Appendectomy versus nonoperative management of simple appendicitis: A post hoc analysis of an Eastern Association for the Surgery of Trauma multicenter study using a hierarchical ordinal scale

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BACKGROUND: Controversy exists about the preferred initial treatment of appendicitis. We sought to compare the two treatments for initial management of simple appendicitis.

METHODS: In this post hoc analysis of the Multicenter Study for the Treatment of Appendicitis in America: Acute, Perforated, and Gangrenous database, subjects were divided into appendectomy or nonoperative management (NOM; antibiotics only or percutaneous drainage) cohorts. A novel topic-specific hierarchical ordinal scale was created with eight mutually exclusive categories: mortality, reoperation, other secondary interventions, readmission, emergency department visit, wound complication, surgical site infection, and no complication. Pairwise comparisons of American Association for the Surgery of Trauma Imaging Severity Grade 1 (simple appendicitis) patients were compared using win-lose-tie scoring and the sums of appendectomy/NOM groups were compared.

RESULTS: A total 3,591 subjects were included: 3,262 appendectomy and 329 NOM, with significant differences in baseline characteristics between groups. Across 28 sites, the rate of NOM ranged from 0% to 48%, and the loss to follow-up rate was significantly higher for NOM compared with appendectomy (16.5% vs. 8.7%, $p = 0.024$). In the simple appendicitis hierarchical ordinal scale analysis, 2,319 subjects resulted in 8,714,304 pairwise comparisons; 75% of comparisons resulted in ties. The median (interquartile range) sums for the two groups are as follows: surgical, 400 (400–400), and NOM, 400 (−2,427 to 400) ($p < 0.001$). A larger proportion of appendectomy subjects (88.1%) had an outcome that was equivalent (or better) than at least half of the subjects compared with NOM subjects (NOM, 70.5%; OR [95% confidence interval], 0.3 [0.2–0.4]).

CONCLUSION: In contemporary American practice, appendectomy (compared with NOM) for simple appendicitis is associated with lower odds of developing clinically important unfavorable outcomes in the first year after illness. (*J Trauma Acute Care Surg.* 2022;92: 1031–1038. Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level III.

KEY WORDS: Appendicitis; nonoperative management; appendectomy.

For more than 100 years since the historical publications by Fitz[1] and McBurney,[2] the definitive treatment for appendicitis in the United States has been appendectomy. Although nonoperative management (NOM) with antibiotics has been reported sporadically in the past century,[3,4] surgical intervention has long been the standard of care. Recently, however, NOM with antibiotics alone has gained in popularity[5] because of several recent high-profile European randomized controlled trials comparing appendectomy to NOM, most notably the Appendicitis Acuta (APPAC) trial from Finland.[6] Unfortunately, the ability to extrapolate the findings from this trial to current American practice is limited because of the APPAC trial's low utilization of laparoscopic surgery (~5%) and the requirement for 3 days of intravenous antibiotics for the NOM group. It is well documented in the literature that laparoscopic appendectomy is associated with shorter hospital length of stay and fewer surgical site infections compared with open appendectomy for complicated appendicitis.[7] Furthermore, the APPAC trial enrolled only simple acute (nonperforated) appendicitis and enrolled only adults up to age of 60 years. However, approximately 20% of patients present with complicated appendicitis and approximately 15% of patients with initial computed tomography evidence of simple appendicitis ultimately have complicated appendicitis by the time of surgery.[8] Prior investigators have reported a relatively high failure rate of initial NOM for complicated appendicitis, with up to 35% requiring rescue appendectomy.[9]

The Multicenter Study for the Treatment of Appendicitis in America: Acute, Perforated, and Gangrenous (MUSTANG) study[10] was a prospective multicenter observational study investigating the modern American treatment of simple and complicated appendicitis. Recent clinical trials have started to move away from simple binary outcomes in favor of more nuanced hierarchical ordinal scales comprising patient-centered outcomes.[11–14] We therefore performed a post hoc analysis of the MUSTANG database to compare patients initially treated nonoperatively with those treated initially with surgical appendectomy.

