



Research Article

Unplanned Reoperation and Interventional Radiology Post Appendicectomy: A Meta-Analysis

Adibah Shamsul Badrin¹, Una Maguire¹, Alison Johnston¹,
Magda Bucholc² and Michael Sugrue^{1,2*}

¹Donegal Clinical Research Academy and Department of Surgery
Letterkenny University Hospital, Donegal, Ireland

²EU INTERREG Centre for Personalized Medicine, Intelligent Systems
Research Centre, School of Computing, Engineering and Intelligent Systems,
Ulster University, Magee Campus, Derry-Londonderry, Northern Ireland

Abstract

Introduction: Optimizing delivery of care to patients with appendicitis as part of an emergency general surgery care program is important. Appendicitis is one of the most common emergency surgical presentations and has significant potential morbidity and occasional mortality. Meta-analysis of reinterventions following appendicectomy has not been published. This meta-analysis evaluated the prevalence and potential predictors of reoperation and interventional radiological (IR) procedures post appendicectomy.

Methods: A PROSPERO-registered (ID CRD42017069040) meta-analysis following PRISMA guidelines using databases PubMed and Scopus for studies between June 2012 to May 2017 was undertaken. Headings included "reoperation", "return to operation theatre", "complication", "appendicectomy", "outcome", "abscess drainage". Articles scoring ≥ 16 for comparative and ≥ 10 for non-comparative using MINORS criteria were included.

Results: 2810 articles reviewed were reduced to 52 qualifying studies for a final analysis of 319,053 appendicectomies. Overall, 0.9% (range 0.0% to 14.2%) underwent some form of reintervention. The reoperation rate was 0.6% (range 0.0 to 14.2%) and radiologic drainage rate 1.5% (range 0.0% to 11.1%). Reoperations were

significantly associated with a laparoscopic approach, earlier grade of appendicitis and not using drains. Laparoscopy conversion to open and the grade of surgeon performing the appendicectomy did not affect reintervention.

Conclusion: This meta-analysis identified a small but notable reoperation and IR rate, significantly increased by complexity of appendicitis and open surgery. Strategies promoting for earlier presentation and diagnosis with laparoscopic approaches may improve overall outcomes.

Keywords: Appendicectomy; Emergency surgery; Interventional radiology; Reoperation; Quality improvement

Introduction

Optimizing delivery of emergency general surgery care is important as not only does it account for over 10% of all surgical admissions but also accounts for 50% of surgical mortality in the United States [1]. Within the cohort of emergency surgery patients, acute appendicitis is one of the most common reasons for admission [2]. Other common emergency surgery operations include partial colectomy, small bowel resection, cholecystectomy, operative management of peptic ulcer disease, lysis of peritoneal adhesions and laparotomy [3]. Appendicitis and its care are often perceived as a simple, easily treated condition and this may contribute to lack of incisive analysis of outcomes. During the 21st century the pooled incidence of appendicitis or appendicectomy was 100 per 100,000 person-years in North America and 151 per 100,000 person-years in Western Europe [4].

While non-operative treatment of appendicitis has been advocated [5], others have questioned its medium-term results [6], surgery remains the cornerstone of care. Both the disease itself and surgery may be associated with complications such as wound infection, intra-abdominal abscess and ileus [7]. Developing an understanding of adverse events post-appendicectomy is important in improving outcomes. Reintervention post appendicectomy includes potentially both reoperation and interventional radiology (IR) drainage of collections.

Whilst percutaneous drainage is less invasive than surgical drainage, its use is generally reserved for a radiologically accessible unilocular abscess [8]. Open surgical drainage is used in patients requiring urgent management of overwhelming sepsis, or who fail less invasive treatment modalities [9]. Open surgical drainage is associated with high morbidity and mortality, and a length of stay greater than 2 weeks [10-12].

It is a very significant unexpected outcome for patients and their families. Understanding the frequency and cause of reintervention may alter and help future care. In general readmission following appendicectomy occurs in 4.3% of patients undergoing appendicectomy (range 0.0-14.5%) [13]. Recent published comprehensive guidelines from the World Society of Emergency Surgery in the management of

*Corresponding author: Michael Sugrue, Donegal Clinical Research Academy and Department of Surgery, Letterkenny University Hospital, Co. Donegal, Ireland, Tel: +353 749188823; Fax: +353 749188816; E-mail: michael.sugrue@hse.ie

Citation: Badrin AS, Maguire U, Johnston A, Bucholc M, Sugrue M (2020) Unplanned Reoperation and Interventional Radiology Post Appendicectomy: A Meta-Analysis. J Emerg Med Trauma Surg Care 7: 049.

Received: July 13, 2020; **Accepted:** July 28, 2020; **Published:** August 04, 2020

Copyright: © 2020 Badrin AS, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

acute appendicitis do not include guidelines relating to reoperation or reintervention [14]. While many studies report both morbidity and reoperation, no meta-analysis of reintervention has been published [15].

This study undertook a meta-analysis of the prevalence and potential predictors of reoperation and IR drainage post appendicectomy [16].

Methods

Search strategy and study eligibility

A systematic review and meta-analysis of all published English articles was conducted in July 2017, using PubMed and Scopus electronic databases and manual troll for literature in a 5-year period from June 2012 to May 2017. Medical search headings included 'reoperation', 'return to operation theatre', 'complications', 'appendicectomy', 'outcomes', 'abscess drainage' with Boolean operators AND or OR.

The method of analysis and inclusion criteria were specified in advance to avoid selection bias and documented in a protocol which was registered and published with the International Prospective Register of Systematic Reviews (PROSPERO) on 09/06/17 (ID CRD42017069040). This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Studies were included in the systematic review if the following criteria were met; studies that involved open or laparoscopic appendicectomy which reported reoperation rates and IR drainage rates, and full articles that were available in the English language. Studies were not included for any of the following reasons; studies that were reviews, meta-analyses, case reports, letters or protocols, studies that did not report key outcomes, interval appendicectomy, antibiotics as a primary intervention, series with less than 50 appendicectomy patients and those which data was inadequate for interpretation via meta-analysis.

Eligibility assessment was performed independently in a blinded standardised manner by two reviewers (ASB, UM). Disagreements between reviewers were resolved by discussion between the two review authors. If no agreement could be reached, a third reviewer decided (AJ).

Definitions

Appendicectomy was defined as the surgical removal of the appendix by either laparoscopic or open methods. Reintervention was defined as unplanned or unexpected reoperation or IR within 30 days of index appendicectomy. Reoperation was expressed as return to operating room (OR), and IR defined as imaging guided draining of a collection. The American Association for Surgery Trauma grading system was used to measure the anatomical severity of appendicitis (Table 1) [17].

