Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Recurrent appendicitis following successful drainage of appendicular abscess in adult without interval appendectomy during COVID-19. Prospective cohort study

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ABSTRACT

Background: COVID-19 infection is a global pandemic that affected routine health services and made patients fear to consult for medical health problems, even acute abdominal pain. Subsequently, the incidence of complicated appendicitis increased during the Covid-19 pandemic. This study aimed to evaluate recurrent appendicitis after successful drainage of appendicular abscess during COVID-19.

Material and methods: A prospective cohort study conducted in the surgical emergency units of our Universities' Hospitals between March 15, 2020 to August 15, 2020 including patients who were admitted with the diagnosis of an appendicular abscess and who underwent open or radiological drainage. Main outcomes included incidence, severity, and risk factors of recurrent appendicitis in patients without interval appendectomy.

Results: A total of 316 patients were included for analysis. The mean age of the patients was 37 years (SD ± 13). About two-thirds of patients were males (60.1%). More than one-third (39.6%) had co-morbidities; type 2 diabetes mellitus (T2DM) (22.5%) and hypertension (17.1%) were the most frequent. Approximately one quarter (25.6%) had confirmed COVID 19 infection. About one-third of the patients (30.4%) had recurrent appendicitis. More than half of them (56.3%) showed recurrence after three months, and 43.8% of patients showed recurrence in the first three months. The most frequent grade was grade I (63.5%). Most patients (77.1%) underwent open surgery. Age, T2DM, hypertension, COVID-19 infection and abscess size >3 cm were significantly risking predictors for recurrent appendicitis.

Conclusions: Interval appendectomy is suggested to prevent 56.3% of recurrent appendicitis that occurs after 3 months. We recommend performing interval appendectomy in older age, people with diabetes, COVID-19 infected, and abscesses more than 3 cm in diameter.

Research question: Is interval appendectomy preventing a high incidence of recurrent appendicitis after successful drainage of appendicular abscess during COVID-19 pandemic?

Hypothesis. Recurrent appendicitis is high during the COVID-19 pandemic, and interval appendectomy prevents a high incidence of

; T2DM : type 2 diabetes mellitus, WHO: World Health Organization; IA: Interval Appendectomy, AA:Appendicular Abscess.

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recurrent appendicitis after successful drainage of appendicular abscess during the COVID-19 pandemic.

1. Introduction

The novel coronavirus SARS-CoV-2 (causing COVID-19) was first discovered in Wuhan in China at the end of 2019, and then at the beginning of 2020, the World Health Organization (WHO) announced COVID-19 as a global pandemic [1]. Because the virus is highly infectious, hospitals worldwide became overloaded by COVID-19 infected patients, and a state of emergency was announced, and the population was advised to stay at home. Moreover, as people were afraid to become infected by the virus, a marked reduction in the number of medical consultations was evidenced, even for acute abdominal cases [2,3].

Acute appendicitis is the commonest cause of acute abdomen in all ages with an incidence risk of 7%–8% worldwide [4]. Complicated appendicitis represents nearly 4–25% of cases [5]. Appendicular abscess (AA) formation occurs in 2–7% of patients with perforated appendicitis [6]. Delay in medical consultation is a leading cause for developing complicated appendicitis [5].

In patients with AA, a non-operative treatment with ultrasonography (US) or computerized tomography (CT) guided drainage plus wide spectrum antibiotic treatment can be initially performed, followed by an interval appendectomy (IA). This approach decreases peri- and post-operative complications [7–10].

Surgeons who advocate for IA believe that the incidence of recurrent appendicitis is high and by performing IA a potential underlying pathology (e.g. Crohn's disease or malignancy) can be diagnosed and treated in time [11]. Others have opposed this concept as the reported incidence of recurrent appendicitis is ranging from 3.4% to 25.5%, with the greatest risk during the first three months after the initial episode [12,13].

The aim of this study was to evaluate incidence, severity, and risk factors for recurrent appendicitis in patients who were treated without IA following successful drainage of AA during the pandemic of COVID-19.

2. Material and Methods

Study design and setting: Prospective cohort study conducted in the surgical emergency units of our University Hospitals between Mar 15, 2020 to Aug 15, 2020 on 316 patients admitted during the study period with the clinical diagnosis of AA and who were managed by open or radiological drainage. This study is compliant with the STROCSS criteria [14]. Registration at clinicaltrials.gov protocol registration quality control review criteria: [NCT05048745] retrospective registered at 15-8-2021.