PATIENTS AND METHODS

We performed a post hoc analysis of the MUSTANG study, which was sponsored and supported by the Eastern Association for the Surgery of Trauma. The inclusion/exclusion criteria for the original MUSTANG study have been previously reported,[10] and for this post hoc analysis, we did not apply any further exclusion criteria. The MUSTANG study prospectively enrolled adults with appendicitis from 28 centers in the United States between January 2017 and June 2018 with follow-up (medical chart review) completed at 1 year after index hospitalization. This study conforms with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, and a complete checklist has been uploaded as Supplemental Digital Content (Supplementary Table 1, http://links.lww.com/

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TA/C368). Subjects were divided into appendectomy or NOM (defined as initial treatment plan of antibiotics only or percutaneous drainage) cohorts. A composite endpoint was defined to include surgical site infection, intra-abdominal abscess, wound complication, any Clavien-Dindo complication,[15] secondary intervention, emergency department (ED) visit, readmission, and mortality up during the follow-up period to 1 year after hospital discharge. The Comprehensive Complication Index (CCI)[16] was calculated for all patients, and the median CCI was compared between groups. Outcome assessors at all sites were trained to review the electronic health record after 1 year had elapsed from hospital discharge and review all clinical encounters. Patients without any clinical encounters were considered lost to follow-up and were not included in the final outcome analysis (listwise deletion).

The American Association for the Surgery of Trauma (AAST) Image severity is graded as follows: Grade 1, appendiceal thickening >6 mm with mild periappendiceal edema; Grade 2, appendiceal thickening >6 mm with severe periappendiceal edema; Grade 3, appendiceal thickening >6 mm, severe periappendiceal thickening with free intraperitoneal fluid in the right lower quadrant/pelvis; Grade 4, appendiceal thickening >6 mm or nonvisualized appendix with abscess or phlegmon; and Grade 5, appendiceal thickening >6 mm or nonvisualized appendix with free intraperitoneal fluid >1 quadrant.[17]

Using our previously defined endpoints from the original MUSTANG study, we created a novel topic-specific hierarchical ordinal scale in a fashion similar to that described by Novack et al.[11] All simple appendicitis patients' outcomes were assigned to one of eight mutually exclusive categories, which were arranged in decreasing order of importance: (1) mortality, (2) reoperation, (3) any other secondary intervention other than operation, (4) hospital readmission, (5) ED visit, (6) wound complication, (7) surgical site infection, and (8) no complications. Patients who experienced multiple outcomes (e.g., wound complication and hospital readmission) were assigned to the category corresponding with the most serious outcome. The MUSTANG subjects were assigned a clinical severity grading score according to the validated AAST grading schema for emergency general surgery conditions.[17,18] All subjects with an AAST Imaging Grade of 1 were selected and separated to those who received appendectomy and NOM. Each subject was then compared with every other subject and assigned a score based on which subject had a better clinical outcome (win, +1; lose, −1; tie, 0). For example, if one subject survives and the other does not, the pairwise scores are +1 and −1, respectively. If both subjects die, they are both assigned a score of 0. If both subjects survive, then they are next compared regarding reoperation and so forth. After a subject is compared with every other subject, the points are summed to obtain a cumulative score for that subject. Based on the hierarchical ordinal scale described previously, all pairs of patients were ranked to determine which patient did better for each of these pairs. In each pair, we assigned either +1 (patient one in pair was better), −1 (patient two in pair was better), or 0 (patients had equivalent outcomes). Then, the sum of each patient's comparison with every other patient is compared between the two treatments to determine how patients fare relative to the rest via a Wilcoxon rank-sum test. The idea is that, if the sum is negative, then their clinical outcome was either worse or equal to at least half the population and, for positive sums, the clinical outcome was better or equal to at least half the population. Also, the sum itself indicates the net difference between the number of patients whom they performed better than and those whom they performed worse than. For example, a sum of 40 means that there were 40 more pairwise comparisons where that patient had a more favorable outcome versus unfavorable. A p value of <0.05 was considered statistically significant, and all analyses were performed in R version 3.6.1.

RESULTS

A total of 3,591 subjects were included: 3,262 appendectomy and 329 NOM. Across 28 sites, the rate of NOM ranged from 0% to 48%. The two groups differed in several important baseline characteristics such as age, diabetes, comorbidities, duration of symptoms before presentation, clinical severity, and imaging severity (Table 1). The NOM group was more likely to experience the composite endpoint (65% vs. 24%, $p < 0.001$), although the CCI was higher in the appendectomy group (Table 1).

