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Appendectomy During the COVID-19 Pandemic in Italy. A Multicenter Ambispective Cohort Study by the Italian Society of Endoscopic Surgery and new technologies (the CRAC study).

Alberto Sartori
Presidio Ospedaliero di Montebelluna
Mauro Podda (mauropodda@ymail.com)
Department of Emergency Surgery, Cagliari University Hospital, Cagliari (Italy) https://orcid.org/0000-0001-9941-0883
Emanuele Botteri
Department of Surgery, Montichiari Hospital
Roberto Passera
Division of Nuclear Medicine, University of Torino
Alberto Arezzo
University of Turin Department of Surgical Sciences: Universita degli Studi di Torino Dipartimento di Scienze Chirurgiche
Ferdinando Agresta
Adria Hospital: Ospedale di Adria

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Abstract

Background To determine on a national basis the surgical activity regarding appendectomies during the first Italian wave of the COVID-19 pandemic.

Major surgical societies advised using non-operative management of appendicitis and suggested against laparoscopy during the COVID-19 pandemic.

Methods Multicenter, observational study investigating the outcomes of patients undergoing appendectomy in the two months of March-April 2019 vs. March-April 2020. The primary outcome was the number of appendectomies performed during each of the two months, classified according to the American Association for the Surgery of Trauma (AAST) score. Secondary outcomes were the type of surgical technique employed (laparoscopic vs. open), and the complication rates.

Results 1541 patients with acute appendicitis underwent surgery during the two study periods. 1337 (86.8%) patients met the study inclusion criteria. 546 (40.8%) patients underwent surgery for acute appendicitis in 2020 and 791 (59.8%) in 2019. Patients with complicated appendicitis operated in 2019 were 76 (9.6%) vs. 87 (15.9%) in 2020 ($p = 0.001$). An increase in the number of post-operative complications was found in 2020 (15.9%) compared to 2019 (9.6%) ($p < 0.001$). The following determinants increased the likelihood of complication occurrence: undergoing surgery during 2020 (+ 67%), having a unit AAST (+ 26%) increase, having waited for surgery > 24 h (+ 58%), being the surgeon aged > 40 years (+ 47%), undergoing open surgery (+ 112%) and being converted to open surgery (+ 166%).

Conclusions In Italian hospitals, in March and April 2020, the number of appendectomies has drastically dropped. Patients undergoing surgery during the first pandemic wave were more frequently affected by more severe appendicitis than the previous year's timeframe and a higher complication rate was reported.

Trial registration: ResearchRegistry ID 5789.

Background

With about 60 million global infections and more than 1,5 million deaths at the end of 2020, the COVID-19 pandemic has radically changed the world [1]. Hospitals and healthcare systems had to face a significant number of infected patients needing treatment. Consequently, surgical activity has been significantly reduced in the elective setting, which was calculated in a reduction of about 30 million surgical procedures worldwide in a period of 12 weeks [2]. Nevertheless, emergency and oncological surgery cannot be postponed, so surgeons issued their recommendations [3–5] suggesting caution while performing surgery. Especially at the beginning of the pandemic, major surgical societies and colleges clearly advised using non-operative management of appendicitis and suggested against laparoscopy [6–7].

In the beginning, the main focus was the safety of the operators, but later came first the potential worsening of SARS-CoV-2 pneumonia, which has shown a high lethality rate, especially after surgery under general anesthesia [2]. Despite the growing consciousness of the phenomenon, very little attention focused to the effects of the delay in diagnosis and management of surgical diseases. A recent international web survey reported increased non-operative management of acute appendicitis during the COVID-19 outbreak [8].

The lifetime risk of acute appendicitis is 6,7% for women and 8,6% for males [9]. It is estimated that about 300.000 patients in the U.S. undergo appendectomy annually, with a raw incidence of 98 cases/100,000 people [10]. Even though the option of non-operative management can be proposed as an initial approach for uncomplicated cases [11], laparoscopic appendectomy remains the gold standard for the treatment of appendicitis [12].

The present study aims to evaluate on a national basis the surgical activity regarding appendectomy during the first wave of the Italian COVID-19 pandemic that occurred between march and April 2020, in comparison with the same time interval of the previous year.

Methods

The CRAC study (ChiRurgia Appendiciti COVID-19, COVID-19 Appendicitis Surgery) is a national multicenter, observational ambispective study to assess the surgical outcomes of patients undergoing an appendectomy. The study compares data collected in the two months of March-April 2019 with those of March-April 2020. The study was endorsed by the Italian Society of Endoscopic Surgery and new technologies (SICE). The study obtained the approval of the Ethical Committee for Clinical Trials of Treviso and Belluno on May 7th, 2020 (ID: approval 883/CE Marca, Italy).

