11) In fact, a study by Aminian et al. reported an uncommonly high mortality rate after four frequent procedures during the COVID-19 pandemic: cholecystectomy, hernia repair, gastric bypass, and hysterectomy.(12) These findings were confirmed by the work of the COVIDSurg collaborative that reported a 30-day mortality rate of 24% in over 1100 COVID-19 patients after elective surgery.(13) Mortality was strongly associated with postoperative pulmonary complications, especially in elderly men (age >70 years).

The bias of data mostly reported from high-volume hospitals (not representative of the entire healthcare system) could be amended by information on a larger scale. Nationwide solid data on the decrease of elective surgery during the lockdown period are lacking.(14-16)

The objective of the present study was to assess the impact of lockdown on postoperative mortality and on surgical activity in elective digestive surgery on a national scale using administrative data covering the entire healthcare system in France.

# Methods

## Study design

This is an analytical observational study comparing surgical activity during the COVID-19 pandemic lockdown with the surgical activity of a historical control group from the corresponding period of 2019.

Data were collected from a National Health Database (the *Programme de Médicalisation des Systèmes d'Informations*, PMSI), which is a mandatory billing tool for all hospital stays in France, either for public or private institutions.(17) The purpose of this database is to establish the financial budget of hospitals based on the number of patients admitted and the type of procedures performed. Information in the database includes patient and hospital identifier, length of stay, date of admission and discharge, any diagnosis reported according to the international classification of diseases, 10<sup>th</sup> version (ICD-10), and any surgical procedure coded according to specific procedural classification (the *Classification Commune des Actes Médicaux*, CCAM), which is used in France to classify any surgical, endoscopic or radiological act. (18) The validity of this database has been tested by cross-referencing with other cohort databases. (19-21) Access to the database was requested from and granted by the National Commission on Informatics and Liberty (CNIL). As the identifier is anonymous, patient consent was not required.

## Population

All adult patients operated on for elective digestive resections, as defined by Appendix 1, were included. These comprised oesophageal, gastric, colic, rectal, pancreatic, and hepatic resections. Patients with multiple resections (more than 2 procedures) and patients undergoing emergency surgery (defined by a hospital admission after an emergency department visit) were excluded.

All data from January 1<sup>st</sup> 2019 to June 30<sup>th</sup> 2020 were extracted from the database. Two groups were created: the lockdown group defined by hospital admissions between March 17<sup>th</sup> 2020 and May 11<sup>th</sup> 2020, corresponding to the lockdown period in France, and the control group selected as hospital admissions occurring between March 19<sup>th</sup>, 2019 and May 13<sup>th</sup> 2019 (i.e., corresponding to the same calendar days, from the 2<sup>nd</sup> day of the 12<sup>th</sup> week of the year, to the 1<sup>st</sup> day of the 20<sup>th</sup> week of the year).

## Covariates

Patient characteristics and demographics extracted from the database included: age, gender, hospital, and region. The ICD-10 codes of previous hospital stays in the past 3 years were used in order to calculate the comorbidity index according to the Charlson Comorbidity Index (CCI) defined in Appendix 2, and neoadjuvant chemotherapy or radiotherapy (codes Z511 and Z510).(22, 23) Nutritional status (E43, E44, E46) and obesity (E66) were also recorded.

Data on the type of surgical resection were collected. Different groups of surgery were created in order to match patients: esophagectomy; total and partial gastrectomy; right, transversal, left and total colectomy; low anterior rectal resection, rectal resection associated with colo-anal anastomosis, total colo-proctectomy with ileo-anal anastomosis, abdomino-perineal resection and prolapsus surgery; minor or major ( $\geq 3$  segments) hepatectomy; pancreatic head or other pancreatic resections.

The volume of resection per week per centre was categorized using the quartiles of surgical activity.

The COVID-19 infection status was defined according to the ICD-10<sup>th</sup> codes, and classified as symptomatic (U0710, U0711, U0714, and U0715) or asymptomatic (U0712 and U0713) defined in the appendix 3. A high viral spreading zone was defined as a rate over 0.1 of outpatients for COVID-19 at emergency departments in a region or as a rate over 0.8 of intensive care unit hospitalization for COVID-19 in a region on 4<sup>th</sup> May, 2020 (governmental announcement defining the type of zone).