In the hierarchical ordinal scale analysis, we focused exclusively on subjects who were assessed to have simple appendicitis (i.e., AAST Appendicitis Imaging Grade 1) (Table 2). This involved 2,319 patients for a total of 8,714,304 pairwise comparisons. Of all the patient combinations, 75% of the pairwise comparisons resulted in ties that could not be broken; this includes the 2,952 self-comparisons (0.03%) that should have resulted in ties. The median (interquartile range) sums for the two groups are as follows: appendectomy, 400 (400–400), and NOM, 400 (−2,427 to 400) ($p < 0.001$). Although the medians are equal in both groups, the lower tails of the two distributions are responsible for the detected difference. For appendectomy patients, most of the population had positive sums, while a substantial portion of the NOM patients have negative sums suggesting inferior performance.

The between-group comparisons for sums are displayed in Table 3. Using the hierarchical ordinal scale comparison, if the sum is 0 or greater, then the subject has done either as well as or better than at least half of the subjects in the study, while, if it is less than 0, then they did worse or as badly as at least half. Thus, a larger proportion of the subjects who underwent appendectomy (88.1%) had an outcome that was equivalent (or better) than at least half of the subjects compared with those subjects who received NOM (70.5%) (OR [95% confidence interval], 0.3 [0.2–0.4]).

DISCUSSION

While the debate between appendectomy and NOM continues, our results support surgical intervention for simple appendicitis. When comparing clinically important, patient-centered outcomes ranked on an ordinal scale, patients with simple appendicitis undergoing appendectomy were more likely to have better outcomes than those undergoing NOM.

Our results are consistent with other studies. In a review of the Nationwide Inpatient Sample spanning from 1998 to 2014, Horn et al.[5] reported that NOM was increasing in popularity

TABLE 1. Surgery Versus Nonoperative Management of Appendicitis

	All (n = 3,591)	Appendectomy (n = 3,262)	Nonoperative Management (n = 329)	*p*
Age, y	41 (16.7)	40 (16.1)	50.5 (19.5)	<0.001
Female, n (%)	1,586 (44.2)	1,450 (44.5)	136 (41.3)	0.1
BMI, kg/m^2	28.6 (6.6) Missing = 108	28.7 (6.6) Missing = 102	28.0 (6.1) Missing = 6	0.07
Diabetes mellitus, n (%)	275 (7.6)	231 (7.1)	44 (13.4)	<0.001
Charlson Comorbidity Index, median (IQR)	0 (0–1)	0 (0–1)	1 (0–3)	<0.001
Prior abdominal surgery, n (%)	807 (23)	729 (22)	78 (24)	0.62
Duration of symptoms before presentation, n (%)				
<6 h	305 (8.9)	294 (9.5)	11 (3.4)	
6–11 h	480 (14.1)	465 (15.1)	15 (4.7)	
12–17 h	453 (13.3)	445 (14.4)	8 (2.5)	
18–23 h	351 (10.3)	336 (10.9)	15 (4.7)	
24–29 h	491 (14.4)	474 (15.4)	17 (5.3)	
30–35 h	61 (1.8)	56 (1.8)	5 (1.6)	
36–41 h	55 (1.6)	48 (1.6)	7 (2.2)	
42–47 h	114 (3.3)	105 (3.4)	9 (2.8)	<0.001
48–53 h	317 (9.3)	290 (9.4)	27 (8.4)	
54–59 h	13 (0.4)	11 (0.4)	2 (0.6)	
60–65 h	11 (0.3)	9 (0.3)	2 (0.6)	
66–71 h	40 (1.2)	34 (1.1)	6 (1.9)	
72–77 h	218 (6.4)	190 (6.2)	28 (8.7)	
78–83 h	3 (0.1)	2 (0.1)	1 (0.3)	
84–89 h	4 (0.1)	3 (0.1)	1 (0.3)	
90–96 h	42 (1.2)	30 (1.0)	12 (3.7)	
>96 h	442 (13.0)	286 (9.3)	156 (48.4)	
Clinical AAST severity grade, n (%)				
Grades 1, 2, and 3	3,295 (96.7)	2,996 (97.2)	299 (92.9)	
Grade 4	31 (0.9)	13 (0.4)	18 (5.6)	<0.001
Grade 5	53 (1.6)	50 (1.6)	3 (0.9)	
Tobacco, n (%)				
Never	623 (18.3)	568 (18.4)	55 (17.1)	
Former	513 (15.0)	449 (14.6)	64 (19.9)	0.06
Current	2,261 (66.3)	2,058 (66.8)	203 (63.0)	
Image AAST severity grade, n (%)	(n = 3,403)	(n = 3,262)	(n = 141)	<0.001
Grade 1	2,319 (68)	2,234 (73)	85 (26)	
Grade 2	94 (3)	93 (3)	1 (<1)	
Grade 3	513 (15)	481 (16)	32 (10)	
Grade 4	397 (12)	214 (7)	183 (57)	
Grade 5	80 (2)	59 (2)	21 (7)	
Outcomes at 1 y, n (%)*	993 (28)	778 (24)	215 (65)	<0.001
Surgical site infection	83 (2)	77 (2)	6 (2)	
Intra-abdominal abscess	180 (5)	120 (4)	60 (18)	
Wound complication	47 (1)	43 (1)	4 (1)	
Secondary intervention	289 (8)	119 (4)	170 (52)	
ED visit	532 (15)	432 (13)	100 (30)	
Hospital readmission	285 (8)	163 (5)	122 (37)	
Mortality	27 (1)	18 (1)	9 (3)	
Clavien-Dindo score, n (%)				<0.001
Grade 1	179 (5)	170 (5)	9 (3)	
Grade 2	77 (2)	66 (2)	11 (3)	
Grade 3a	51 (1)	32 (1)	19 (6)	
Grade 3b	41 (1)	20 (0.6)	21 (6)	
Grade 4a	12 (0.3)	10 (0.3)	2 (0.6)	
Grade 4b	7 (0.2)	5 (0.2)	2 (0.6)	