One-hundred fifty-eight surgical units of the 448 units registered in the Italian Ministry of Health registry (35%) adhered to the study, and 113 (71.5%) contributed to sharing data. Data were collected through a Google form. The study's primary outcome was the number of appendectomies performed during each of the two months, classified according to the American Association for the Surgery of Trauma (AAST) score [13]. Secondary outcomes were the type of surgical technique (laparoscopic vs. open), the number of complications classified according to the Dindo-Clavien grading system, and the mortality at 30 days [14]. Inclusion criteria were age > 18 years and occurrence of appendectomy not associated with other surgical procedures. Gender, age, year of surgery, and AIR score were collected for each included patient [15]. For each included patient, we also analyzed the delay of appendectomy since the diagnosis (less or more than 24 hours) and the conversion to open in case of a laparoscopic approach. The following post-operative data were collected: hospital stay, length of antibiotic therapy (short = 1 day, medium = 2–5 days, long > 5 days), the rate of post-operative complications (30-day follow-up), and their classification according to Dindo-Clavien, the eventual occurrence of radiological re-intervention within 30 days and/or surgical re-intervention within 30 days from surgery, and the mortality within 30 days.

Statistical Analysis

Descriptive and Inferential Statistics

The descriptive statistics for continuous variables were reported as the median-interquartile range (IQR), while those categorical were absolute/relative frequencies. The inferential statistics, either the Mann-Whitney/Kruskal Wallis or the Fisher exact test, were applied to continuous and categorical covariates. A complete set of the uni-and multivariate binary logistic regression model estimated the likelihood of a surgical complication occurrence (dependent variable in statistics, target in machine learning). Nine predictors (independent variables in statistics, features in machine learning) were tested for their potential impact on complications: three were treated as continuous (age, AIR and AAST scores), while the other six as categorical (sex [male vs. female], the year during which surgery was performed [2020 vs. 2019], surgery timing [≥ 24 vs. <24 h], age of the surgeon [≥ 40 vs. <40 yrs], the surgical technique [laparotomy vs. laparoscopy] and conversion to laparotomy [yes vs. no]). AIR and AAST, despite their categorical ordinal nature, were treated as continuous covariates due to the high number of levels (risk of over-parametrization). All p-values were obtained by the exact two-sided method at the conventional 5% significance level. Data were analyzed as of December 2020 using R 4.0.3 packages Lares version 4.9.8 and h2o version 3.32.0.1 [16].

Development and Validation of ML Models

The function h2o_automl of the R package lares was applied to access H2O for R, an open-source distributed machine learning (ML) platform [17–18]. Six different supervised ML algorithms for binomial classification were trained for target prediction (complications occurrence): GLM (Generalized Linear Model), GBM (Gradient Boosting Machine), XGBoost (Extreme Gradient Boosting machine), Distributed Random Forest (DRF), DNN (multilayer artificial Deep Neural Network) and NB (Naïve Bayes classifier) as well as two Stacked Ensemble models, one containing all the models, the second only the best from each algorithm class. For all models, the target was balanced in the training data via resampling, and no missing-values replacement was needed (only four data were missing). The original dataset was randomly split for train into 80% training set and 20% test one; to decrease the risk of model overfitting, five-fold cross-validation was used to compare the classifiers. The model's performance was investigated on the test set, and the best prediction performance was identified by the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curve.

Results

Demographic characteristics of the cohort

The database included 1541 patients with acute appendicitis who underwent surgery during the ambispective periods, of whom 1337 (86.8%) adhered to the study inclusion criteria and therefore represented the cohort of the study in the analysis. The study flow diagram is shown in Fig. 1.

Five-hundred forty-six patients (40.8%) underwent surgery for acute appendicitis in 2020 and 791 (59.8%) in 2019, with a decreased appendectomy rate between the two study periods of 31%. Five-hundred sixty-three patients were female (42.1%), and 774 were male (57.9%). The median age of the patients was 38 years (IQR 25–55). The surgical technique used was laparoscopy in 1206 (90.2%) cases and laparotomy in 131 (9.8%), while the conversion rate was 62 (4.2%). Surgery was performed within 24 hours from admission in 1108 (80.8%) patients and > 24 hours in 229 (19.2%) of cases. All patients received perioperative antibiotics: 680 (50.9%) received a short course therapy, 158 (11.8%) a medium course therapy, and 499 (37.3%) a long course therapy. The median hospital stay was three days (IQR 2–5). Complications were reported in 163 (12.2%) patients, while no complications occurred in 1174 patients (87.8%). Further treatment was necessary for 69 (5.2%) patients within 30 days from the surgical operation, of whom 15 patients (1.1%) required a radiological intervention and 54 (4%) patients required further surgery. Three patients (0.2%) died within 30 days from surgery due to sepsis.