Quality assessment and data extraction

The descriptive and quantitative data from the screened studies was extracted by the same reviewer (ASB) for the following variables: country of study, study type, study timeline, study size, number of hospital sites, type of procedure, inclusion and exclusion criteria of each study.

Grades	Operative AAST description of appendicitis
Normal	Normal appendix
Grade 1	Acutely inflamed appendix intact
Grade 2	Gangrenous appendix intact
Grade 3	Perforated appendix with local contamination
Grade 4	Perforated appendix with peri appendiceal phlegmon or abscess
Grade 5	Perforated appendix with generalized peritonitis

Table 1: AAST grading system for appendicitis [17].

Methodological Index for Non-Randomised Studies (MINORS) criteria [18], was used to assess quality as it is designed for the quality assessment of comparative and non-comparative surgical studies using a 3-point scale (0 not reported, 1 reported but inadequate, 2 reported and adequate) on eight items for non-comparative studies and 12 items for comparative studies. The ideal global score for non-comparative and comparative studies was chosen at 16 and 24, respectively. All collated studies including randomised controlled trials were marked against the MINORS criteria to assess the studies with the best methodologies to include in the final analysis. The studies with a MINORS score of ≥ 16 out of 24 for comparative and ≥ 10 out of 16 for non-comparative were included in the final analysis [19-22].

Data extracted included reintervention rate and potential risk factors. These included the methods of surgical procedure, the grade of surgeon performing the operation, and the pathology of the appendicitis [23].

Statistical analysis

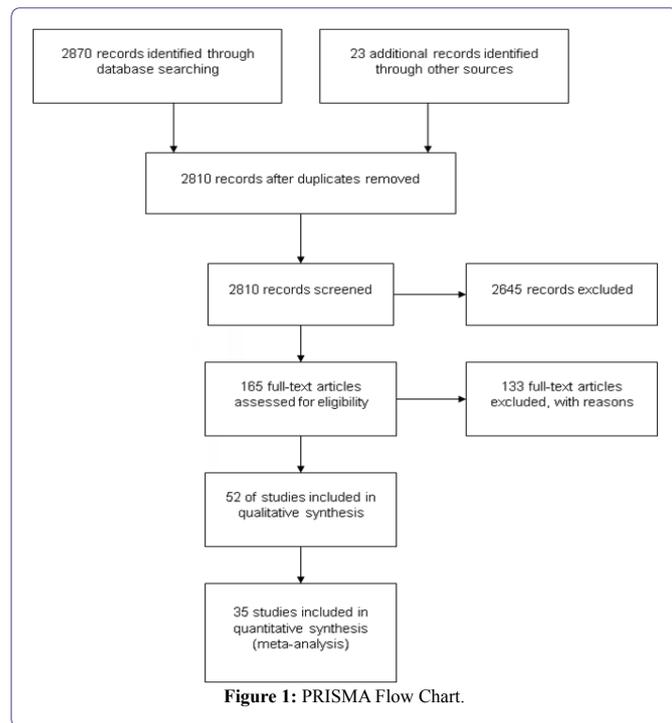
Overall rates calculation and funnel plots were created using Microsoft Excel 2017. The forest plots and statistical analysis were performed on Revman 5. A dichotomous fixed-effect meta-analysis using the Mantel-Haenszel method was used to determine any statistical significance between the reintervention rates between two groups that were homogenous studies, and random-effect models were used for heterogeneous studies. A sensitivity analysis was performed to investigate the impact of different decisions on the result by comparing fixed-effect and random-effect models. The results were presented in a pooled odds ratio and a 95% confidence interval in a forest plot. Statistical significance was defined as $p < 0.05$. I^2 of $> 50\%$ is considered to be substantially heterogeneous [24-30].

Results

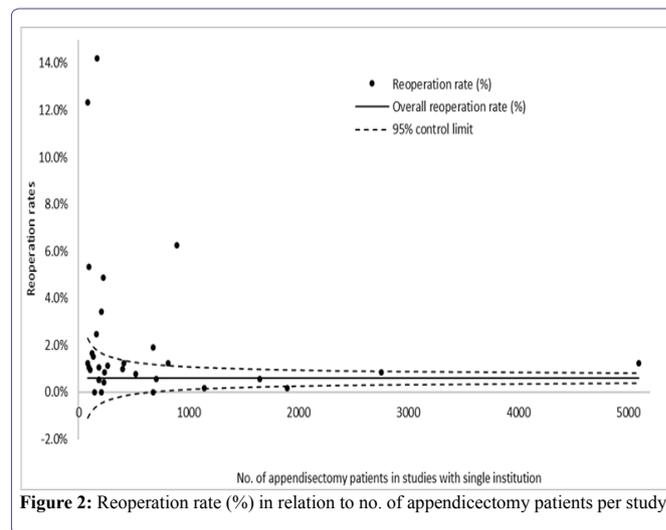
Rate of reintervention

The study reviewed 2810 articles of which 165 were found to be potentially suitable. After applying the MINORS cut off score, 52 were used for reintervention rates. Of the 52, 35 had comparative groups to facilitate forest plot meta-analysis. Figure 1 provides a PRISMA flow chart for identification and inclusion of relevant papers.

This meta-analysis included reported outcomes on a total of 319,053 appendicectomies. The study characteristics are shown in Table 2. Overall, 0.9% (2728/319053) (range 0.0 to 14.2%) underwent some form of reintervention. Subdividing reintervention into reoperation and IR drainage, the reoperation rate was 0.6% (2013/313778) which ranged from 0.0 to 14.2% and IR drainage was 1.5% (583/39799) which ranged from 0.0% to 11.1% [31-33].



There was no correlation ($r=-0.2$) or statistical significance ($p=0.3$) between the sample sizes of single institutions and reoperation rate (Figure 2). Similarly, there was also no correlation ($r=-0.3$) or statistical significance ($p=0.4$) between the sample size institutions and drainage rate (Figure 3).