Continued next page

TABLE 1. *(Continued)*

	All (n = 3,591)	Appendectomy (n = 3,262)	Nonoperative Management (n = 329)	*p*
Grade 5	5 (0.1)	4 (0.1)	1 (0.3)	
CCI, median (IQR)	0 (0–0)	0 (0–1)	0 (0–0)	<0.001

*Subcategories of the composite endpoint are not mutually exclusive.
BMI, body mass index; IQR, interquartile range.

and was significantly associated with older patients with medical comorbidities. However, even after controlling for age and medical comorbid conditions, these investigators found that NOM was associated with a significantly higher risk of death. Other investigators have also reported that, in American practice, NOM is associated with longer hospital length of stay and higher rates of in-hospital complications.[19] A review of an American insurance administrative database from 2007 to 2015 reported that only 5% of patients with simple appendicitis underwent NOM and that this group was more likely to develop abscess and also require appendicitis-associated readmissions.[20] Although NOM patients had lower index hospitalization cost, they also required more follow-up visits in the subsequent year, and thus, the total cost of care was higher. Our study differs from these previous studies in several ways. First, our data reflect modern practice patterns regarding the use of laparoscopy and early discharge. In contrast to retrospective analyses of administrative databases collected for nonresearch purposes, the MUSTANG research study was conducted in a prospective fashion and collected extremely detailed data with intense efforts to ensure data completeness and fidelity. In addition, our data extend out to 1 year of follow-up, and the outcomes are defined to be patient centric and clinically important.

One of the most influential trials in the field of appendicitis research is inarguably the 2015 Scandinavian APPAC trial,[6] which randomized adults between age 18 and 60 years with computed tomography–proven simple appendicitis to NOM or appendectomy. It is interesting to note that the APPAC trial failed to meet their prespecified criterion for noninferiority, yet the prevailing interpretation of this trial remains that NOM is a viable alternative to appendectomy. Criticisms of the APPAC trial include the fact that abdominal and incisional pain comprised a very large proportion of the "complications" in the surgical group (who were overwhelmingly treated with open appendectomy) and also that appendicitis recurrences in the NOM group were not considered complications of treatment.[21] Despite a NOM failure rate of 27% at 1 year and increasing up to 39% by 5 years,[22] the authors and others[23] assert that this trial "supports the feasibility of antibiotic treatment alone as an alternative to surgery for uncomplicated acute appendicitis."[22] Controversy about the best treatment approach remains, and it is likely that the decision will require shared decision making with the patient.