Outcomes of patients undergoing appendectomy in 2019 vs. 2020

The median age of the patients operated in 2019 was 37 years (IQR 25–64) vs. 39 years (IQR 23–65) of those operated in 2020 ($p = 0.526$). Surgery was delayed > 24 hours from the admission for 146 (18.5%) patients in 2019 vs. 83 (18.5%) in 2020 ($p = 0.122$). An open technique was used in 77 (9.7%) patients during 2019 vs. 54 (9.9%) during 2020 ($p = 0.926$). Conversion to open was necessary in 31 (3.9%) patients in 2019 vs. 31 (5.7%) during 2020 ($p = 0.147$). Seventy-six patients (9.6%) had a complicated appendicitis in 2019 vs. 87 (15.9%) in 2020 ($p = 0.001$).

In 2019, 684 (58.3%) patients were operated on by surgeons aged > 40 years, whereas in 2020 whereas in 2020, surgeons aged > 40 years performed the majority of appendectomies (117, 71.8%, $p = 0.001$). The analysis of the complications according to the Dindo-Clavien grading system showed a statically significant increased rate of adverse events in 2020 (87 cases, 15.9%) compared to 2020 (76 cases, 9.6%) ($p < 0.001$).

The median post-operative hospital stay in 2019 was three days (IQR 2–4) vs. three days (IQR 2–5) in 2020 ($p = 0.722$). The mortality rate was 0.25% in 2019 and 0.2% in 2020. Data about the cohort of patients stratified by year of surgery are summarized in Table 1.

Table 1
Patients' characteristics: Cohort of patients stratified by year of surgery.

Variable	Patients operated during 2019 (791)	Patients operated during 2020 (546)	*P*
Age: years (IQR)	37(25–64)	39 (23–65)	0.526
Gender (M vs. F). N. patients (%)	435 (55.0%)	339 (62.1%)	0.011
Complications. N. patients (%)	76 (9.6%)	87 (15.9%)	0.001
AIR score. N. patients (%)			0.036
1–4	193 (24.1%)	111 (20.3%)	
5–8	498 (62.9%)	333 (60.9%)	
9–12	100 (12.6%)	102 (18.6%)	
AAST score. N. patients (%)			0.008
1	379 (47.9%)	223 (40.8%)	
2	172 (21.7%)	105 (19.2%)	
3	82 (10.4%)	69 (12.6%)	
4	115 (14.5%)	112 (20.5%)	
5	43 (5.4%)	37 (6.8%)	
Surgery timing (≤ 24 vs. >24 h): N. patients (%)	146 (18.5%)	83 (15.2%)	0.122
Surgical approach (lap vs. open): N. patients (%)	77 (9.7%)	54 (9.9%)	0.926
Conversion to open (no vs. yes): N. patients (%)	31 (3.9%)	31 (5.7%)	0.147
Age of the operating surgeon (≤ 40 vs. >40 yrs): N. patients (%)	684 (58.3%)	117 (71.8%)	0.001
Antibiotic prophylaxis/therapy (short pr- long pr- ther): N. patients			0.247
Short course	97 (12.3%)	61 (11.2%)	
Medium course	306 (38.7%)	192 (35.2%)	
Long course	387 (49.0%)	293 (53.6%)	

Variable	Patients operated during 2019 (791)	Patients operated during 2020 (546)	*P*
Dindo score. N. patients (%)			< 0.001
0	2 (0.3%)	2 (0.4%)	
1	664 (84.1%)	402 (73.8%)	
2	95 (12.0%)	108 (19.8%)	
3	19 (2.4%)	29 (5.3%)	
4	8 (1.0%)	3 (0.6%)	
5	2 (0.3%)	1 (0.2%)	
Hospital stay: days (IQR)	3 (2–4)	3 (2–5)	0.722

Post-operative complications

A post-operative complication was registered in 163 patients, while 1174 patients did not experience any adverse outcome following an appendectomy.

Eighty-seven (53.4%) patients with post-operative complications were operated on in 2020.

Thirty-two patients (19.6%) who had post-operative complications were operated on with an open technique ($p < 0.001$), while for 19 (11.7%) patients with post-operative complications, a conversion from the planned laparoscopy to an open technique was reported ($p < 0.001$). The median age of patients without complications was 37 years (IQR 18–96) vs. 47 years (IQR 16–93) for patients who experienced a complication ($p < 0.001$). The hospital stay was three days (IQR 2–11) for patients without complications and seven days (IQR 3–12) for patients with complications ($p < 0.001$).