Ethical approval was given by our Faculty of Medicine medical ethical committees [HWD202120371].

Patient selection: Inclusion criteria included age >16 years. Children are generally developed minor Covid-19 disease. They are operated upon by pediatric surgeons and therefore were not included in this study.

Men and women who underwent successful drainage of AA. Exclusion criteria included: patients 16≤ years, generalized peritonitis, pregnancy, suspected cases of colon cancer, inflammatory bowel disease, failure or difficult initial drainage e.g. pelvic abscess, appendectomy performed at the time of drainage, non-compliant patients for regular follow up, and AA less than 3 cm if showed improvement of clinical and radiological signs within three days of antibiotic therapy alone.

2.1. Types of outcome measures

The outcomes were incidence, severity, and risk factors of RA in patients without IA (clinical or radiological at any time point during follow-up period).Outcomes measures: The diagnosis of the AA was based on presentation with right lower quadrant abdominal pain, fever, palpable or suspicious mass with tenderness. The abscess was confirmed in all patients by US or CT. Morbidity and mortality were evaluated by Dindo and Clavien classification [15]. Successful drainage was confirmed by the absence of symptoms and normalization of laboratory and radiological investigations (WBCs and sonographic). RA was diagnosed clinically if recurrent abdominal pain was associated with tenderness/rebound tenderness with or without fever. The severity of RA was measured by The American Association for the Surgery of Trauma grading score for emergency surgery conditions [16].

Procedure: Appendectomy was performed either by open approach (77.1% of cases) or laparoscopic approach in the remaining cases (22.9%). Steps of operations were according to standard steps described in the previous study [17]. All removed appendices were sent for histological examination. All Covid-19 patients were isolated in special section of the surgical word. They were operated upon in dedicated theatre with standard PPE.

2.2. Follow-up

Following successful drainage of AA (7% by open drainage, 82.3% by radiological guided drainage either Ultrasound Scan (USS) or Computed Tomography (CT) guided drainage and 10.7% by open approach after failure of radiological drainage).

Patients were discharged from the hospital when normal white blood cell count (below 12,000 cells/mm3), absent fever, no abdominal pain nor tenderness, and ability to tolerate oral intake. Patients were typically discharged on oral antibiotics for a week in the form of third-generation cephalosporin (Cefpodoxime proxetil: 400 mg orally twice daily) and metronidazole (500 mg three time daily). Those discharged from the hospital were followed up in an outpatient department monthly for the first three months, and once every three months for the following nine months. During the outpatient interviews, all patients were clinically examined. Colonoscopy and CT were performed routinely on patients above the age of 40 years. Patients with recurrent symptoms of appendicitis were offered appendectomy. The patients not attending the outpatient visit were also contacted by telephone or email to obtain information on their status. The mean follow up time was 5 ± 1.4 months.

2.3. Statistical analysis

Data management and statistical analysis were done using SPSS version 25. (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using Kolmogorov–Smirnov test and direct data visualization methods. According to normality testing, numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Quantitative data were compared according to recurrence using independent *t*-test. Categorical data were compared using the Chi-square test. Multivariate logistic regression analysis was done for the prediction of RA. The odds ratio and the 95% confidence interval were calculated. Kaplan Meier curve was done for time to recurrence. All statistical tests were two-sided. P values less than 0.05 were considered significant.

3. Results

A total of 332 patients with successful drainage of AA were initially included but 16 patients were excluded from the study because five patients did not meet inclusion criteria, three patients refused to participate, and eight patients were lost during follow up periods (five patients refused to come for the subsequent follow-up visits, two patients died from COVID-19 during the observation period and one was

diagnosed as appendicular base adenocarcinoma treated with right hemicolectomy and was excluded from the study). Accordingly, 316 patients' data were collected and analyzed.

3.1. General characteristics

The mean age of patients was 37 years (standard deviation, SD: 13). About two-thirds of the patients were men (60.1%). More than one-third (39.6%) had co-morbidities; type 2 diabetes mellitus (T2DM) (22.5%) and hypertension (17.1%). Approximately one quarter (25.6%) had confirmed COVID 19 infection. The abscess size was >3 cm in two-thirds (63.0%). The most frequent type of abscess drainage was US guidance percutaneous drainage in 82.3%. The mean duration till drainage was four days. Regarding ASA classification, more than two-thirds (67.4%) were grade I. One-quarter of the patients showed grade II, and only 7.6% were grade III. The mean WBCs was 15.8 x10^9/l, with a SD of 0.7 (Table 1).