While the original APPAC trial enrolled only simple appendicitis patients, the study by Mentula et al.[24] specifically enrolled patients with appendiceal abscess, randomizing them to either laparoscopic surgery or NOM. Patients randomized to appendectomy required fewer additional interventions (such as percutaneous drainage) and unplanned admissions. On the other hand, a meta-analysis of nonrandomized, mostly retrospective, studies concluded that NOM is superior to appendectomy for complicated appendicitis regarding complication and reoperation rate.[25] One theoretical concern about adopting NOM in all patients is the potential delayed diagnosis or treatment of early occult malignancy masquerading as appendicitis. The APPAC investigators also conducted a trial enrolling appendicitis abscess patients treated successfully with NOM and then randomized to either interval appendectomy or expectant management with follow-up magnetic resonance imaging.[26] This study was terminated prematurely at interim analysis because of the finding of a high rate of neoplasms, particularly in patients older than age 40. Other investigators have previously reported the increased risk of neoplasm associated with complicated appendicitis[27] and a post hoc analysis of the MUSTANG database also confirmed that age older than 40 years is significantly associated with an increased risk of appendiceal malignancy.[28]

The American multicenter Comparison of Outcomes of antibiotic Drugs and Appendectomy (CODA) trial is the largest randomized trial addressing the question of appendectomy or NOM.[29] The CODA was a pragmatic noninferiority trial randomizing patients with simple and complicated appendicitis to either antibiotic therapy (10-day course) or appendectomy. In contrast to the APPAC trial, subjects randomized to antibiotics in CODA were allowed to be treated as outpatients (nearly 50%), and the overwhelming majority (96%) of subjects assigned to surgery underwent laparoscopic appendectomy. In this trial, antibiotics were found to be noninferior to appendectomy regarding the primary endpoint of 30-day health status. When comparing secondary outcomes at 90 days, though, subjects randomized to antibiotics had a significantly higher rate of complications, specifically drainage procedures, ED visits, hospital readmissions, complications, and reactions to antibiotics requiring health care encounters. The strengths of the CODA trial include its large sample size, pragmatic design, patient-centric and validated composite endpoint, reasonably low rate of protocol violations, and high rate of follow-up. The results are internally valid, consistent, and generalizable. However, follow-up was limited to only 90 days, and the open-label design combined with the subjective primary endpoint could have resulted in biased assessments. The APPAC investigators also performed an investigation of quality of life (QoL) in enrolled subjects.[30] From the original cohort of 530 patients, 423 (80%) were contacted by phone at a medium follow-up of 7 years. Using validated measures, Sippola et al.[30] reported that the QoL was very similar between the two groups, although patients undergoing appendectomy were more satisfied with their treatment compared with patients initially randomized to antibiotic therapy. This difference

