Laparoscopy in management of appendicitis in high-, middle-, and low-income countries: a multicenter, prospective, cohort study

GlobalSurg Collaborative

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Abstract

Background Appendicitis is the most common abdominal surgical emergency worldwide. Differences between high- and low-income settings in the availability of laparoscopic appendectomy, alternative management choices, and outcomes are poorly described. The aim was to identify variation in surgical management and outcomes of appendicitis within low-, middle-, and high-Human Development Index (HDI) countries worldwide.

Methods This is a multicenter, international prospective cohort study. Consecutive sampling of patients undergoing emergency appendectomy over 6 months was conducted. Follow-up lasted 30 days.

Results 4546 patients from 52 countries underwent appendectomy (2499 high-, 1540 middle-, and 507 low-HDI groups). Surgical site infection (SSI) rates were higher in low-HDI (OR 2.57, 95% CI 1.33–4.99, \( p = 0.005 \)) but not middle-HDI countries (OR 1.38, 95% CI 0.76–2.52, \( p = 0.291 \)), compared with high-HDI countries after adjustment. A laparoscopic approach was common in high-HDI countries (1693/2499, 67.7%), but infrequent in low-HDI (41/507, 8.1%) and middle-HDI (132/1540, 8.6%) groups. After accounting for case-mix, laparoscopy was still associated with fewer overall complications (OR 0.55, 95% CI 0.42–0.71, \( p < 0.001 \)) and SSIs (OR 0.22, 95% CI 0.14–0.33, \( p < 0.001 \)). In propensity-score matched groups within low-/middle-HDI countries, laparoscopy was still associated with fewer overall complications (OR 0.23 95% CI 0.11–0.44) and SSI (OR 0.21 95% CI 0.09–0.45).

Conclusion A laparoscopic approach is associated with better outcomes and availability appears to differ by country HDI. Despite the profound clinical, operational, and financial barriers to its widespread introduction, laparoscopy could significantly improve outcomes for patients in low-resource environments.

Trial registration: NCT02179112.

Keywords Appendicitis · Appendectomy · Global surgery · Laparoscopic · Operative standards · Postoperative care · Postoperative complications · Surgical site infection

The global burden of diseases requiring emergency surgery is poorly described and represents a significant health problem [1]. Most of the world’s population do not have access to safe, affordable and timely surgery, with access inequitably distributed in favor of high Human Development Index (HDI) countries [2]. It is estimated that in 2010, approximately 17 million deaths resulted from conditions requiring surgical care, far greater than the combined burden of HIV/AIDS, malaria, and tuberculosis [3]. There is an urgent need to increase access to surgical treatment across the world.

Appendicitis is one of the commonest diseases requiring emergency abdominal surgery, yet little data exist to allow comparison of management and outcomes at a patient level globally [4]. Recently published trends predict a significant increase in the prevalence of appendicitis in newly industrialized countries [5]. Data from the Global Burden of Disease Study (2016) show a higher prevalence of appendicitis in lower socio-economic countries, together with a greater
proportion of years-of-life-lost as a result of the disease [6]. Appendicitis is usually treated with surgery, although management purely with antibiotics has been investigated [7]. Appendectomy can be performed by a traditional open procedure, but a laparoscopic approach has become common in many countries [8]. Significant variation in practice still exists in high-income settings [9].

The role of laparoscopy in low-resource healthcare settings has been debated [10]. Those arguing against its use suggest that the required initial financial and training investment, together with the on-going costs of equipment upkeep and consumables, make it unviable when compared to relatively straightforward open surgery. This argument has resonance: when a healthcare system is struggling to deliver basic surgical procedures, the introduction of a more complex intervention must be considered carefully. On the other hand, there are broad advantages to having laparoscopy available, particularly the ability to perform diagnostic laparoscopy in the absence of expensive CT imaging. Lower postoperative complication rates [9] and consequent healthcare costs are commonly reported to be associated with laparoscopy in the absence of expensive CT imaging. Lower postoperative complication rates [9] and consequent healthcare costs are commonly reported to be associated with laparoscopic appendectomy. Whether laparoscopy has the same advantage in low-resource settings is unknown.

The GlobalSurg Collaborative has recently demonstrated the feasibility of conducting international data collection in low-resource settings [4, 11]. Using these approaches, this study aimed to investigate the surgical management of appendectomy worldwide, including the use of laparoscopy, and to examine outcomes following surgery.