Study	Country	No. of participating hospitals	Prospective/Retrospective	Ages	Sample size	Reoperation	IR drainage	Overall reinter-vention
Akkoyn 2012	Turkey	1	Retrospective	1 - 15 y	234	0.9%		0.9%
Almstrom 2014	Sweden	1	Retrospective	1 - 15 y	2756	0.8%		0.8%
Andersson 2014	Sweden	All national hospitals	Retrospective	All	169896	0.2%		0.2%
Bansal 2012	Switzerland	1	Prospective	< 15 y	187	1.1%	1.6%	2.7%
Chang 2013	South Korea	1	Retrospective	Children	186	0.5%	1.6%	2.2%
Collaborative 2013	UK	95	Prospective	All	3326			2.9%
Columbo 2012	UK	1	Retrospective	> 16 y	205	3.4%		3.4%
Da silva 2014	Brazil	1	Retrospective	< 16 y	94	5.3%		5.3%
Di Saverio 2014	Italy	1	Prospective	>14 y	210	0.0%	1.4%	1.4%
Emil 2014	Canada	1	Retrospective	10 - 20 y	1145	0.2%	1.7%	1.8%
Frutos 2013	Spain	1	Prospective	> 11 y	184	0.5%		0.5%
Galli 2013	USA	1	Retrospective	> 15 y	169	14.2%		14.2%
Gonenc 2012	Turkey	1	Prospective	> 15 y	107	0.9%		0.9%
Graat 2012	Netherlands	1	Retrospective	All	894	6.3%		6.3%
Kocatas 2013	Turkey	1	Prospective	> 15 y	96	1.0%		1.0%
Kang 2016	South Korea	1	Retrospective	All	133	1.5%		1.5%
Kapishke 2013	Germany	1	Retrospective	< 16 y	163	2.5%		2.5%
Kelly 2014	USA	57	Prospective	2 - 18 y	5097	1.2%		1.2%
Kim 2015	South Korea	1	Retrospective	All	2587	0.2%		0.2%
Kim 2016	South Korea	1	Retrospective	< 18 y	400	1.0%		1.0%
Kronman 2016	USA	23	Retrospective	3 - 18 y	24984	0.2%		0.2%
LaRieveire 2013	USA	All hospitals in Washington state	Retrospective	< 18 y	36525	1.7%		1.7%
Lebere 2017	USA	1	Retrospective	> 18 y	681	0.0%		0.0%
Lee 2013	South Korea	1	Prospective	> 16 y	229	0.4%		0.4%
Mason 2012	USA	Multiple	Prospective	> 16 y	13330	1.5%		1.5%
Michailidou 2015	USA	1	Retrospective	< 21 y	264	1.1%		1.1%

Author (Year)	Country	No. of Patients	Study Design	Age Group	Total Patients	IR Drainage Rate (%)	Reoperation Rate (%)	Overall Rate (%)
Michailidou 2015	USA	50	Retrospective	2 - 18 y	2812	1.3%		1.3%
Moazzez 2012	USA	Multiple	Retrospective	> 65 y	3674	2.7%		2.7%
Mohamed 2013	Egypt	1	Retrospective	All	214		7.5%	7.5%
Nadeem 2016	Pakistan	3	Retrospective	All	68	1.5%		1.5%
Ndofor 2016	South Africa	1	Retrospective	All	120	1.7%	4.2%	5.8%
Putnam 2017	USA	1	Prospective	< 18 y	410	1.2%		1.2%
Reinisch 2017	Germany	1	Retrospective	> 12 y	680	1.9%		1.9%
Rickert 2015	Germany	9	Prospective	> 16 y	104	2.9%		2.9%
Sadot 2013	Israel	1	Retrospective	All	1899	0.2%		0.2%
Sauvain 2016	Switzerland	6	Retrospective	> 16 y	2559	0.5%		0.5%
Schlottman 2016	Argentina	1	Retrospective	All	225	4.9%	3.1%	8.0%
Shelton 2014	UK	1	Retrospective	All	517	0.8%		1.4%
Siam 2017	Israel	1	Retrospective	> 16 y	1649	0.5%		0.5%
Sivrikoz 2015	USA	Multiple	Retrospective	> 18 y	1211	1.7%		1.7%
Skarda 2015	USA	1	Retrospective	All	708	0.6%	1.3%	1.8%
Soll 2016	Switzerland	1	Retrospective	All	813	1.2%		1.2%
Suh 2016	South Korea	1	Retrospective	All	145	0.0%	0.7%	0.0%
Sulkowski 2014	USA	44	Retrospective	< 18 y	33482	0.9%	1.4%	2.3%
Swank 2014	Netherlands	5	Retrospective	>18 y	1036		1.4%	1.4%
Taguchi 2016	Japan	1	Retrospective	>19 y	81	1.2%	11.1%	12.3%
Teoh 2012	Hong Kong	Multiple	Retrospective	18 - 75 y	200			3.0%
Thomson 2015	USA	1	Retrospective	> 12 y	81	12.3%	1.2%	13.6%
Van Rossem 2016	Netherlands	8	Prospective	All	415			7.0%
Van Rossem 2016	Netherlands	8	Prospective	> 18 y	1378	2.0%	0.9%	2.8%
Yang 2015	South Africa	5	Prospective	All	134	3.0%		3.0%
Yeom 2014	South Korea	1	Retrospective	All	84		2.4%	2.4%

Table 2: Study Characteristics.

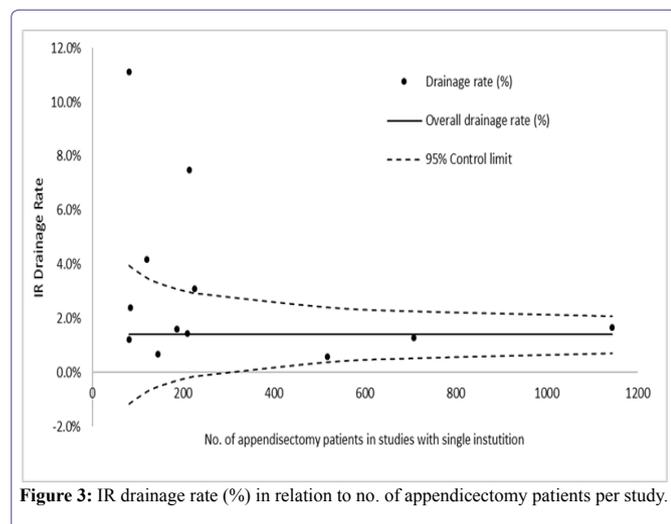


Figure 3: IR drainage rate (%) in relation to no. of appendicectomy patients per study.

Reasons for reintervention

There were 121 documented reasons for reoperation. 59(48.8%) had organ/space surgical site infection, 7(5.8%) sepsis, 4(3.3%) haematomas, 3(2.5%) superficial incisional surgical site infections, 3(2.5%) small bowel obstructions, 3(2.5%) appendiceal stump complication, 2(1.7%) iatrogenic ileal injuries, 2(1.7%) incisional hernias and 38 had other reasons [34].

For radiological reintervention, there were 558 documented reasons. 551(98.7%) had intra-abdominal abscess, 6(1.1%) had intra-abdominal sepsis and 1(0.2%) had intra-abdominal fluid collection [35].