TABLE 2. Demographics and Outcomes of AAST Appendicitis Imaging Severity Grade 1

	All (n = 2,319)	Appendectomy (n = 2,234)	Nonoperative Management (n = 85)	*p*
Age, y	40.0 (16.2)	39.5 (15.7)	53.1 (23.2)	<0.001*
BMI, kg/m^2	28.8 (6.6) Missing = 84	28.8 (6.59) Missing = 82	27.5 (6.49) Missing = 2	0.07557*
Diabetes mellitus, n (%)	168 (7.2) Missing = 7	153 (6.8) Missing = 7	15 (17.6)	<0.001**
Charlson Comorbidity Index, median (IQR)	0 (0–1.0)	0 (0–1)	0 (0–5)	<0.001†
Prior abdominal surgery, n (%)	542 (23.4)	515 (23.1)	27 (31.8)	0.08323**
Duration of symptoms before presentation, n (%)				<0.001‡
<6 h	246 (10.6)	238 (10.7)	8 (9.4)	
6–11 h	386 (16.6)	375 (16.8)	11 (12.9)	
12–17 h	352 (15.2)	347 (15.5)	5 (5.9)	
18–23 h	267 (11.5)	254 (11.4)	13 (15.3)	
24–29 h	354 (15.3)	346 (15.5)	8 (9.4)	
30–35 h	43 (1.9)	41 (1.8)	2 (2.4)	
36–41 h	42 (1.8)	40 (1.8)	2 (2.4)	
42–47 h	62 (2.7)	61 (2.7)	1 (1.2)	
48–53 h	195 (8.4)	188 (8.4)	7 (8.2)	
54–59 h	10 (0.4)	10 (0.4)	0 (0)	
60–65 h	2 (0.09)	2 (0.1)	0 (0)	
66–71 h	26 (1.1)	23 (1.0)	3 (3.5)	
72–77 h	109 (4.7)	105 (4.7)	4 (4.7)	
78–83 h	2 (0.09)	1 (0.045)	1 (1.2)	
84–89 h	3 (0.1)	3 (0.1)	0 (0)	
90–96 h	26 (1.1)	23 (1.0)	3 (3.5)	
>96 h	193 (8.3)	176 (7.9)	17 (20.0)	
	Missing = 1	Missing = 1		
				0.04337‡
Tobacco, n (%)				
Never	1,589 (68.5)	1,538 (68.8)	13 (15.3)	
Former	318 (13.7)	297 (13.3)	21 (24.7)	
Current	407 (17.6)	394 (17.6)	51 (60.0)	
	Missing = 5	Missing = 5		
Lost to follow-up, n (%)	209 (9)	195 (8.7)	14 (16.5)	0.02423**
Outcomes at 1 y, n (%)				
Surgical site infection	10 (0.43)	10 (0.4)	0 (0)	0.0678‡
Intra-abdominal abscess	18 (0.78)	14 (0.6)	4 (4.7)	0.003472‡
Wound complication	4 (0.17)	4 (0.1)	0 (0)	1
Clavien-Dindo complication	156 (6.73)	139 (6.2)	17 (20)	<0.001‡
Secondary intervention	35 (1.51)	14 (0.6)	21 (25)	<0.001‡
ED visit	181 (7.81)	165 (8.0)	16 (23.2)	<0.001‡
Hospital readmission	77 (3.32)	68 (3)	9 (10.6)	0.00163‡
Mortality	2 (0.08)	2 (0.08)	0 (0)	1‡
Clavien-Dindo score, n (%)				
Grade 1	81 (3.8)	79 (3.5)	2 (2.4)	0.02739‡
Grade 2	35 (1.6)	32 (1.4)	3 (3.5)	
Grade 3a	16 (0.7)	12 (0.5)	4 (4.7)	
Grade 3b	14 (0.7)	8 (0.4)	6 (7.1)	
Grade 4a	6 (0.3)	5 (0.2)	1 (1.2)	
Grade 4b	1 (0.04)	0 (0)	1 (1.2)	
Grade 5	1 (0.04)	1 (0.04)	0 (0)	
CCI, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.414†

**t* Test.
**χ^2 Test.
†Wilcoxon rank-sum test.
‡Fisher exact test.
BMI, body mass index; CCI, Comprehensive Complication Index; ED, Emergency Department.

TABLE 3. Between-Group Comparisons of Cumulative Scores for Hierarchical Composite Endpoint

	NOM	Surgery
Sum ≥0	179 (70.5%)	2,376 (88.1%)
Sum <0	75 (29.5%)	322 (11.9%)

Odds ratio (95% confidence interval), 0.3 (0.2–0.4).

was largely driven by those who failed NOM and required rescue appendectomy, a common occurrence (39%) by 5 years.[22]

Similar to APPAC, the recently published Conservative versus Open ManageMent of Acute uncomplicated Appendicitis trial randomized patients with simple appendicitis to antibiotic therapy or appendectomy.[31] The 1-year recurrence rate was similar (25%) to APPAC, but the patients assigned to initial appendectomy reported improved QoL at both 3 months and 12 months after enrollment despite missing an average of nearly 4 more days of work. The improvement of QoL in the appendectomy group was not apparent in the first month after randomization, but at 12 months, the appendectomy patients had a higher proportion of patients in full health compared with the antibiotic group. Even when patients experiencing antibiotic treatment failure were removed from that analysis, patients in the antibiotics-only group demonstrated a persistent and significant reduction in QoL at 1 year. Although the MUSTANG study did not specifically collect data regarding QoL, the findings of the current post hoc analysis are consistent with the secondary outcomes of the CODA trial: patients receiving initial NOM of simple appendicitis experience higher rates of complications and higher utilization of health care resources at 1 year after the index hospitalization.