3.2. Recurrence of appendicitis

About one-third of the patients (30.4%) had RA. More than half of them (56.3%) showed recurrence after three months, and more than one-third (43.8%) showed recurrence in the first three months. The most frequent severity grade was grade I (63.5%), while the least frequent grade was grade III (7.3%) (Fig. 1). Those with RA showed a mean temperature of 38.3° centigrade and mean WBCs of 15.9x10^9/l. Computed Tomography (CT) scan is the gold standard cross sectional imaging in diagnosing appendicitis. The most frequent method for diagnosing recurrence was CT (76.0%), while US was used in about one-quarter of the patients (24.0%) (Table 2).

Table 1
General characteristics of the studied patients.

General characteristics	
Age (years) Mean ± SD	37 ± 13
Gender	
Males	190 (60.1%)
Females	126 (39.9%)
Diabetes mellitus	71 (22.5%)
Hypertension	54 (17.1%)
Covid infection	81 (25.6%)
Size of abscess	
<3 cm	117 (37.0%)
>3 cm	199 (63.0%)
Type of abscess drainage	
Open	22 (7.0%)
Percutaneous	260 (82.3%)
Percutaneous then open	34 (10.7%)
Type of radiological drainage	
CT	56 (17.7%)
Sonar	260 (82.3%)
Duration till drainage (days) Mean ± SD	4 ± 1
ASA	
I	213 (67.4%)
II	79 (25.0%)
III	24 (7.6%)
WBCs (Mean ± SD)	15.8 ± 0.7

ASA: American Society of Anesthesiologists.

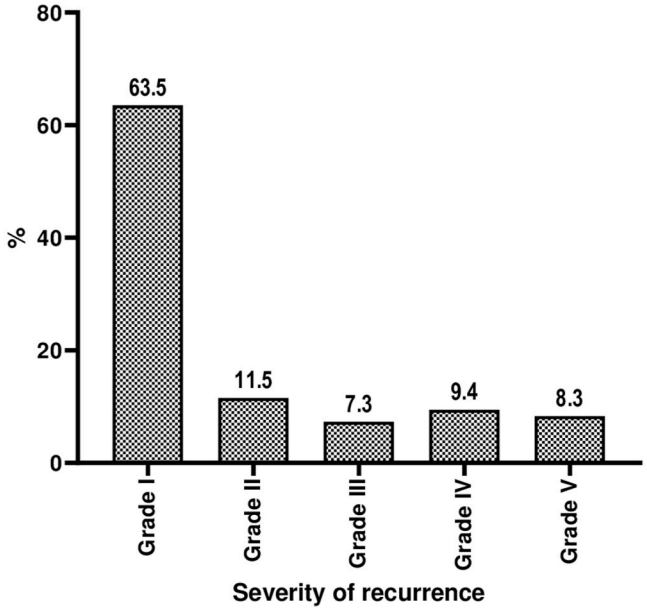

Fig. 1. Severity of recurrence in the studied patients.

Table 2
Recurrent appendicitis and its characteristics.

Recurrent appendicitis	96 (30.4%)
Time of recurrence[a]	
<3 months	42 (43.8%)
>3 months	54 (56.3%)
Severity of recurrence[a]	
Grade I	61 (63.5%)
Grade II	11 (11.5%)
Grade III	7 (7.3%)
Grade IV	9 (9.4%)
Grade V	8 (8.3%)
Temperature[a] Mean ± SD	38.3 ± 0.4
WBCs[a] Mean ± SD	15.9 ± 0.7
Diagnosis of recurrence[a]	
CT	73 (76.0%)
sonar	23 (24.0%)

[a] Statistics were calculated based on a total of 96 patients with recurrence.

3.3. Operative and postoperative findings

Most patients (77.1%) underwent open surgery. The mean operative time was 58 min. Intra-operative complications were reported in 7.3%, and the most frequent one was appendicular artery bleeding (28.6%). The median hospital stay was 2 days and ranged from 2 to 14 days. Postoperative complications were reported in 15.6% (Table 3).

3.4. Postoperative complications

The most frequent postoperative complication was wound infection (66.7%), followed by intra-abdominal collection (33.3%), incisional hernia (26.7%), intestinal obstruction (6.7%), and ileus (6.7%). Regarding Clavien-Dindo classification, about two-thirds (66.7%) showed grade III, and one-third (33.3%) showed grade I. As regards dealing with complications, about half of the patients (53.3%) underwent conservative management, and the other half (46.7%) underwent re-operation (Table 4).