Methods

Study setting

A collaborative, international, multicenter, prospective, observational cohort study was conducted according to a pre-specified, published protocol (ClinicalTrials.gov identifier: NCT02179112) [12]. The collaborative network methodology has been described elsewhere [13]. Briefly, the study was conducted by teams of local investigators coordinated by a national lead investigator. Investigators were recruited via the GlobalSurg network and through dissemination on social media and other personal contacts. Consecutive sampling of patients undergoing emergency abdominal surgery was undertaken during 2-week periods within a 6-month study window. Investigators in a hospital could choose one or multiple 2-week periods. There was an absolute requirement for all cases in the chosen period(s) to be included, but no minimum number set to avoid bias against smaller centers. A UK National Health Service Research Ethics Service, reference NR/1404AB12); individual centers obtained their own audit, ethical or institutional approval. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14]. Pre-specified sub-group analyses included the examination of patients undergoing appendectomy as compared with other abdominal surgical procedures. At each participating center, data collection was performed by teams following the same standardized protocol [12].

Patients and procedures

The study inclusion period was 01 July 2014 to 31 December 2014. Consecutive patients undergoing emergency appendectomy were eligible for inclusion. No limits were placed on age or operative approach. Emergency surgery was defined as any unplanned, non-elective operation, including re-operation after a previous procedure. Elective (planned) or semi-elective procedures (where a patient initially admitted as an emergency was then discharged from hospital and re-admitted at later time for surgery) were excluded.

Data

Data were selected to be objective, standardized, easily transcribed and internationally relevant, to maximize record completion and accuracy. Patients were followed for 30 days after surgery or for the length of their inpatient stay where follow-up was not feasible. Records were uploaded by local investigators to a secure online website, provided using the Research Electronic Data Capture (REDCap) system [15]. The lead investigator at each site was responsible for “signing off” patient records. Data were checked with primary data sources if necessary. The local lead was responsible for ensuring consecutive sampling (i.e., no excluded cases) for each site. The submitted data were then checked centrally and where missing data were identified, the local lead investigator was contacted and asked to investigate. Once vetted, the record was accepted into the dataset for analysis.

Patient variables included age, gender, American Society of Anesthesiologists (ASA) physical status classification system, diabetes history, smoking and diagnostic category. Service variables included use of the WHO surgical safety checklist, the experience of surgeon/anesthetist, and compliance with selected evidence-based standards. Prophylactic antibiotic use was defined as antibiotics administered either at induction, or during surgery but before opening of a contaminated space.
Outcome variables

The primary outcome measure was overall complication rate, defined using the Clavien–Dindo grade occurring within 30 days of the index operation. The criteria required for each outcome were defined a priori in the protocol [12]. Major complication (Clavien–Dindo IV) was defined as a life-threatening illness requiring critical care management. In low-resource settings, investigators could report “complication requiring critical care, but facilities unavailable.”

The US Centre for Disease Control and Prevention (CDC) definitions for SSI and organ space infection (OSI) were used [16]. SSI: one of (1) purulent drainage from the incision; (2) at least two of following: pain or tenderness, localized swelling, redness, heat, fever, and the incision is opened deliberately to manage infection; (3) wound organisms AND pus cells from aspirate/swab. OSI: intra-abdominal/pelvic detected clinically/symptomatically, radiologically, or intra-operatively.

Power considerations

The sample size was limited by practical factors and estimation of power by uncertainty over critical quantities such as clustering and variation by diagnosis. An indicative calculation for overall complication rate showed that considerable precision was likely with 520 patients per HDI comparison group (a 6% point difference in overall complication rate; baseline rate 16% with alpha = 0.05, beta = 0.2, and accounting for missing data/loss to follow-up).

Statistical analysis

Variation across different international health settings was assessed by stratifying participating centers by country into three tertiles according to HDI rank. This is a composite statistic of life expectancy, education, and income indices published by the United Nations (http://hdr.undp.org/en/statistics). Differences between HDI tertiles were initially tested with the Pearson chi-squared and Kruskal–Wallis tests for categorical and continuous variables respectively.