Interestingly, 63% of eligible patients in the CODA trial declined to be randomized, indicating a treatment preference and possible selection bias. Patient preference is increasingly recognized as a potential confounding factor in appendicitis research. For example, a recent survey reported that respondents overwhelmingly preferred appendectomy for themselves or their child.[32] Thus, patients who agree to enroll in a study with a 50% chance of being randomized to NOM may be fundamentally different from those who decline to participate.

To summarize, in recent years, NOM of acute appendicitis has become increasingly accepted based on a European trial (APPAC) that failed to demonstrate noninferiority of NOM. A more recent American trial (CODA) did demonstrate noninferiority of NOM using a primary endpoint of 30-day QoL but reported significantly increased rate of unfavorable outcomes at 90 days. Our study confirms the American experience at the 1-year mark. These findings should temper the enthusiasm for NOM in American appendicitis patients, as the conclusions of the APPAC trial may not be generalizable to current American practice.

Limitations

There are several limitations of this study that must be acknowledged. First and foremost, because this is an unplanned post hoc analysis of an observational study database, we can only describe associations without making any inferences about causality. Our findings should be interpreted with caution as only hypothesis generating. As with all post hoc analyses, there is a risk for type 1 error (false positive) when performing multiple comparisons on the same data set. We acknowledge this major limitation, which would be best overcome by formal hypothesis testing in a well-designed and adequately powered prospective randomized trial. A selection bias is possible and could explain our findings in Table 1. For example, a surgeon's decision to operate is usually predicated on the assumption that the appendix can be safely removed and that the suture line or staple line will hold against the appendiceal stump tissue. If this is not the case, such as with an end stage phlegmon, surgery may not be considered in the short term, and NOM may be more appropriate. Indeed, in Tables 1 and 2, the NOM group was significantly older, had a higher comorbidity index, and had higher AAST Image severity grades than the surgical group. These differences in baseline characteristics between groups may influence the primary endpoint analysis. Furthermore, the difference in loss to follow-up rates between groups can contribute to a selection bias and potentially affect the results of our analysis. We advise caution when interpreting our findings and recommend an individualized approach to each case. Third, we were limited in our data analysis to only those data fields that were collected during the original MUSTANG study. Additional data such as number of sick days, abdominal pain symptoms, hospital charges, and QoL measures are important but, unfortunately, unavailable. Furthermore, because of the purely observational nature of the original MUSTANG study, we are unable to provide information about the indication for operative versus NOM at the individual patient level. However, we did observe variation in NOM rates between enrolling centers (D.D.Y., unpublished data), and so individual surgeon preference and center effect are likely factors in the decision to operate or management without surgery. A survival type of analysis to account for censoring was not possible because of the lack of specific time to event information. Finally, the win-lose-tie analysis of the hierarchical ordinal scale is a relatively uncommon method of analyzing data and has unique limitations. For example, since a loss is tallied for any unfavorable outcome regardless of severity, this method may overestimate the importance of relatively minor complications such as wound complication or surgical site infection. However, in reviewing the actual incidence of these minor complications (Table 1), they were relatively uncommon and greatly outnumbered by more serious complications such as secondary interventions, ED visits, and hospital readmissions. Despite these limitations, our study has several strengths, which make it a unique contribution to the existing literature. The MUSTANG study was a detailed and labor-intensive observational study, which collected extensive appendicitis-specific data that are not available in other large administrative databases. The study was prospective, and extensive data verification effort was expended ensuring completeness and accuracy of data. Thus, MUSTANG represents a highly accurate and geographically diverse modern "snapshot" of contemporary American practice, with detailed follow-up information extending out to 1 year after discharge from index hospitalization. Another unique feature of this study is the use of a hierarchical ordinal scale, which is patient-centered and more aligned with actual nuanced clinical practice compared with simple null hypothesis significance testing.

CONCLUSION

In contemporary American practice, surgical appendectomy for simple appendicitis is associated with lower odds of developing treatment-related complications in the first year after illness compared with NOM.

AUTHORSHIP

All authors have reviewed, edited, and approved the article.

DISCLOSURE

The authors declare no conflicts of interest.

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