Table 3
Operative and post-operative characteristics in those with recurrent appendicitis.

Type of operation[a]	
Laparoscopic surgery	22 (22.9%)
Open surgery	74 (77.1%)
Operative duration (minutes)[a] Mean ± SD	58 ± 21
Intraoperative complications[a]	7 (7.3%)
Type of Intraoperative complications[b]	
Appendicular artery bleeding	2 (28.6%)
Difficult dissection	1 (14.3%)
Ileal injury	1 (14.3%)
Obscure anatomy	1 (14.3%)
Omental vessel bleeding	1 (14.3%)
Bladder injury	1 (14.3%)
Hospital stay (days)[a](median"range")	2 (2–14)
Postoperative complications[a]	15 (15.6%)

[a] Statistics were calculated based on a total of 96 patients with recurrence.
[b] Percentage was calculated based on a total of 7 patients with intra-operative complications.

Table 4
Types of post-operative complications.

	n (%)
Wound infection[a]	10 (66.7%)
Incisional hernia[a]	4 (26.7%)
Intra-abdominal collection[a]	5 (33.3%)
Intestinal obstruction[a]	1 (6.7%)
Ileus[a]	1 (6.7%)
Clavien-Dindo classification[a]	
Grade I	5 (33.3%)
Grade III	10 (66.7%)
Dealing with complications[a]	
Conservative	8 (53.3%)
Re-operation	7 (46.7%)

[a] Percentages were calculated based on 15 patients who had post-operative complications.

3.5. Patients' characteristics according to recurrence status

Age was significantly higher in those with RA (40 years) than those without recurrence (35 years); P-value was 0.001. Also, T2DM and hypertension were significantly higher in those with recurrent appendicitis (31.3% and 29.2%, respectively) than those without recurrence (18.6% and 11.8%, respectively); P-values were 0.013 and < 0.001, respectively. In addition, Covid-19 infection was significantly higher in those with recurrence (70.8%) than those without (5.9%); P-value was <0.001. The size of the abscess was significantly associated with RA (P-value < 0.001); abscess size >3 cm was significantly higher in those with recurrence (94.8%) than those without (49.1%). Furthermore, ASA grading was significantly associated with RA (P-value < 0.001); ASA grade I was lower in patients with recurrence (43.8) than patients without (77.7%), while grade III was higher in those with recurrence (15.6%) than those without (4.1%). No significant differences were observed between those with and without recurrence regarding gender (P-value = 0.353), type of abscess drainage (P-value = 0.243), type of radiological drainage (P-value = 0.746), WBCs (P-value = 0.076), and duration till drainage (P-value = 0.847) (Table 5).

Prediction of recurrence: Multivariate logistic regression analysis was done for the prediction of RA. It showed that abscess size >3 cm, ASA II and III, COVID-19 infection, and diabetes mellitus were significant independent predictors for the development of recurrent appendicitis (Table 6).

Time to recurrence: Kaplan-Meier curve was done for the time to recurrence. It showed that at three months, the rate of recurrence was 13.3%. At six months, it was 22.5%. At one year, it was 30.4% (Fig. 2). There were no mortality and some patients developed pulmonary symptoms, others are asymptomatic but they are all Covid-19 positive by PCR test. No one needed intensive care unit admission for organ support, this was possibly because they are relatively younger population. All our patients were not suffering from respiratory failure due to Covid-19 and their oxygen saturation was acceptable, no attempt was done to use spinal or epidural anesthesia. This is possibly an important consideration in patients with inadequate respiratory function.

4. Discussion

Our study evaluated RA (incidence, severity, and risk factors) after successful drainage of AA during one year follow up in the era of COVID-19 pandemic when there is a global tendency for postponing non-emergent surgeries, including IA following drainage of an AA.

To our knowledge, this is the first study analyzing recurrent appendicitis following complicated appendicitis drainage in the COVID-19 pandemic. Based on our results, we found that recurrent appendicitis occurred in 30.4% of patients who underwent successful drainage of AA during 1 year follow up (43.7% within the first 3 months after drainage

Table 5
Patients' characteristics according to recurrence status.