Patients with higher AAST appendicitis scores had higher complication rates, as shown in Table 2. Regarding the surgical timing, 22.7% of the patients who reported a post-operative complication underwent an appendectomy > 24 hours from the admission. The operating surgeon's age was > 40 years for 71.8% of patients who reported a post-operative complication.

Table 2
Patients' characteristics: Cohort of patients stratified by complication occurrence.

Variable	Patients without complications (1174)	Patients with complications (163)	*P*
Age: years (IQR)	37(18–96)	47 (16–93)	< 0.001
Gender (M vs. F). N. patients (%)	665 (56.6%)	109 (66.9%)	0.014
Surgery: year (2019 vs. 2020). N. patients (%)	459 (39.1%)	87 (53.4%)	0.001
AIR score. N. patients with (%)			0.003
1–4	286 (24.4%)	18 (11%)	
5–8	721 61.4%)	110 (67.5%)	
9–12	167 (14.2%)	35 (21.5%)	
AAST score. N. patients (%)			< 0.001
1	562 (47.9%)	40 (24.5%)	
2	246 (21.0%)	31 (19.0%)	
3	127 (10.8%)	24 (14.7%)	
4	178 (15.2%)	49 (30.1%)	
5	61 (5.2%)	19 (11.7%)	
Surgery timing (≤ 24 vs. >24 h): N. patients (%)	192 (16.4%)	37 (22.7%)	0.046
Surgical approach (lap vs. open): N. patients (%)	99 (8.4%)	32 (19.6%)	< 0.001
Conversion to open (no vs. yes): N. patients (%)	43 (3.7%)	19 (11.7%)	< 0.001
Age of the operating surgeon (≤ 40 vs. >40 yrs): N. patients (%)	684 (58.3%)	117 (71.8%)	0.001
Antibiotic prophylaxis/therapy (short pr- long pr- ther): N. patients			< 0.001
Short course	156 (13.3%)	2 (1.2%)	
Medium course	457 (39.0%)	41 (25.2%)	
Long course	560 (47.7%)	120 (73.6%)	

Variable	Patients without complications (1174)	Patients with complications (163)	*P*
Dindo score. N. patients (%)			< 0.001
0	1012 (86.6%)	54 (33.1%)	
1	141 (12.0%)	62 (38.0%)	
2	14 (1.2%)	34 (20.9%)	
3	0 (0%)	11 (6.7%)	
4	1 (0.1%)	2 (1.2%)	
5			
Hospital stay: days (IQR)	3 (2–11)	7 (3–12)	< 0.001

The characteristics of the cohort of patients stratified according to the occurrence of post-operative complications are summarized in Table 2.

Analysis of complications: univariate and multivariate models

The logistic regression model results are reported in Table 3. In the univariate model series, all the eight selected covariates played a critical role in complication occurrence. These results were confirmed by the multivariate model, where age and gender were confounded by the other risk factors. Six determinants thus increased the likelihood of complication occurrence: undergoing surgery during 2020 (+ 67%), having a unit AIR (+ 9%) or AAST (+ 26%) increase, having waited for surgery > 24 h (+ 58%), being the surgeon aged > 40 years (+ 47%), undergoing open surgery (+ 112%) and being converted to open surgery (+ 166%). The multivariate logistic model AUC was 0.726, and this value can be compared to those deriving from ML modeling. By initially running automatic ML by the lares function, the best AUC was obtained by the GLM model (0.713), outperforming all the other classifiers in the target prediction. By manually tuning the GLM algorithm by the h2o function, its AUC moderately increased to 0.725, comparable to that deriving from the classical approach (multivariate binary logistic regression). The ranking of the features of this GLM tuned model is shown in Fig. 2 [18].

Table 3
Univariate and multivariate logistic regression models (outcome: complications).

	univariate model			multivariate model		
Risk factors	OR	95% CI	P	OR	95% CI	P
Age	1.02	(1.01–1.03)	< 0.001	1.01	(0.99–1.02)	0.123
Gender (M vs. F)	1.55	(1.10–2.19)	0.013	1.23	(0.85–1.77)	0.266
Surgery year (2020 vs. 2019)	1.78	(1.28–2.47)	< 0.001	1.67	(1.18–2.35)	0.004
AIR	1.19	(1.10–1.28)	< 0.001	1.09	(1.01–1.19)	0.028
AAST	1.49	(1.33–1.68)	< 0.001	1.26	(1.19–1.44)	0.001
Surgery timing (> 24 vs. ≤24 h)	1.50	(1.01–2.23)	0.046	1.58	(1.03–2.42)	0.041
Surgical approach (open vs. lap)	2.71	(1.75–4.20)	< 0.001	2.12	(1.32–3.40)	0.003
Conversion to open (yes vs. no)	3.46	(1.96–6.11)	< 0.001	2.66	(1.12–3.78)	0.024