Risk factors

Significantly fewer reinterventions occurred in the laparoscopic group compared to open (OR=0.65, CI=0.55-0.76, P=< 0.0001, I²=40%). This reintervention related to less reoperations in the laparoscopic group (OR=0.62, CI=0.52-0.73, P=<0.0001, I²=50%) rather than IR drainage (OR=1.18, CI=0.65-2.15, P=0.58, I²=0%) (Figure 4).

Single port laparoscopy (SILS) versus triple port laparoscopy did not appear to affect reintervention rates (OR=0.23, CI=0.05-1.05, P=0.06, I²=0) (Figure 5). There was also no statistical difference between those completed laparoscopically compared to those undergoing conversion from laparoscopy to open (OR=0.59, CI=0.01-23.86, P=0.94, I²=72%).

Paediatric and general surgeons had similar outcomes (OR=2.50, CI=0.66-9.47, P=0.18, I²=0%), as did resident and senior surgeons (OR=1.42, CI=0.86-2.35, P=0.17, I²=0%). Results show an increased rate of reoperations in AAST grades 3 to 5 by 4.62 times (OR=4.62, CI=2.95-7.22, P=<0.00001, I²=25%) (Figure 6).

There were statistically more reoperations after readmission compared to before patient discharge (OR = 0.09, CI = 0.03 - 0.30, P =

< 0.0001, I² = 0%), and there was a higher rate of reoperation in those who had an intra-abdominal drainage for complicated appendicitis during surgery than those without (OR = 11.01, CI = 1.82 - 66.60, P = 0.009, I² = 24%).

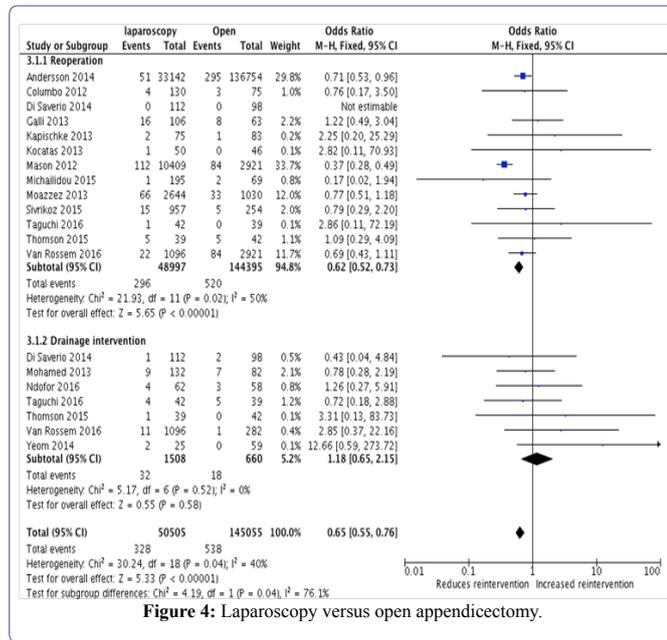


Figure 4: Laparoscopy versus open appendicectomy.

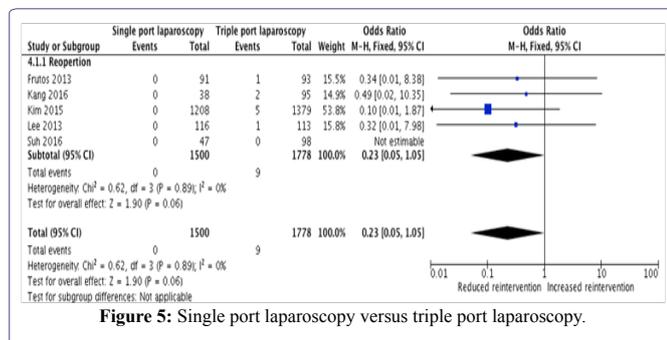


Figure 5: Single port laparoscopy versus triple port laparoscopy.

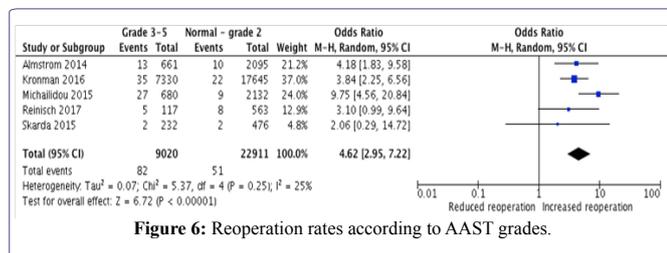


Figure 6: Reoperation rates according to AAST grades.

Discussion

This meta-analysis identified 52 studies contributing to a cohort of over 300,000 patients undergoing appendicectomy, with an overall incidence of reintervention of <1%. Not all 52 studies documented both rates of reoperation and IR data was only extracted if the study clearly stated whether or not reintervention was performed. As a result, the total cohort of patients undergoing reoperation and IR was varied [36-41].

There was a variation with the rate of reintervention from 0.0% to 14.2%. The reasons for this variation are complex and are related to the heterogeneous variables of the studies including sample size, region, age range of participants and inclusion and exclusion criteria [42-45].

Scott, et al. in a US based study of national inpatients from emergency surgery, between 2008-2011, ranked appendicectomy as the 8th most common procedure to result in mortality. Appendicectomy mortality ranked after the following procedures; excision of large intestine, excision of small intestine, laparotomy, operative control of peptic ulcer disease, lysis of peritoneal adhesion, cholecystectomy and total colectomy accordingly [1,46-50].

Small series which only included complicated appendicitis such as Galli et al. and Thomson et al. reported high reintervention rate. Galli et al in a retrospective based US based adult study, that only included complicated appendicitis, had the largest reintervention rate of 14.2% [29, 51-56]. Thomson et al. had the second highest reintervention rate of 13.6%, a retrospective study of complicated appendicitis [57-64]. Lower rates of reintervention are more likely to be seen in series using large databases, where data has great chance of not being recorded [65-69].

The categorization and reported grading of appendicitis was somewhat problematic. A binary categorical division into complicated and uncomplicated appendicitis is over simplified and limits robust analysis of complications. The American Association for the Surgery of Trauma (AAST) offers a more comprehensive view of the spectrum of the initial disease, thus affording a more robust analysis of outcomes linked to original disease severity [17]. This applies particularly to grade 3 to 5 which are more likely to have complications and reinterventions.

Of the 52 studies included in this meta-analysis there were 7 studies which only included grade 3 to 5 appendicitis [24, 29, 46, 54, 60, 62, 64]. The average rate of reintervention for complicated appendectomies of these 7 studies was higher at 2.5% (2.2-14.2%).