Multivariable binary logistic regression models were constructed to adjust for case-mix and measures of hospital facilities and service, to explore the nature of differences in outcome. Subsequently, three-level hierarchical multivariable logistic regression models were made to account for hospital- and country-level variation (”hospital” and “country” as random effects with constrained gradients). Variable selection was incremental and accounted for both clinical and statistical significances. Model fit was guided log-likelihood methods including the Akaike Information Criterion (AIC). Discrimination was defined by the area-under-the receiver-operator-curve (c-statistic). Calibration across the range of observed probabilities was checked. All two-way interactions were investigated. Bayesian simulation methods are described in the supplementary digital content.

In a further propensity-score matched study, patients from low- and middle-HDI countries were analyzed separately to those from high-HDI countries. Patients who had undergone laparoscopic surgery were matched with those who underwent open surgery using a “nearest neighbor” approach, based on probabilities of group membership determined with multivariable logistic regression. The matching algorithm used age, gender, smoking status, ASA score, and perforation status. Pre- and post-matching balance was checked for all relevant variables.

All analyses were undertaken using the R Foundation Statistical Program (R 3.1.1, R Foundation for Statistical Computing) and Stan (Stan: A C++ Library for Probability and Sampling, Version 2.10.0. URL http://mc-stan.org/).

Results

4546 patients underwent laparoscopic or open appendectomy for acute appendicitis over the data collection period.

Demographics

Patients were from 52 countries with high-HDI (n = 2499), middle-HDI (n = 1540), and low-HDI (n = 507) groups (Table 1). Patients in low-HDI countries were younger (Pearson’s χ² test, p < 0.001) and more likely to be male (low-HDI (295/507, 58%), middle-HDI (783/1540, 51%), high-HDI (1344/2499, 54%), p = 0.012). There were numerically more patients considered to have severe systemic disease (ASA 3 or greater) in the low-HDI group (p = 0.021).

Surgical characteristics

There were clear differences in management between HDI groups (Table 1). A laparoscopic approach was used in 67.7% of patients in the high-HDI group and in < 10% in the low- and middle-HDI groups (Pearson’s χ² test, p < 0.001). There was more operating through the night in low- and middle-HDI groups (Pearson’s χ² test, p < 0.001), while more patients were operated upon > 24 h after admission in high-HDI countries. Seniority of both the surgeon and anesthetist was higher in high-HDI countries. Prophylactic antibiotics and use of the WHO surgical safety checklist was less common in low- and middle-HDI groups.

Outcomes

In univariable analyses, associations were seen between HDI and overall and minor complications, as well as surgical site
There was no strong association between HDI and reintervention, major complication, or death.

The overall complication rate was higher in low-HDI (odds ratio (OR) 1.55, 95% confidence interval (CI) 1.19–1.99, \( p = 0.001 \)) and middle-HDI (OR 1.24, 95% CI 1.03–1.49, \( p = 0.020 \)) countries compared with the high-HDI group (Tables 2, 3). When the analysis was adjusted in a multilevel model accounting for patient, disease, and