## Outcomes

The primary outcome was the in-hospital postoperative mortality, which is defined as death occurring during the hospital stay for surgery, irrespective of the time between the surgery and the event.

The secondary outcomes were the change in the number of hospital admissions for digestive surgery and in the postoperative morbidity rate. The decrease in surgical activity was calculated by reporting the difference between 2020 and 2019. In the assessment of postoperative morbidity, we included the following complications: surgical site infection; bleeding; thromboembolic disease; pulmonary complication; and renal failure. The ICD-10 codes used to identify any selected complication are reported in Appendix 3.

## Statistical analysis

Description of data was performed with absolute values and percentage for categorical variables and mean and standard deviation for continuous variables. Univariate analysis was realized with a univariate general linear model. A propensity score was calculated on the probability of being operated on in 2020 using the age, gender, CCI, (22, 23) nutritional status, cancer status, neoadjuvant chemotherapy or radiotherapy, and hospital volume. A matching between the lockdown and control groups was performed using the nearest neighbour for propensity score and the exact method for surgical procedure and region, in order to perfectly match on the same procedure in the same region where the surgery was performed. A multivariate analysis for in-hospital mortality was conducted on this matched population including the group (lockdown and control) and type of COVID-19 infection (none, asymptomatic, symptomatic) in a general linear model. The same type of analysis was performed using morbidity as dependent variable. Odds ratio (OR) and 95% confidence intervals (CI) were estimated. Statistical analyses were performed with R software. The R-package *Matchit* was used to perform the group matching.(24, 25)



# Results

## Characteristics of the study population

The overall population included 15,217 patients, 5,892 in the lockdown group and 9,325 in the control group. Patients' characteristics are summarized in Table 1. The mean age was  $65 \pm 15$  years, with 54% being male patients. In the lockdown group, there were more severe patients as the CCI was higher (control= $2.2 \pm 2.7$  vs. lockdown= $2.3 \pm 2.5$ ,  $p < 0.0001$ ), with a higher prevalence of resection for cancer (control= 5791, 62% vs. lockdown=4445, 75%;  $p < 0.0001$ ). Moreover, neoadjuvant chemotherapy or radiotherapy were more common among patients in the lockdown group (control=1,504, 16% vs. lockdown=1,064, 18%;  $p = 0.002$ ). In total, 574/5892 (8.7%) surgical patients were diagnosed COVID-19 positive in 2020, and 61 (1.0%) were classified as symptomatic. The characteristics according type of COVID-19 infection is reported in the appendix 4. Patients with infection were more severe patients as the CCI was higher, with a higher rate of malnutrition. The most common symptom of COVID-19 infection was respiratory symptoms ( $n = 56/61$ , 92%).

## Decrease in surgical activity

Figure 1 compares the overall surgical activity during 2019 and 2020. The overall activity decreased by 37% during the lockdown period. The lowest activity per week occurred during the 15<sup>th</sup> week of 2020 (6<sup>th</sup>–12<sup>th</sup> April 2020). A resumption of activity was observed the week after the lockdown without reaching the activity of 2019. The drop of activity in 2019 between the 15<sup>th</sup> and 24<sup>th</sup> weeks occurred during the Easter holidays and national holidays.

Table 2 reports the decrease in activity by type of surgery. Hepatic resections were the most impacted by the lockdown with a significant decrease of 44% ( $p = 0.02$ ). The decrease was more important in a high viral propagation zone (high viral spreading zone: 44%, low viral spreading zone: 32%,  $p < 0.001$ ).

The decrease of "high" volume center (> more than 4 resections by week) was more important than the decrease of activity of lower volume center ( $p = 0.001$ ).

## Mortality during the lockdown period

The in-hospital mortality was 2.5% ( $n = 233/9325$ ) in the historical control group and 3.0% ( $n = 174/5892$ ) in the lockdown group ( $p = 0.1$ ). After matching, 5823 patients were included in each group. The

characteristics of patients after matching are presented in Appendix 4. There was no significant difference between groups in the variables included in the propensity score, region, and type of surgery.