Our meta-analysis identified that IR intervention occurred almost 3 times as frequently as reoperation. The leading cause for IR intervention is largely post-operation intra-abdominal abscess followed by intra-abdominal sepsis and fluid collection. Strategies to reduce intra-abdominal sepsis, as outlined by de Saverio (recent guidelines) should be adopted and analysed [14]. International databases to document IR with clearly defined outcomes would help identify clearer indications and pitfalls.

Allaway, et al. did a study of 4900 post-appendicectomy patients and the role of early laparoscopic washout for persistent sepsis. In their retrospective study 41 (0.8%) patients had a laparoscopic washout, 16 (0.3%) had percutaneous drainage, and 6 (0.1%) open drainage. The mean time after appendicectomy to discharge was significantly shorter for laparoscopic washout (4.1 days vs. 10.1 and 9.0 days). The mean time for resolution of SIRS was significantly shorter (2.0 days vs. 3.3 and 5.2 days). They felt that early laparoscopic washout for persistent intra-abdominal sepsis may be an alternative to non-operative management and delayed intervention for intra-abdominal abscess and may have better outcomes than either percutaneous drainage or open drainage [70].

Our meta-analysis found the commonest indication for reoperation was for organ/space surgical site infection, followed by post-operative septic collections and haematoma. These trends seem to be universal irrespective of whether previous studies were from single institutions, registry based, and on the countries studied.

With increasing use of guidelines and opportunities to reduce surgical site infection [71], strategies to optimise surgery need to be considered to reduce reintervention and reoperation rate. These include the hazards of non-operative management and the potential for increased complications in patients who fail non-operative management [72]. The role of delay to definitive surgery in complicated grade 3 - 5 appendicitis results in potential increase of reintervention rate [73].

Reduction of surgical site infection (SSI) may lead to a reduction in reintervention. The use of a bundle may help achieve this and involve multiple elements including wound ring protectors [74], appropriate prophylactic antibiotics [75] and administering prophylactic antibiotics less than 120 minutes before incision [76]. In a new development, a recent meta-analysis by Hureibi et al. showed no reduction in SSI with delayed primary closure [77]. This may help earlier discharge of patients post appendectomy and reduce need for dressing and associated costs.

Ninh and colleagues in a review of 72,538 patients undergoing appendectomy found that those who developed sepsis post-operatively were more likely to return to the operating room (24.8% vs. 0.8%, be re-admitted (53.4% vs. 2.7% and die within 30 days of surgery, 5.5% vs. 0.05%) [69]. Patients with multiple risk factors may benefit from non-operative management in mild cases however surgery is still indicated with increasing grades and complexity of appendicitis. Several meta-analysis have supported the efficacy of non-operative management and decreased risk of sepsis [78-82]. Identifying appropriate patients for non-operative management is crucial as up to 40% will get recurrent appendicitis.

Patients who present with appendicular mass or abscess are a select group whereby depending on surgical preference may either be subjected to a non-operative Ochsner-Sherren type regimen or surgery. Non-operative management involves marking of the palpable mass size on the patient's skin and commencing antibiotic therapy. Non-surgical treatment of appendicular abscess or phlegmon succeeds in over 90% with an overall rate of recurrence of 7.2%, and 19.7% of cases require percutaneous drainage [83]. Fugazzola, et al. found that children tend to have better results in terms of readmission and complication rate in those managed non-operatively [84]. On the other hand, Mentula et al. demonstrated that laparoscopic appendectomy had a better outcome in these patients with significant reduction in unplanned readmission. Percutaneous drainage was required in only 7% of the laparoscopic appendectomy group compared to 30% of the controls with a greater uneventful recovery rate of 90% in the laparoscopic group compared to 50% of conservative group [85]. The issue therefore remains somewhat controversial.

Reoperation for small bowel obstruction was uncommon, counting for only 2.5% of the overall group. Sakari et. al, a recent retrospective study of 402 patients undergoing surgery for small bowel obstruction in Scandinavia, identified that post appendectomy complications accounted for 29% of the overall population undergoing reoperation for small bowel obstruction [86]. Consideration should potentially be given to the prevention of adhesions developing with the use of icodextrin 4% solution [87,88].

In conclusion, this meta-analysis of reoperation and radiological reintervention post appendectomy identified a low but not insignificant risk. Patients and their families need to be well informed of these risks. Strategies should be implemented to include pathway and bundle in appendectomy management to reduce the potential risk of such events occurring.

Conflict of Interest: None

This project is supported by the European Union's INTERREG VA Programme, managed by the Special EU Programmes Body (SEUPB) and Donegal Clinical and Research Academy.

References

1. Scott JW, Olufajo OA, Brat GA, Rose JA, Zogg CK, et al. (2016) Use of National Burden to Define Operative Emergency General Surgery. *JAMA Surg* 02115: e160480.
2. Addiss DG, Shaffer N, Fowler BS, Tauxe RV (1990) The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 132: 910-925.
3. McCarthy M (2016) Seven procedures account for 80% of emergency general surgery operations, deaths, and complications, US study finds. *BMJ* 353: i2498.
4. Ferris M, Quan S, Kaplan BS, Molodecky N, Ball CG, et al. (2017) The Global Incidence of Appendicitis. *Ann Surg* 266: 237-241.
5. Di Saverio S, Sibilio A, Giorgini E, Biscardi A, Villani S, et al. (2014) The NOTA Study (Non Operative Treatment for Acute Appendicitis). *Ann Surg* 260: 109-117.
6. Wilms IMH, de Hoog DE, de Visser DC, Janzing HM (2011) Appendectomy versus antibiotic treatment for acute appendicitis. *Cochrane Database Syst Rev* 9: CD008359.
7. Esposito C, Calco AI, Castagnetti M, Alicchio F, Saurez C, et al. (2012) Open versus laparoscopic appendectomy in pediatric population: a literature review and analysis of complications. *J Laparoendosc Adv Surg Tech A* 22: 834-839.
8. Johnson WC, Gerzof SG, Robbins AH, Nabseth DC (1981) Treatment of abdominal abscesses: comparative evaluation of operative drainage versus percutaneous catheter drainage guided by computed tomography or ultrasound. *Ann Surg* 194: 510-520.
9. Brolin RE, Noshier JL, Leiman S, Lee WS, Greco RS (1984) Percutaneous catheter versus open surgical drainage in the treatment of abdominal abscesses. *Am Surg* 50: 102-108.
10. Dobremez E, Lavrand F, Lefevre Y, Boer M, Bondonny JM, et al. (2003) Treatment of post-appendectomy intra-abdominal deep abscesses. *Eur J Pediatr Surg* 13: 393-397.
11. Gorter RR, Meiring S, van der Lee JH, Heij HA (2016) Intervention not always necessary in post-appendectomy abscesses in children; clinical experience in a tertiary surgical centre and an overview of the literature. *Eur J Pediatr* 175: 1185-1191.
12. Brolin RE, Noshier JL, Leiman S, Lee WS, Greco RS (1984) Percutaneous catheter versus open surgical drainage in treatment of abdominal abscess. *Am Surg* 50: 102-108.
13. Bailey K, Choynowski M, Kabir SMU, Lawler J, Badrin A, et al. (2019) Meta-analysis of unplanned readmission to hospital post-appendectomy: an opportunity for a new benchmark. *ANZ J Surg* 89: 1386-1391.
14. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augstin G, et al. (2020) Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg* 15: 27.