| Table 1 | Patient and operative characteristics | Human development index (HDI) | \( p \) Value |
|---------|--------------------------------------|-----------------------------|--------------|
|         |                                      | High \((n = 2499)\) | Middle \((n = 1540)\) | Low \((n = 507)\) |
| Age in completed years |                                             |                            |              |
| Mean (SD) | 31.2 (18.2) | 26.9 (14.6) | 24.1 (12.1) | < 0.001 |
| Gender |                                             |                            |              |
| Male | 1344 (53.8) | 783 (50.8) | 295 (58.2) | 0.012 |
| Female | 1155 (46.2) | 757 (49.2) | 212 (41.8) |              |
| Diabetes history |                                             |                            |              |
| No | 2435 (97.4) | 1493 (96.9) | 489 (96.4) | 0.390 |
| Yes | 64 (2.6) | 47 (3.1) | 18 (3.6) |              |
| Smoking currently |                                             |                            |              |
| No | 1977 (79.1) | 1295 (84.1) | 446 (88.0) | < 0.001 |
| Yes | 521 (20.8) | 244 (15.8) | 60 (11.8) |              |
| Missing | 1 (0.0) | 1 (0.1) | 1 (0.2) |              |
| ASA score |                                             |                            |              |
| 1 | 1724 (69.0) | 1098 (71.3) | 344 (67.9) | 0.021 |
| 2 | 613 (24.5) | 332 (21.6) | 102 (20.1) |              |
| ≥ 3 | 104 (4.2) | 74 (4.8) | 33 (6.5) |              |
| Missing | 58 (2.3) | 36 (2.3) | 28 (5.5) |              |
| Procedure start time |                                             |                            |              |
| 0800–1800 (daytime) | 1345 (53.8) | 615 (39.9) | 188 (37.1) | < 0.001 |
| 1800–2200 (evening) | 616 (24.6) | 412 (26.8) | 137 (27.0) |              |
| 2200–0800 (night-time) | 538 (21.5) | 513 (33.3) | 182 (35.9) |              |
| Surgical safety checklist used |                                             |                            |              |
| No, not available in this hospital | 182 (7.3) | 570 (37.0) | 187 (36.9) | < 0.001 |
| No, but available in this hospital | 35 (1.4) | 103 (6.7) | 161 (31.8) |              |
| Yes | 2282 (91.3) | 867 (56.3) | 159 (31.4) |              |
| Prophylactic antibiotics |                                             |                            |              |
| No | 223 (8.9) | 205 (13.3) | 62 (12.2) | < 0.001 |
| Yes | 2276 (91.1) | 1335 (86.7) | 445 (87.8) | < 0.001 |
| Senior surgeon > 5 years training |                                             |                            |              |
| No | 108 (4.3) | 769 (49.9) | 210 (41.4) | < 0.001 |
| Yes | 2391 (95.7) | 770 (50.0) | 297 (58.6) |              |
| Missing | 0 (0.0) | 1 (0.1) | 0 (0.0) |              |
| Senior anesthetist > 5 years training |                                             |                            |              |
| No | 115 (4.6) | 789 (51.2) | 265 (52.3) | < 0.001 |
| Yes | 2384 (95.4) | 751 (48.8) | 242 (47.7) |              |
| Laparoscopic approach |                                             |                            |              |
| No | 806 (32.3) | 1408 (91.4) | 466 (91.9) | < 0.001 |
| Yes | 1693 (67.7) | 132 (8.6) | 41 (8.1) |              |
| Perforated viscus |                                             |                            |              |
| No | 2150 (86.0) | 1380 (89.6) | 394 (77.7) | < 0.001 |
| Yes | 348 (13.9) | 159 (10.3) | 109 (21.5) |              |
| Missing | 1 (0.0) | 1 (0.1) | 4 (0.8) |              |

Data are \( n \) (%) unless otherwise stated.

SD standard deviation.
hospital structural factors, there was no independent association between overall complications and HDI group.

A further prominent association was seen with more surgical site infection (SSI) in low-HDI (OR 3.81, 95% CI 2.78–5.19, \(p < 0.001\)) and middle-HDI (OR 2.99, 95% CI 2.34–3.84, \(p < 0.001\)) compared with high-HDI (Tables 2, 4). In the multilevel model, the association persisted in low-HDI (OR 2.57, 95% CI 1.33–4.99, \(p = 0.005\)) but not middle-HDI (OR 1.38, 95% CI 0.76–2.52, \(p = 0.291\)) countries.

There was no association in multilevel models between HDI and OSI (Table S1, Supplemental Digital Content).

Determining any influence of laparoscopy compared with an open approach is difficult given the inherent selection bias and the lower availability in low-HDI and middle-HDI countries. This is highlighted by the different populations undergoing laparoscopic compared with open procedures (Table S2, Supplemental Digital Content). Differences in the laparoscopic group included more females, lower ASA score, a greater likelihood of senior surgeon and anesthetist involvement, and lower perforation rates. Two approaches were taken to attempt to reduce the effect of this imbalance: multilevel logistic regression modeling and a propensity-score matched analysis.