Discussion

The CRAC study showed that in a selected cohort of Italian hospitals, in March and April 2020, the number of appendectomies has drastically dropped and that during the first wave of the COVID-19 pandemic, patients undergoing surgery were more frequently affected by more severe forms of appendicitis compared to the same timeframe of the previous year. This is the outcome of data analysis of over 1,300 individual patients undergoing appendectomy for acute appendicitis, a much more comprehensive dataset than previous international and national surveys [8, 19, 20] and multicenter retrospective studies [21, 22] had suggested or highlighted.

How this is to be interpreted is questionable. The reduction in the overall number of appendectomies performed may have several explanations. First, individuals affected by acute appendicitis may have renounced to approach emergency rooms in hospitals for fear of SARS-CoV-2 contagion. Simultaneously, we cannot exclude that surgeons restricted the indications for surgery to more severe cases, offering milder clinical cases the opportunity of conservative medical therapy at home. The vast majority of patients with uncomplicated appendicitis can safely be managed by active observation and pain control [23], and this is what might have happened during the first wave of the pandemic.

Since the outbreak of the COVID-19 pandemic in Europe and the U.S., several recommendations issued by surgical societies and institutional bodies have supported surgery's decision-making processes, including emergency scenarios. Although the overall level of evidence of such recommendations was low, there has been a significant impact of these documents on surgeons' daily clinical practice. Globally, during the first wave of the COVID-19 pandemic, recommendations on the treatment of acute appendicitis suggested the

use of appropriate non-operative treatments whenever possible in order to avoid overloading hospitals, already heavily burdened by SARS-CoV-2 patients. Our findings are in line with the ACIE Appy international survey on the global attitudes in managing acute appendicitis during the pandemic, which showed a statically significant decrease in the number of acute appendicitis patients referred to the hospitals, with only 10% of surgical units reporting > 20 referrals per month [8]. According to 34% of respondents to the survey, patients had more advanced disease features at a presentation during the COVID-19 pandemic. Results from the CRAC study confirmed this change in behavior by considering real-patient data and assessing a reduction of more than 30% in the number of appendectomies compared to 2019.

Whatever the reason, our study demonstrates that the severity of appendicitis during appendectomy significantly increased during the first wave of the pandemic, bringing together an increase of complication rate including the severity of complications, but not mortality. The impression that appendectomies could have been delayed after admission to the emergency room does not correspond to the truth. This is a promising finding, as it is known that the rate of complications increases in delayed surgery cases. This means that despite the apparent difficulties in the emergency area organization in hospitals, this did not affect the efficiency of the surgical activity. Nevertheless, complications observed were significantly more in 2020 as well as their severity.

Perforated appendicitis occurs in up to 15% of cases [24]. We found a relative increase of surgical referrals for complicated acute appendicitis with phlegmon, abscess, or diffuse peritonitis, as defined by the grades 4–5 of the American Association for the Surgery of Trauma (ASST) classification. In our study, 20% of patients in 2019 presented to observation with perforated appendicitis according to the ASST classification, whereas the rate increased to 27% in 2020, with a statistically significant difference. The CRAC study found that patients undergoing surgery > 24 hours from the hospitalization were more prone to experience post-operative complications following appendectomy than those who underwent surgery within the first 24 hours. The United Kingdom National Surgical Research Collaborative found that in a cohort of more than 2,500 patients with acute appendicitis, of whom 32% had complex findings, delaying appendectomy for over 48 hours was related to a statically significant increased risk of surgical site infection and 30-day adverse events [25]. Our study reached similar results, as surgical delay > 24 hours was a risk factor for post-operative complications both at the univariate and multivariate analyses. Our results are in line with those published by Alore et al., who found that appendectomies performed on hospital day three had significantly worse outcomes, as demonstrated by increased 30-day mortality and all major post-operative complications compared to operations taking place on hospital day one [26]. Since in our study, the rate of complicated appendicitis reported during the pandemic period of 2020 was higher than that usually found during 2019, and generally, in the contemporary literature, we argue that it may be reasonable to prioritize patients reporting symptoms lasting for over 24 hours for operative management.