15. <http://www.icd9data.com/2012/Volume1/800-999/996-999/998/998.9.htm>
16. Protocol for the surveillance of surgical site infection, version 6 (2013) Public Health England.
17. Hernandez MC, Aho JM, Habermann EB, Choudhry AJ, Morris DS, et al. (2017) Increased anatomic severity predicts outcomes: Validation of the American Association for the Surgery of Trauma's Emergency General Surgery score in appendicitis. *J Trauma Acute Care Surg* 82: 73-78.
18. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, et al. (2003) Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. *ANZ J Surg* 73: 712-716.
19. Akkoyun I, Tas Tuna A (2012) Advantages of abandoning abdominal cavity irrigation and drainage in operations performed on children with perforated appendicitis. *J Pediatr Surg* 47: 1886-1890.
20. Almström M, Svensson J, Patkova B, Svenningsson A, Wester T (2016) In-hospital Surgical Delay Does Not Increase the Risk for Perforated Appendicitis in Children: A Single-center Retrospective Cohort Study. *Ann Surg*. 265: 616-621.
21. Andersson R (2014) Short-term complications and long-term morbidity of laparoscopic and open appendicectomy in a national cohort. *BMJ Brit Med J* 101: 1135-1142.
22. Bansal S, Banever G, Karrer F, Partrick D (2012) Appendicitis in children less than 5 years old: Influence of age on presentation and outcome. *Am J Surg* 204: 1031-1035.
23. Bhangu A, Richardson C, Torrance A, Pinkney T, Battersby C, et al. (2013) Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy. *BMJ Brit Med J* 100: 1240-1252.
24. Chang H, Han S, Choi S, Oh J (2013) Feasibility of a laparoscopic approach for generalized peritonitis from perforated appendicitis in children. *Yonsei Med J* 54: 1478-1483.
25. Colombo F, Andreani S, Gravante G, Davies A (2012) Laparoscopic vs. open appendicectomies: Results obtained by junior surgeons at a british University Hospital. *Eur Rev Med Pharmacol* 16: 687-690.
26. Da Silva PS, de Aguiar VE, Waisberg J (2014) Pediatric surgeon vs general surgeon: Does subspecialty training affect the outcome of appendicitis? *Pediatr Int* 56: 248-253.
27. Emil S, Elkady S, Sibat L, Youssef F, Baird R, et al. (2014) Determinants of postoperative abscess occurrence and percutaneous drainage in children with perforated appendicitis. *Pediatr Surg Int* 30: 1265-1271.
28. Frutos MD, Abrisqueta J, Lujan J, Abellan I, Parrilla P (2013) Randomized prospective study to compare laparoscopic appendectomy versus umbilical single-incision appendectomy. *Ann Surg* 257: 413-418.
29. Galli R, Banz V, Fenner H, Metzger J (2013) Laparoscopic approach in perforated appendicitis: Increased incidence of surgical site infection? *Surg Endosc* 27: 2928-2933.
30. Gonenc M, Gemici E, Kalayci M, Karabulut M, Turhan A, et al. (2012) Intracorporeal Knotting Versus Metal Endoclip Application for the Closure of the Appendiceal Stump During Laparoscopic Appendectomy in Uncomplicated Appendicitis. *J Laparoendosc Adv Surg Tech A* 22: 231-235.
31. Graat L, Bosma E, Roukema J, Heisterkamp J (2012) Appendectomy by Residents Is Safe and Not Associated with a Higher Incidence of Complications. *Ann Surg* 255: 715-719.
32. Kang B, Yoon K, Jung S, Lee G, Lee H (2016) Feasibility of single-incision laparoscopic appendectomy in a small hospital. *Ann Surg Treat Res* 91: 74-79.
33. Kapischke M, Pries A, Caliebe A (2013) Short term and long-term results after open vs. laparoscopic appendectomy in childhood and adolescence: a subgroup analysis. *BMC Pediatr* 13: 154.
34. Kelly K, Fleming F, Aquina C, Probst C, Noyes K, et al. (2014) Disease severity, not operative approach, drives organ space infection after pediatric appendectomy. *Ann Surg* 260: 466-773.
35. Kim J, Kim H, Park S, Lee J, Heo D, et al. (2015) Single-incision Laparoscopic Appendectomy Versus Conventional Laparoscopic Appendectomy. *Ann Surg* 262: 1054-1058.
36. Kim Y, Jung K, Ryu Y, Moon S (2016) Pediatric appendectomy: the outcome differences between pediatric surgeons and general surgeons. *Surg Today* 46: 1181-1186.
37. Kocataş A, Gönenç M, Bozkurt M, Karabulut M, Gemici E, et al. (2013) Comparison of open and laparoscopic appendectomy in uncomplicated appendicitis: A prospective randomized clinical trial. *Ulus Travma Acil Cerrahi Derg* 19: 200-204.
38. Kronman M, Oron A, Ross R, Hersh A, Newland J, et al. (2016) Extended-Versus Narrower-Spectrum Antibiotics for Appendicitis. *Pediatrics* 138: e20154547
39. Lariviere C, McAteer J, Huaco J, Garrison M, Avansino J, et al. (2013) Outcomes in pediatric surgery by hospital volume: A population-based comparison. *Pediatr Surg Int* 29: 561-570.
40. Leberer D, Elliott J, Dominguez E (2016) Patient characteristics, outcomes and costs following interhospital transfer to a tertiary facility for appendectomy versus patients who present directly. *Am J Surg pii: S0002-9610: 30725-30750*.
41. Lee W, Choi S, Lee J, Kim K, Park Y, et al. (2013) Single-Port Laparoscopic Appendectomy Versus Conventional Laparoscopic Appendectomy. *Ann Surg* 257: 214-218.
42. Mason RJ, Moazzez A, Moroney JR, Katkhouda N (2012) Laparoscopic vs. open appendectomy in obese patients: Outcomes using the American College of Surgeons National Surgical Quality Improvement Program database. *J Am Col Surg* 215: 88-99.
43. Michailidou M, Goldstein S, Sacco Casamassima M, Salazar J, Elliott R, et al. (2015) Laparoscopic versus open appendectomy in children: The effect of surgical technique on healthcare costs. *Am J Surg* 210: 270-275.
44. Michailidou M, Sacco Casamassima M, Goldstein S, Gause C, Karim O, et al. (2015) The impact of obesity on laparoscopic appendectomy: Results from the ACS National Surgical Quality Improvement Program pediatric database. *J Pediatr Surg* 50: 1880-1884.
45. Moazzez A, Mason R, Katkhouda N (2013) Thirty-day outcomes of laparoscopic versus open appendectomy in elderly using ACS/NSQIP database. *Surg Endosc*. 27: 1061-1071.
46. Mohamed A, Mahran K (2013) Laparoscopic appendectomy in complicated appendicitis: Is it safe? *J Minim Access Surg* 9: 55-58.
47. Nadeem M, Khan S, Ali S, Shafiq M, Elahi M, et al. (2016) Comparison of extra-corporeal knot-tying suture and metallic endo-clips in laparoscopic appendiceal stump closure in uncomplicated acute appendicitis. *Int J Surg Open* 2: 11-14.
48. Ndofof B, Mokotedi S, Koto M (2016). Comparing laparoscopic appendectomy to open appendectomy in managing generalised purulent peritonitis from complicated appendicitis: The uncharted path. *S Afr J Surg* 54: 30-34.
49. Putnam L, Ostovar-Kermani T, Le Blanc A, Anderson K, Holzmann-Pazgal G, et al. (2017). Surgical site infection reporting: more than meets the agar. *J Pediatr Surg* 52: 156-160
50. Reinisch A, Heil J, Woeste G, Bechstein W, Liese J (2017) The meteorological influence on seasonal alterations in the course of acute appendicitis. *J Surg Res* 7: 1-7.
51. Rickert A, Kruger C, Runkel N, Kuthe A, Koninger J, et al. (2015) The TICAP-Study (titanium clips for appendicular stump closure): A prospective multicentre observational study on appendicular stump closure with an innovative titanium clip. *BMC Surg* 15: 85.