After accounting for case-mix imbalance, laparoscopy was still associated with significantly fewer complications (OR 0.55, 95% CI 0.42–0.71, \(p < 0.001\), Table 3) and SSRIs (OR 0.22, 95% CI 0.14–0.33, \(p < 0.001\), Table 4). To try and communicate these differences more meaningfully, a simple simulation was performed using different patient baseline characteristics (Table 5). This analysis shows an absolute risk reduction (ARR) in overall complication

### Table 2 Outcomes

| Human development index (HDI) | High (n = 2499) | Middle (n = 1540) | Low (n = 507) | \(p\) Value |
|-----------------------------|----------------|------------------|--------------|-------------|
| Overall complications (Clavien–Dindo I, II, III, IV, or V) |               |                  |              |             |
| No                          | 2182 (87.3)    | 1303 (84.7)      | 414 (81.7)   | 0.001       |
| Yes                         | 317 (12.7)     | 235 (15.3)       | 93 (18.3)    |             |
| Missing                     | 0 (0.0)        | 2 (0.1)          | 0 (0.0)      |             |
| Minor complication (Clavien–Dindo I/II) |               |                  |              |             |
| No                          | 2219 (88.9)    | 1314 (86.1)      | 423 (84.1)   | 0.002       |
| Yes                         | 278 (11.1)     | 212 (13.9)       | 80 (15.9)    |             |
| Missing                     | 2 (0.1)        | 14 (0.9)         | 4 (0.8)      |             |
| Reintervention (Clavien–Dindo III) |               |                  |              |             |
| No                          | 2431 (97.3)    | 1501 (97.6)      | 494 (97.4)   | 0.828       |
| Yes                         | 68 (2.7)       | 37 (2.4)         | 13 (2.6)     |             |
| Missing                     | 0 (0.0)        | 2 (0.1)          | 0 (0.0)      |             |
| Major complication (Clavien–Dindo IV) |               |                  |              |             |
| No                          | 2474 (99.0)    | 1520 (98.8)      | 498 (98.2)   | 0.325       |
| Yes                         | 25 (1.0)       | 18 (1.2)         | 9 (1.8)      |             |
| Missing                     | 0 (0.0)        | 2 (0.1)          | 0 (0.0)      |             |
| Surgical site infection (SSI) |               |                  |              |             |
| No                          | 2389 (95.6)    | 1340 (88.0)      | 432 (85.2)   | <0.001      |
| Yes                         | 109 (4.4)      | 183 (12.0)       | 75 (14.8)    |             |
| Missing                     | 1 (0.0)        | 1 (0.1)          | 0 (0.0)      |             |
| Organ/space infection (OSI) |               |                  |              |             |
| No                          | 2397 (96.0)    | 1486 (96.4)      | 494 (97.4)   | 0.023       |
| Yes                         | 101 (4.0)      | 39 (2.7)         | 13 (2.6)     |             |
| Missing                     | 1 (0.0)        | 15 (1.0)         | 0 (0.0)      |             |
| Length of stay after surgery (days) |         |                  |              |             |
| Mean (SD)                   | 3 (3.4)        | 2.9 (3.2)        | 4.1 (4.7)    | <0.001      |
| 30-day mortality            |               |                  |              |             |
| Alive                       | 2496 (99.9)    | 1532 (99.5)      | 504 (99.4)   | 0.061       |
| Dead                        | 3 (0.1)        | 2 (0.1)          | 3 (0.6)      |             |
| Missing                     | 0 (0.0)        | 6 (0.4)          | 0 (0.0)      |             |

Data are n (%) unless otherwise stated
SD standard deviation
Table 3  Overall complications