The multivariate analysis on in-hospital mortality is reported in Table 3. There was no difference in mortality before and after adjustment on COVID-19 infection between the two groups (OR: 1.05 [95%CI: 0.83–1.34],  $p=0.669$ ). An asymptomatic COVID-19 infection was a risk factor for a twofold increased mortality (OR=2.00, 1.27–3.05,  $p=0.002$ ), whereas a symptomatic COVID-19 infection was associated with a tenfold increased mortality (OR=10.51, 5.35–19.31,  $p<0.001$ ).

## Postoperative complications

Table 3 reports postoperative complications. In the univariate analysis on the matched groups, overall morbidity and other postoperative complications were not different between the control and lockdown groups. In the multivariate analysis, the lockdown group was not associated with higher overall morbidity (OR: 0.95 [95%CI: 0.87–1.03],  $p=0.227$ ).

The overall morbidity was higher in the asymptomatic group compared to the COVID-19-free group (No infection= 27% vs. Asymptomatic=47%,  $p<0.001$ ) and even higher in the symptomatic group (No infection= 27% vs. Symptomatic=80%,  $p<0.001$ ). The rates of pulmonary complications, surgical site infection, and thromboembolic disease were higher for COVID-19-infected patients compared to COVID-19-free patients.

## Discussion

In this nationwide data analysis, the overall postoperative mortality after elective digestive surgery during the COVID-19 pandemic lockdown was comparable to the mortality rate observed during the same period in 2019. However, COVID-19 infection, either symptomatic or asymptomatic, was a strong independent risk factor of postoperative mortality and morbidity. We observed a reduction of more than 3400 procedures (37%) in gastrointestinal surgical resections during the lockdown.

During the most acute phase of the pandemic, several national and international guidelines indicated that nonurgent surgery had to be postponed in order to allocate more resources to COVID-19 patients' care. (1, 2, 10, 26) Elective surgery decreased more markedly in regions where the viral surge was higher, probably due to restrictions to favour COVID-19 patients' treatment. As reported in other countries, reduction of activity was motivated by reallocation of anaesthesiologists, nursing staff and mechanical ventilators in medical-COVID-19 units or ICU-COVID-19 units. (27, 28) Soreide et al. furthermore described operating theatres and surgical intensive care units converted to rescue additional ICU units for severe COVID patients requiring mechanical ventilation.(29) Those facts contributed to a higher decrease in surgical activity, especially in high viral spreading zones.

In our study, despite the important reduction in elective surgery during the lockdown period, the percentage of patients operated on for cancer increased. In fact, all guidelines published in that context recommended to postpone nonurgent elective surgery, primarily delaying surgery for benign conditions. This could explain why in 2020 patients were older and presented with more severe comorbidities. (8, 10) In the present study, the comparison between groups showed a greater proportion of patients who had a higher Charlson Comorbidity Index and received neoadjuvant treatment during the lockdown period.

For the overall population, we did not observe any significant difference in postoperative mortality between the lockdown period and the corresponding period in 2019, before and after matching. The only increase was observed in the COVID-19-infected population, as already reported by several

authors. Effectively, we reported a twofold increased mortality for asymptomatic COVID-19 infection, whereas a symptomatic COVID-19 infection was associated with a tenfold increased mortality. Doglietto et al. analysed 41 surgical patients with positive results at the COVID-19 screening and showed results similar to ours in symptomatic COVID-19 patients.(30) The COVIDSurg collaborative study also reported a mortality rate of 24% for patients undergoing surgery with an active COVID-19 infection.(13) The observed increase in mortality rate in the COVID-19-positive patients supports the need for systematic screening prior to elective surgery and we think that, whenever possible, elective surgery for cancer in COVID-19-free patients should not be delayed in order to limit a potential increased risk of over staging. This fact is supported by a recent study showing a low risk of postoperative mortality for patients operated on for oncologic elective surgery with a COVID-19-free surgical pathway.(31) In light of these results, we think that surgery for benign disease or for early cancer should be postponed after a positive screening. On the other hand, for locally advanced cancer, in case of symptomatic COVID-19 infection, the surgery should be delayed because of a high risk of post-operative death. In case of asymptomatic COVID-19 infection, the decision should be discussed in multidisciplinary staff included anaesthesiologist, oncologist and surgeon.