52. Sadot E, Wasserberg N, Shapiro R, Keidar A, Oberman B, et al. (2013) Acute Appendicitis in the Twenty-First Century: Should We Modify the Management Protocol? *J Gastroint Surg* 17: 1462-1470.
53. Sauvain M, Slankamenac K, Muller M, Wildi S, Metzger U, et al. (2016) Delaying surgery to perform CT scans for suspected appendicitis decreases the rate of negative appendectomies without increasing the rate of perforation nor postoperative complications. *Langenbeck's Arch Surg* 401: 643-649.
54. Schlottmann F, Reino R, Sadava E, Campos Arbulú A, Rotholtz N (2016) Could an abdominal drainage be avoided in complicated acute appendicitis? Lessons learned after 1300 laparoscopic appendectomies. *Int J Surg* 36: 40-43.
55. Shelton J, Brown J, Young J (2014) Preoperative C-reactive protein predicts the severity and likelihood of complications following appendectomy. *Ann R Coll Surg Eng* 96: 369-372.
56. Siam B, Al-Kurd A, Simanovsky N, Awesat H, Cohn Y, et al. (2017). Comparison of Appendectomy Outcomes Between Senior General Surgeons and General Surgery Residents. *JAMA Surg* 152: 679-685.
57. Sivrikoz E, Karamanos E, Beale E, Teixeira P, Inaba K, et al. (2015) The effect of diabetes on outcomes following emergency appendectomy in patients without comorbidities: A propensity score-matched analysis of National Surgical Quality Improvement Program database. *Am J Surg* 209: 206-211.
58. Skarda D, Rollins M, Andrews S, McFadden M, Barnhart D, et al. (2015) One hospital, one appendectomy: The cost effectiveness of a standardized doctor's preference card. *J Pediatr Surg* 50: 919-922.
59. Soll C, Wyss P, Gelpke H, Raptis D, Breitenstein S (2016) Appendiceal stump closure using polymeric clips reduces intra-abdominal abscesses. *Langenbeck's Arch Surg* 401: 661-666.
60. Sulkowski J, Asti L, Cooper J, Kenney B, Raval M, et al. (2014) Morbidity of peripherally inserted central catheters in pediatric complicated appendicitis. *J Surg Res* 190: 235-241.
61. Swank H, Van Rossem C, Van Geloven A, In't Hof K, Kazemier G, et al. (2014) Endostapler or endoloops for securing the appendiceal stump in laparoscopic appendectomy: A retrospective cohort study. *Surg Endosc* 28: 576-583.
62. Taguchi Y, Komatsu S, Sakamoto E, Norimizu S, Shingu Y, et al. (2016) Laparoscopic versus open surgery for complicated appendicitis in adults: a randomized controlled trial. *Surg Endosc* 30: 1705-1712.
63. Teoh A, Chiu P, Wong T, Poon M, Wong S, et al. (2012) A double-blinded randomized controlled trial of laparoendoscopic single-site access versus conventional 3-port appendectomy. *Ann Surg* 256: 909-914.
64. Thomson J, Kruger D, Jann-Kruger C, Kiss A, Omshoro-Jones J, et al. (2015) Laparoscopic versus open surgery for complicated appendicitis: a randomized controlled trial to prove safety. *Surg Endosc* 29: 2027-2032.
65. van Rossem C, Bolmers M, Schreinemacher M, van Geloven A, Bemelman W (2015) Prospective nationwide outcome audit of surgery for suspected acute appendicitis. *Br J Surg* 103: 144-151.
66. Van Rossem C, Schreinemacher M, Van Geloven A, Bemelman W, Van Acker G, et al. (2016) Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. *JAMA Surg* 151: 323-329.
67. Yang E, Cook C, Kahn D (2015) Acute appendicitis in the public and private sectors in cape town, south africa. *World J Surg* 39: 1700-1707.
68. Yeom S, Kim M, Park S, Son T, Jung Y, et al. (2014) Comparison of the outcomes of laparoscopic and open approaches in the treatment of periappendiceal abscess diagnosed by radiologic investigation. *J Laparoendosc Adv Surg Tech A* 24: 762-769.
69. Ninh A, Wood K, Bui AH, Leitman IM (2019). Risk Factors and Outcomes for Sepsis after Appendectomy in Adults. *Surg Infect* 20: 601-606.
70. Allaway MGR, Clement K, Eslick GD, Cox MR (2019) Early Laparoscopic Washout may Resolve Persistent Intra-abdominal Infection Post-appendectomy. *World J Surg* 43: 998-1006.
71. Helmer K, Robinson E, Lally K, Vasquez J, Kwong K, et al. (2002) Standardized patient care guidelines reduce infectious morbidity in appendectomy patients. *Am J Surg* 183: 608-613.
72. Podda M, Cillara N, Di Saverio S, Lai A, Feroci F, et al (2017) Antibiotics-first strategy for uncomplicated acute appendicitis in adults is associated with increased rates of peritonitis at surgery. A systematic review with meta-analysis of randomized controlled trials comparing appendectomy and non-operative management with antibiotics. *Surgeon* 15: 303-314.
73. Saar S, Talving P, Laos J, Pödräng T, Sokirjanski M, et al. (2016) Delay between Onset of Symptoms and Surgery in Acute Appendicitis Increases Perioperative Morbidity: A Prospective Study. *World J Surg* 40: 1308-1314.
74. Ahmed K, Connelly TM, Bashar K, Walsh SR (2016) Are wound ring protectors effective in reducing surgical site infection post appendectomy? A systematic review and meta-analysis. *Ir J Med Sci* 185: 35-42.
75. Kasatpibal N, Nørgaard M, Sørensen HT, Schönheyder HC, Jamulitrat S, et al. (2006) Risk of surgical site infection and efficacy of antibiotic prophylaxis: A cohort study of appendectomy patients in Thailand. *BMC Infect Dis* 6: 111.
76. de Jonge SW, Gans SL, Atema JJ, Solomkin JS, Dellinger PE, et al. (2017) Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection: A systematic review and meta-analysis. *Medicine* 96: e6903.
77. Hureibi K, Abraham P, Al-Sunidar O, Alaraimi B, Elzaidi E (2019) To close or not to close? A systemic review and meta-analysis of wound closure in appendectomy. *Int J Surg* 16: 9-13.
78. Kirby A, Hobson RP, Burke D, Cleveland V, Ford G, et al. (2015) Appendectomy for suspected uncomplicated appendicitis is associated with fewer complications than conservative antibiotic management: A meta-analysis of post-intervention complications. *J Infect* 70: 105-110.
79. Liu K, Fogg L (2011) Use of antibiotics alone for treatment of uncomplicated acute appendicitis: A systematic review and meta-analysis. *Surgery* 150: 673-683.
80. Mason RJ, Moazzez A, Sohn H, Katkhouda N (2012) Meta-Analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect* 13: 74-84.
81. Varadhan KK, Neal KR, Lobo DN (2012) Safety and efficacy of antibiotics compared with appendectomy for treatment of uncomplicated acute appendicitis: Meta-analysis of randomized controlled trials. *BMJ* 344: e2156-e2156.
82. Findlay JM, Kafsi J el, Hammer C, Gilmour J, Gillies RS, et al (2016) Nonoperative management of appendicitis in adults: A systematic review and meta-analysis of randomized controlled trials. *J Am Coll Surg* 223:814-824.
83. Andersson R, Petzold M (2017) Nonsurgical treatment of appendiceal abscess or phlegmon: a systematic review and meta-analysis. *Ann Surg* 246: 741-748.
84. Fugazzola P, Coccolini F, Tomasoni M, Stella M, Ansaloni L, et al. (2019) Early appendectomy vs. conservative management in complicated acute appendicitis in children: a meta-analysis. *J Pediatric Surg* 54: 2234-2241.
85. Mentula P, Sammalkorpi H, Leppäniemi A (2015) Laparoscopic surgery or conservative treatment for appendiceal abscess in adults? A randomized controlled trial. *Ann Surg* 262: 237-242.