The technique adopted during the pandemic did not differ from the previous habit. Open appendectomy for patients with intra-abdominal sepsis of appendiceal origin or those with the non-resolving disease

following antibiotic treatment was initially recommended [27–29]. Recommendations that claimed to avoid the use of laparoscopy were based on previous findings that activated corynebacterium, papillomavirus, HBV, and HIV had been detected in surgical smoke and the assumption that SARS-CoV-2 infection aerosol should not have been any exception [30]. Such recommendations need to be contextualized within the scenario in which European surgeons had been facing the viral spread during the first wave of the pandemic, characterized by the lack of availability of ultrafiltration systems, the paucity of personal protective equipment, the shortage of surgical workforce, and the impossibility of routine testing of all patients. However, a year after the first case of SARS-CoV-2 infection was identified in China, the virus has not been isolated so far from the laparoscopic plumes within the peritoneal cavity of infected subjects.

Consequently, the potential of viral spreading during laparoscopy is not known. In circumstances where operating theatre resources are available and based on surgeon judgment, laparoscopic appendectomy should continue to be performed, as the safe performance of laparoscopic appendectomy allows short hospitalization. Data from the CRAC study showed that, in Italy, the rate of laparoscopic appendectomy performed in March-April 2020 was comparable to that in the same two months in 2019 (90.1% vs. 90.3%). The reason for this finding, which is in contrast with the trend in favor of open appendectomy reported in other countries [31], might be found in the enormous effort made by surgeons in Italy to equip operating rooms with systems for the safe evacuation of laparoscopic plumes, first with home-made systems, and then with the certified ones introduced on the market by companies [32].

The CRAC results have also highlighted Italian surgeons' attitudes on the use of antibiotic therapy after appendectomy. It is well known that a single dose of broad-spectrum antibiotics given preoperatively is highly effective in decreasing wound infection and post-operative intra-abdominal abscess following appendectomy [33]. So that, guidelines recommend against post-operative antibiotics for patients with uncomplicated appendicitis [34]. In patients with complicated acute appendicitis, conversely, post-operative broad-spectrum antibiotics are recommended. For those who had undergone an adequate surgical source control through an appendectomy, the outcomes after fixed-duration antibiotic therapy (approximately 3–5 days) are similar to those after a long course of antibiotics [35]. The results of our study, which have confirmed the attitude towards the prolonged use of post-operative antibiotics for more than five days, both in the pre-pandemic (49%) and in the pandemic (53%), poses serious concerns, as we are currently experiencing a worldwide increase in infections caused by multi-drug resistant organisms as a result of widespread antibiotic use and excessive antimicrobial prescribing practice.

Our study results must be interpreted within the context of some limitations. First, due to the urgent need for evidence on appendicitis management during the first wave of the COVID-19 pandemic, data collection was limited to short-term follow-up. The study design did not allow us to assess post-operative visits after 30 days from the surgical intervention. As a consequence, longer-term complications, such as post-operative adhesions and incisional hernia, might be missed. Second, due to the ambispective design, the quality of data collected depended on the quality of medical records and the researcher's interpretation of charted notes. Third, there is a considerable variation in the organization of the

emergency surgical departments across the country, and the most relevant source of bias is probably the heterogeneity of the diagnostic pathways adopted in the various centers involved. Ultimately, the study has a non-randomized nature, associated with any extensive database. Conclusions from non-randomized studies can be misleading because there is always a chance for selection bias, leading to underestimating or overestimating the real intervention effect. On the other hand, our study's strength lies in the fact that we demonstrated, through the analysis of individual patients' data, that during the lock-down due to the COVID-19 pandemic, fewer patients sought medical attention for acute appendicitis in Italy. In this context, the rate of complicated appendicitis increased, leading to a relatively higher incidence of post-operative complications than in the past.

Conclusions

In Italy, during the first wave of the COVID-19 pandemic, the number of appendectomies has drastically dropped. Patients undergoing surgery were more frequently affected by more severe forms of appendicitis compared to the same timeframe of the previous year, and a higher complication rate was reported.

Abbreviations

COVID-19
Coronavirus Disease 2019
AAST
American Association for the Surgery of Trauma
CRAC
ChiRurgia Appendiciti COVID-19, COVID-19 Appendicitis Surgery
SICE
Italian Society of Endoscopic Surgery and new technologies
AIR Score
Appendicitis Inflammatory Response Score
IQR
Interquartile Range
ML
Machine Learning
GLM
Generalized Linear Model
GBM
Gradient Boosting Machine
XGBoost
Extreme Gradient Boosting machine
DRF

Distributed Random Forest

DNN

Multilayer artificial Deep Neural Network

NB

Naïve Bayes classifier

AUC

Area Under the Curve

ROC

Receiver Operating Characteristic

Declarations

Ethics approval and Consent to participate

The study obtained the approval of the Ethical Committee for Clinical Trials of Treviso and Belluno on May 7th, 2020 (IDapproval 883/CE Marca). A written informed consent was obtained from all enrolled patients for being included in the study. Additional written informed consent for the treatment of personal and sensible data was obtained from all patients prior to the data collection and evaluation.