The analysis of postoperative morbidity showed increased risks of several complications after COVID-19 infection in patients operated on in 2020 such as: thromboembolic disease, surgical site infection and pulmonary complications. This finding is consistent with other studies.(8, 30) Doglietto et al. also reported 10% of thrombotic complications and 60% of pulmonary complications for COVID-19 patients group (n=41).(30)

This study has some limitations. First, the real impact of COVID-19 infection on postoperative mortality and morbidity should be interpreted with caution. Data on systematic screening in each institution and delay of reverse transcription polymerase chain reaction prior to surgery were not available. Hence, undiagnosed asymptomatic patients could have been assigned to the COVID-free group. This ascertainment bias has already been suggested for the aforementioned study of the COVIDSurg collaborative, and could also be argued in our analysis. (32) Moreover, the mortality of COVID-19 patients could be associated to a more severe patient status, not permitting to postpone surgery. We

tried to limit this bias by excluding patients operated in an emergency setting, and adjusting for neoadjuvant treatment and surgery for cancer in the statistical analysis. We think that the strong association between mortality and COVID-19 status could not be only attributed to a selection bias. Secondly, the PMSI database does not allow accurate screening of the cause of death because of unavailable information.

The main strength of this study is the data source. As the PMSI database is mandatory for all hospitals and clinics, it gives a pragmatic and comprehensive picture of the surgical activity on a national scale, allowing a true assessment of in-hospital mortality.

## Conclusion

Despite a considerable reduction in the surgical activity for elective digestive resections during the lockdown period, mortality remained stable on a nationwide scale in COVID-free patients. In contrast an asymptomatic COVID-19 infection was a risk factor for a twofold increased mortality, whereas a symptomatic COVID-19 infection was associated with a tenfold increased mortality.

These findings support that systematic SARS-CoV-2 screening should be advocated prior to elective GI surgery and that all efforts should be made to maintain elective surgical resection for cancer during the second wave of the pandemic viral infection in COVID-free patients.

## Legend

**Figure 1.** Overall digestive elective resections according years per weeks

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**Table 1.** Characteristics of patients

Variable		Control (n=9325)	Lockdown (n=5892)	p-value
Age, mean (sd)		65 ± 15	66 ± 14	< 0.001
Male		4951 (53)	3225 (55)	0.05
Obesity		1251 (13)	764 (13)	0.44
Malnutrition		2129 (23)	1339 (23)	0.90
Charlson score, mean (sd)		2.18 ± 2.65	2.34 ± 2.53	< 0.001
Charlson score categorization	0	3,458 (37)	1,719 (29)	< 0.001
	1-2	3509 (38)	2608 (44)	
	3-4	1046 (11)	755 (13)	
	>4	1312 (14)	810 (14)	
Number of resections per week per center	0-1	1,931 (21)	1,154 (20)	0.02
	>1-2	2135 (23)	1416 (24)	
	>2-4	2999 (32)	1915 (33)	
	>4-17	2260 (24)	1407 (24)	
Resection for cancer		5791 (62)	4445 (75)	< 0.001
Neoadjuvant chemotherapy or radiotherapy		1504 (16)	1064 (18)	0.002
Type of Covid infection	No infection	9,325 (100)	5,318 (90)	< 0.001
	Asymptomatic	0 (0)	513 (9)	
	Symptomatic	0 (0)	61 (1)	

Data are reported as nb (%) unless otherwise specified.