86. Sakari T, Christersson M, Karlbom U (2020) Mechanisms of adhesive small bowel obstruction and outcome of surgery; a population-based study. *BMC Surg* 20: 62.
87. Catena F, Ansaloni L, Di Saverio S, Pinna A (2012) P.O.P.A. study: prevention of postoperative abdominal adhesions by icodextrin 4% solution after laparotomy for adhesive small bowel obstruction. A prospective randomized controlled trial. *J Gastrointestinal Surg* 16: 382-388.
88. Klink C, Schickhaus P, Binnebosel M, Jockenhoewel S, Rosch R, et al. (2013) Influence of 4% icodextrin solution on peritoneal tissue response and adhesion formation. *BMC Surg* 13: 34.



- Advances In Industrial Biotechnology | ISSN: 2639-5665
- Advances In Microbiology Research | ISSN: 2689-694X
- Archives Of Surgery And Surgical Education | ISSN: 2689-3126
- Archives Of Urology
- Archives Of Zoological Studies | ISSN: 2640-7779
- Current Trends Medical And Biological Engineering
- International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X
- Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276
- Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292
- Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370
- Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594
- Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X
- Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562
- Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608
- Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879
- Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397
- Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751
- Journal Of Aquaculture & Fisheries | ISSN: 2576-5523
- Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780
- Journal Of Biotech Research & Biochemistry
- Journal Of Brain & Neuroscience Research
- Journal Of Cancer Biology & Treatment | ISSN: 2470-7546
- Journal Of Cardiology Study & Research | ISSN: 2640-768X
- Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943
- Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771
- Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844
- Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801
- Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978
- Journal Of Cytology & Tissue Biology | ISSN: 2378-9107
- Journal Of Dairy Research & Technology | ISSN: 2688-9315
- Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783
- Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X
- Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798
- Journal Of Environmental Science Current Research | ISSN: 2643-5020
- Journal Of Food Science & Nutrition | ISSN: 2470-1076
- Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X
- Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566
- Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485
- Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662
- Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999
- Journal Of Hospice & Palliative Medical Care
- Journal Of Human Endocrinology | ISSN: 2572-9640
- Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654
- Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493
- Journal Of Light & Laser Current Trends
- Journal Of Medicine Study & Research | ISSN: 2639-5657
- Journal Of Modern Chemical Sciences
- Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044
- Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X
- Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313
- Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400
- Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419
- Journal Of Obesity & Weight Loss | ISSN: 2473-7372
- Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887
- Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052
- Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X
- Journal Of Pathology Clinical & Medical Research
- Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649
- Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670
- Journal Of Plant Science Current Research | ISSN: 2639-3743
- Journal Of Practical & Professional Nursing | ISSN: 2639-5681
- Journal Of Protein Research & Bioinformatics
- Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150
- Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177
- Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574
- Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060
- Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284
- Journal Of Toxicology Current Research | ISSN: 2639-3735
- Journal Of Translational Science And Research
- Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193
- Journal Of Virology & Antivirals
- Sports Medicine And Injury Care Journal | ISSN: 2689-8829
- Trends In Anatomy & Physiology | ISSN: 2640-7752

Submit Your Manuscript: <http://www.heraldopenaccess.us/Online-Submission.php>