Consent for publication

Not applicable

Availability of data and materials. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Alberto Sartori, Mauro Podda, Emanuele Botteri, Roberto Passera, Alberto Arezzo, Ferdinando Agresta have no conflict of interest or financial ties to disclose.

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Authors' contributions. Alberto Sartori, Mauro Podda, Emanuele Botteri, Alberto Arezzo, Ferdinando Agresta: study conception and design, acquisition of data, interpretation of data, final approval of the version to be published. Roberto Passera: study conception and design, acquisition of data, analysis of data, final approval of the version to be published. The CRAC study collaborative group: acquisition of data, final approval of the version to be published.

Research involving human participants. All the investigators conducted the study in accordance with the principles of the Declaration of Helsinki of 1975 (as revised in 2008) and in accordance with the ethical standards of the responsible committee on human experimentation (Independent Ethical Committee for

Clinical Trials of Treviso and Belluno, Italy). All the investigators conducted the study according to the rules of the ethics committee regarding prospective collection of data.

Acknowledgments: not applicable.

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Figures

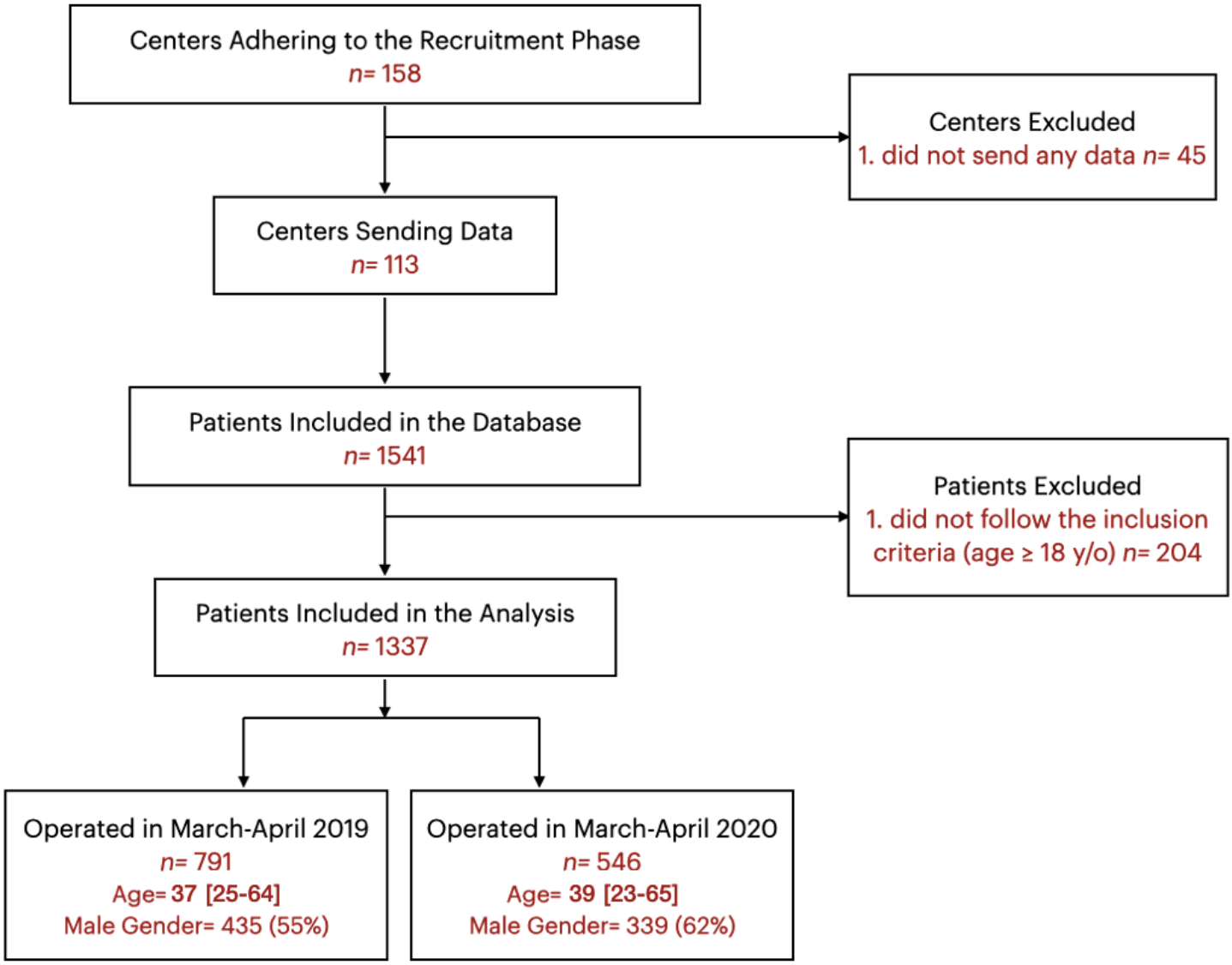

Figure 1

Study flow diagram.

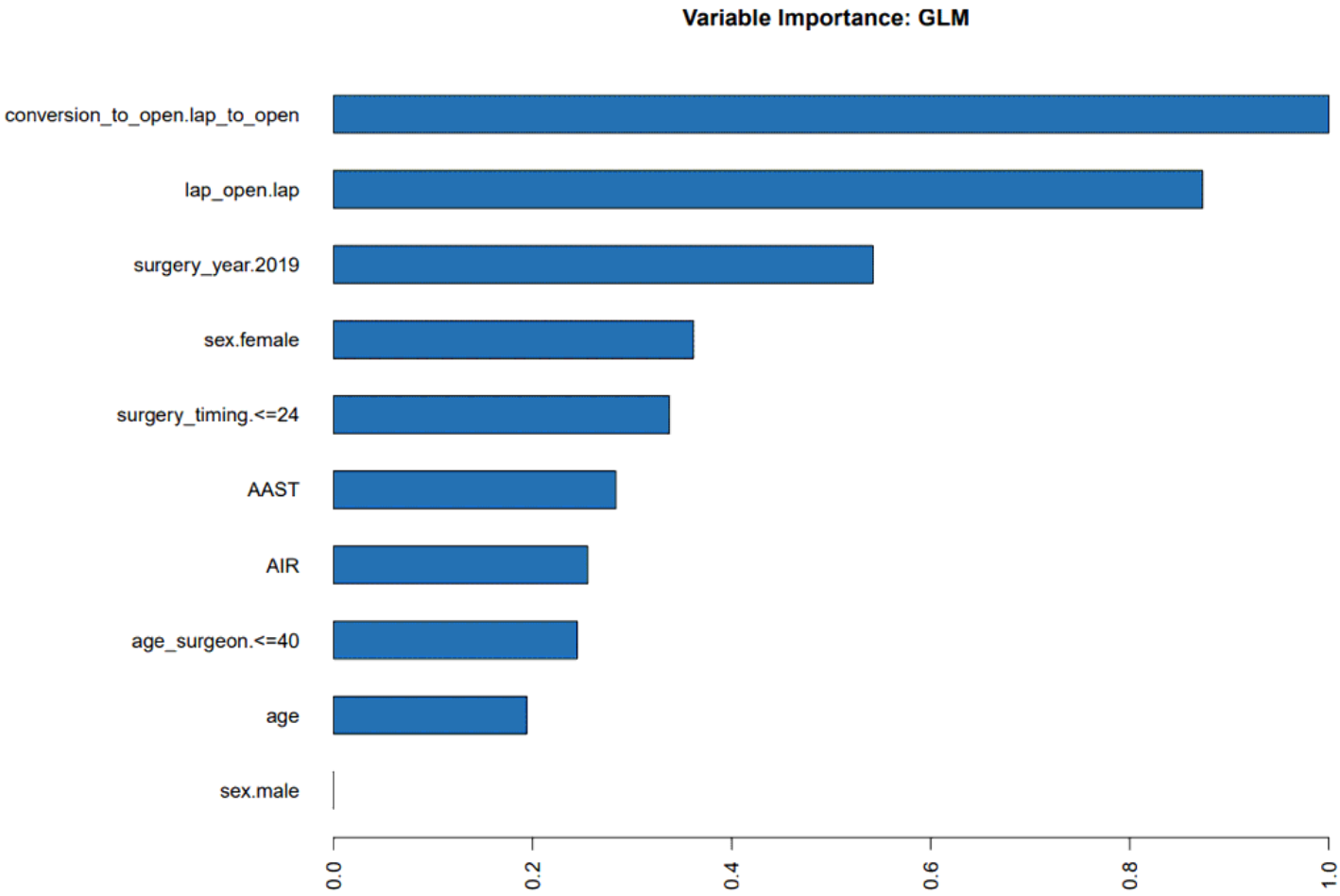

Figure 2

Variable importance for the Generalized Liner Model.

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