	Recurrent appendicitis		P-value
	Yes (n = 96)	No (n = 220)	
Age (years) Mean ± SD	40 ± 14	35 ± 12	0.001
Gender			
Males	54 (56.3)	136 (61.8)	0.353
Females	42 (43.7)	84 (38.2)	
Diabetes mellitus	30 (31.3)	41 (18.6)	0.013
Hypertension	28 (29.2)	26 (11.8)	<0.001
Covid infection	68 (70.8)	13 (5.9)	<0.001
Size of abscess			
<3 cm	5 (5.2)	112 (50.9)	<0.001
>3 cm	91 (94.8)	108 (49.1)	
Type of abscess drainage			
Open	4 (4.2)	18 (8.2)	0.243
Percutaneous	84 (87.5)	176 (80.0)	
Percutaneous then open	8 (8.3)	26 (11.8)	
Radiological drainage			
CT	16 (16.7)	40 (18.2)	0.746
Sonar	80 (83.3)	180 (81.8)	
ASA			
I	42 (43.8)	171 (77.7)	<0.001
II	39 (40.6)	40 (18.2)	
III	15 (15.6)	9 (4.1)	
WBCS (Mean ± SD)	15.9 ± 0.8	15.7 ± 0.7	0.076
Duration till drainage (days) Mean ± SD	4 ± 1	4 ± 1	0.847

Independent *t*-test was used for numerical data. Chi-square test was sued for categorical data.

Table 6
Multivariate logistic regression analysis for prediction of recurrence.

	OR (95% CI)	P-value
Age (years)	1.003 (0.95–1.049)	0.881
Abscess size >3 cm	9.938 (3.168–31.172)	<0.001
ASA II	7.254 (2.086–25.221)	0.002
ASA III	21.551 (3.631–127.902)	0.001
Covid infection	38.773 (16.265–92.43)	<0.001
Diabetes mellitus	0.136 (0.025–0.752)	0.022
Hypertension	2.936 (0.783–11.008)	0.110

OR: Odds ratio 95% CI: 95% Confidence interval.

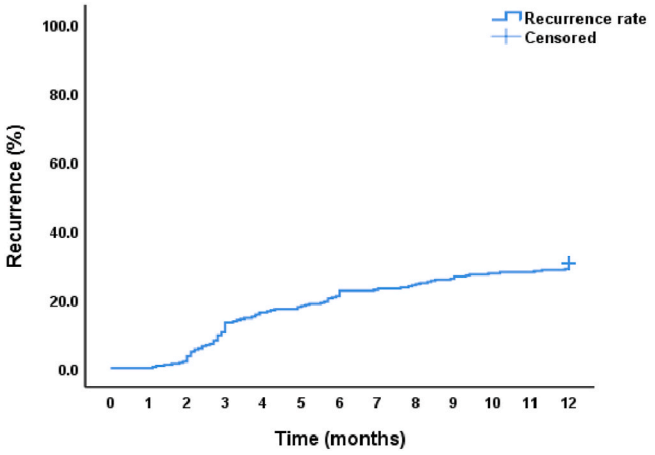

Fig. 2. Kaplan Meier curve for time to recurrence.

and 56.3% after 3 months).

The incidence of RA is high, and this is attributed to the fact that the COVID-19 pandemic induces vasculitis and thrombotic occlusion of arteries, including the appendicular artery [18,19]. Furthermore, the COVID-19 pandemic causes hyperplasia of lymphoid tissue in the appendix wall, causing an obstruction.

Kaplan-Meier curve (Fig. 2) confirmed that the rate of RA is 13.3% in the first 3 months; then, later, the rate of RA increased, reaching up to 30% at one year follow up. So, we recommend performing interval appendectomy that may prevent RA in 56.3% of cases and prevent the high rate of RA after 3rd month.

The incidence of RA varies among different studies and maybe as low as 8.9% [7] and 13% in a recent study published just before COVID-19 [19] up to 27% in a third study [20]. Our study showed a higher recurrence rate (30.4%) that was probably due to infection with COVID-19. A study by Lai et al. [11] reported a 25.5% rate of RA after conservative treatment most recurred within 6 months after discharge (83.3%). The benefit of preventing recurrence is less than 16% if IA is performed 6 weeks after discharge and less than 10% if it is done 12 weeks later. Another prospective study revealed that IA has done at 6 and 12 weeks had prevented 10.6% and 6.7% of RA respectively [21] which], that in 89.4% and 93.3% the %, was unnecessary. Our study showed that IA could prevent 56.3% of RA after three months (higher than the previous study).