**Table 2.** Description of surgical activity according group

Type of surgery	Control (n=9325)	(%)	Lockdown (n=5892)	(%)	(%) of decrease 37	P value
<b>Oesophagectomy</b>	209	<b>(2)</b>	109	<b>(2)</b>	48	0.11
<b>Gastrectomy</b>	390	<b>(4)</b>	263	<b>(4)</b>	33	0.42
Total	148	(2)	146	(2)	1	
Other	242	(3)	117	(2)	52	
<b>Colectomy</b>	<b>5022</b>	<b>(54)</b>	<b>3200</b>	<b>(54)</b>	<b>36</b>	<b>0.59</b>
Right	2292	(25)	1687	(29)	26	
Transversal	157	(2)	95	(2)	39	
Left	2336	(25)	1265	(21)	46	
Total	237	(3)	153	(3)	35	
<b>Rectal resection</b>	<b>2143</b>	<b>(23)</b>	<b>1361</b>	<b>(23)</b>	<b>36</b>	<b>0.88</b>
Low anterior resection	1563	(17)	1011	(17)	35	
Colo-anal or ileo-anal anastomosis	362	(4)	258	(4)	29	
Abdomino-perineal resection	99	(1)	62	(1)	37	
Prolapsus resection	119	(1)	30	(1)	75	
<b>Hepatic resection</b>	<b>988</b>	<b>(11)</b>	<b>555</b>	<b>(9)</b>	<b>44</b>	<b>0.02</b>
Minor	747	(8)	416	(7)	44	
Major	241	(3)	139	(2)	42	
<b>Pancreatic resection</b>	<b>573</b>	<b>(6)</b>	<b>404</b>	<b>(7)</b>	<b>29</b>	<b>0.08</b>
Head	377	(4)	270	(5)	28	
Others	196	(2)	134	(2)	32	
<b>Volume of center in 2019</b>						
Low ≤ 2 per week	3223	(36)	2212	(38)	31	0.001
Medium 2-4 per week	2690	(29)	1624	(28)	39	
High >4 per week	3412	(35)	1997	(34)	41	

Data are reported as nb (%) unless otherwise specified.

**Table 3.** Impact of the Lockdown on mortality and morbidity compared to control group on the matched population and adjusted on the COVID-19 infection

		No death N = 11337	Death N = 309	OR (univariable)	OR (multivariable)
Group	Control	5684 (50)	139 (45)		
	Lockdown	5653 (50)	170 (55)	1.23 (0.98-1.54, p=0.074)	1.05 (0.83-1.34, p=0.669)
COVID-19 infection	No infection	10805 (95)	271 (88)		
	Asymptomatic	484 (4)	25 (8)	2.06 (1.32-3.07, p=0.001)	2.00 (1.27-3.05, p=0.002)
	Symptomatic	48 (1)	13 (4)	10.80 (5.56-19.58, p<0.001)	10.51 (5.35-19.31, p<0.001)

Data are reported as nb (%) unless otherwise specified.

**Table 4.** Univariate analysis of mortality and morbidity for 2020 patients according to COVID-19 infection status

Outcomes	No infection (n=5318)	Asymptomatic (n=513)	Symptomatic (n=61)	p-value (no infection vs asymptomatic)	p-value (no infection vs symptomatic)
<b>Mortality</b>	136 (2.6)	25 (4.9)	13 (21.3)	< 0.001	< 0.001
<b>Overall morbidity</b>	1459 (27.4)	240 (46.8)	49 (80.3)	< 0.001	< 0.001
<b>Bleeding</b>	343 (6.4)	44 (8.6)	6 (9.8)	0.08	0.42
<b>Surgical site infection</b>	744 (14.0)	127 (24.8)	19 (31.1)	< 0.001	< 0.001
<b>Thromboembolic disease</b>	172 (3.2)	28 (5.5)	7 (11.5)	0.01	0.001
<b>Pulmonary infection</b>	155 (2.9)	62 (12.1)	38 (62.3)	< 0.001	< 0.001
<b>Pulmonary insufficiency</b>	305 (5.7)	88 (17.2)	24 (39.3)	< 0.001	< 0.001
<b>Overall pulmonary complications</b>	395 (7.4)	116 (22.6)	40 (65.6)	< 0.001	< 0.001
<b>Renal insufficiency</b>	327 (6.1)	60 (11.7)	13 (21.3)	< 0.001	< 0.001

Data are reported as nb (%) unless otherwise specified.

Figure 1. Overall digestive elective resections according years per weeks