Infection with COVID-19 pandemic is the probable cause of a high incidence of RA after 3 months. Before conducting our study, we thought that RA during the COVID-19 pandemic would be more significant in severity due to vasculitis and lymphoid hyperplasia, but the opposite result we found. We found that although the incidence of RA was high, most cases were low in severity (63.5% grade I). Other studies agreed with these results in that severity of appendicitis is less in COVID-19 [22,23] while other studies stated that patients with AA during COVID-19 pandemic have a more severe disease at presentation [24,25]. Laparoscopic appendectomy is the standard method of management of acute appendicitis. However, during the era of COVID-19, this trend was changed in our hospitals for fear of aerosol-induced transmission of COVID-19 infection; therefore, most cases of recurrent appendicitis (77.1%) operated by open appendectomy. This approach was confirmed by many studies [26–30], while other authors [31] believe that the risks of laparoscopy are less than its benefits.

Our results showed that intraoperative complications occurred in 7.3% of cases, mostly bleeding appendicular artery, while postoperative complications occurred in 15.6% of cases. It is of profound importance to detect risk factors and predictors of RA during the follow-up period. These patients are at significant risk, and IA is intended for those patients. These predictors are older age (ASA III), abscess size > 3 cm, and T2DM. Older age patients are susceptible to COVID-19 infection due to decreased immunity, significantly if associated with other comorbidities like DM and hypertension. Older age is associated with atherosclerosis of the appendicular artery. A study that reported risk factors for recurrent appendicitis [13] showed that gender had a slight influence on recurrent appendicitis (hazard ratio males vs. females = 0.52, 95% CI, 0.27–0.99, P = 0.05). Age, Charlson comorbidity index, type of appendicitis, or percutaneous abscess drainage did not influence recurrence. Interval appendicectomy is a standard practice in some units, but some hospitals offer the procedure on selective basis. Previous studies showed variable recurrence rate and some surgeons do not agree to operate on all patients taking in consideration the surgical complications, cost and logistic problems in current very busy surgical practice.

Limitation and strength: The strengths of this study are the following: multi-center study, precise diagnosis of the participant, timely and relevant topic (recurrent appendicitis in COVID-19), and standardization of methods of follow up. Our study has also some limitations:

Small sample size of total 316 patients and 96 (30.4%) with recurrent appendicitis. The study would be more powerful and the results could be more generalizable with inclusion of more patients.

Open surgery is not the standard technique and we used open technique in compliance with our local and international guidelines during initial phase of the Covid-19 crisis.

The study has relatively short follow up.Longer follow up is expected to show a higher recurrence rate. However, our study also shown that we can predict which patient is likely to develop recurrence and he/or she should be offered interval appendicectomy.

Children were not included in the study, and short follow-up period, and the fact that the high rate of wound infection (66.7%) may be related and influenced by the surgical approach (open; 77% of patients) and this percentage may be possibly reduced in patients treated via laparoscopy.

5. Conclusions

Interval appendectomy after successful drainage of appendicular abscess is beneficial to reduce recurrent appendicitis rates, potential admissions, complications and costs. The incidence of recurrence was remarkably high after 3 month. Interval appendectomy should be especially recommended also in elderly diabetic patients with COVID-19 infection with abscess >3 cm.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

Yes all ethical approval was given by Faculty of Medicine medical ethical committee [HWD202120371].

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Author contribution

Tamer.A.A.M.Habeeb*, Abdulzahra Hussain, Francisco Schlottmann, Mohammad Kermansaravi, Alberto Aiolfi, Ivan Matic, , Osama Abdelazez, Said mohamed negm, Muhammad Ali Baghdadi, Mahmoud Abdou yassin, Ahmed M. Sallam, Hatem Mohammad, Fady Mehaney Habib,Mohamed.I.Abdelhamid, Mohamed Farouk Amin. They are responsible for the idea of the work. Also they the main surgeons of the technique. They shared in the study design, data analysis, writing and critical revision of the manuscript for important intellectual contents. they shared in the final approval of the version to be submitted.

Research registration Unique Identifying number (UIN)

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2. Unique Identifying number or registration ID: NCT05048745
3. Hyperlink to your specific registration (must be publicly accessible and will be checked) https://clinicaltrials.gov/ct2/show/NCT05048745?id=NCT05048745&draw=2&rank=1

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Declaration of competing interest

No conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2021.106200.

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