| Overall complications | No     | Yes    | Univariable logistic regression OR (95% CI, p value) | Multilevel logistic regression OR (95% CI, p value) |
|-----------------------|--------|--------|---------------------------------------------------|---------------------------------------------------|
| HDI tertile           |        |        |                                                   |                                                   |
| High                  | 2182 (56.0) | 317 (49.1) |                                                   |                                                   |
| Middle                | 1303 (33.4) | 235 (36.4) | 1.24 (1.03–1.49, p = 0.020)                      | 0.91 (0.56–1.48, p = 0.701)                      |
| Low                   | 414 (10.6)  | 93 (14.4)  | 1.55 (1.19–1.99, p = 0.001)                      | 1.44 (0.82–2.54, p = 0.209)                      |
| Age in completed years|        |        |                                                   |                                                   |
| Mean (SD)             | 28.2 (16) | 33.3 (19.5) | 1.02 (1.01–1.02, p < 0.001)                      | 1.01 (1.01–1.02, p < 0.001)                      |
| Gender                |        |        |                                                   |                                                   |
| Male                  | 2069 (53.1) | 351 (54.4)  |                                                   |                                                   |
| Female                | 1830 (46.9) | 294 (45.6)  | 0.95 (0.80–1.12, p = 0.523)                      | 0.98 (0.82–1.19, p = 0.873)                      |
| Diabetes history      |        |        |                                                   |                                                   |
| No                    | 3805 (97.6) | 610 (94.6)  | 2.32 (1.54–3.42, p < 0.001)                      | 1.27 (0.80–2.01, p = 0.315)                      |
| Yes                   | 94 (2.4)  | 35 (5.4)  |                                                   |                                                   |
| Smoking currently     |        |        |                                                   |                                                   |
| No                    | 3208 (82.3) | 508 (78.8)  | 1.26 (1.02–1.54, p = 0.029)                      | 0.96 (0.76–1.23, p = 0.770)                      |
| Yes                   | 688 (17.7) | 137 (21.2)  |                                                   |                                                   |
| ASA score             |        |        |                                                   |                                                   |
| 1                     | 2790 (73.6) | 375 (59.4)  |                                                   |                                                   |
| 2                     | 850 (22.4)  | 196 (31.1)  | 1.72 (1.42–2.07, p < 0.001)                      | 1.42 (1.13–1.78, p = 0.003)                      |
| ≥ 3                   | 151 (4.0)  | 60 (9.5)  | 2.96 (2.14–4.04, p < 0.001)                      | 1.64 (1.10–2.46, p = 0.016)                      |
| Procedure start time  |        |        |                                                   |                                                   |
| 0800–1800 (daytime)   | 1854 (47.6) | 292 (45.3)  |                                                   |                                                   |
| 1800–2200 (evening)   | 985 (25.3)  | 180 (27.9)  | 1.16 (0.95–1.42, p = 0.148)                      |                                                   |
| 2200–0800 (night-time)| 1060 (27.2) | 173 (26.8)  | 1.04 (0.85–1.27, p = 0.730)                      |                                                   |
| Surgical safety checklist used |        |        |                                                   |                                                   |
| No, not available in this hospital | 781 (20.0) | 157 (24.3)  |                                                   |                                                   |
| No, but available in this hospital | 250 (6.4)  | 48 (7.4)  | 0.96 (0.67–1.35, p = 0.799)                      | 0.79 (0.48–1.30, p = 0.352)                      |
| Yes                   | 2868 (73.6) | 440 (68.2)  | 0.76 (0.63–0.93, p = 0.008)                      | 0.84 (0.59–1.19, p = 0.327)                      |
| Prophylactic antibiotics |        |        |                                                   |                                                   |
| No                    | 422 (10.8)  | 67 (10.4)  |                                                   |                                                   |
| Yes                   | 3477 (89.2) | 578 (89.6)  | 1.05 (0.80–1.39, p = 0.741)                      | 0.99 (0.72–1.37, p = 0.974)                      |
| Senior surgeon > 5 years training |        |        |                                                   |                                                   |
| No                    | 920 (23.6)  | 167 (25.9)  |                                                   |                                                   |
| Yes                   | 2978 (76.4) | 478 (74.1)  | 0.88 (0.73–1.07, p = 0.207)                      | 1.05 (0.78–1.42, p = 0.745)                      |
| Senior anesthetist > 5 years training |        |        |                                                   |                                                   |
| No                    | 980 (25.1)  | 189 (29.3)  |                                                   |                                                   |
| Yes                   | 2919 (74.9) | 456 (70.7)  | 0.81 (0.67–0.98, p = 0.025)                      | 1.02 (0.75–1.39, p = 0.901)                      |
| Laparoscopic approach |        |        |                                                   |                                                   |
| No                    | 2222 (57.0) | 457 (70.9)  |                                                   |                                                   |
| Yes                   | 1677 (43.0) | 188 (29.1)  | 0.55 (0.45–0.65, p < 0.001)                      | 0.55 (0.42–0.71, p < 0.001)                      |
| Perforated viscus     |        |        |                                                   |                                                   |
| No                    | 3474 (89.2) | 450 (69.8)  |                                                   |                                                   |
| Yes                   | 419 (10.8)  | 195 (30.2)  | 3.59 (2.95–4.37, p < 0.001)                      | 3.66 (2.91–4.62, p < 0.001)                      |

Data are n (%) unless otherwise stated. Hospitals = 339, countries = 52. AIC = 3339.1. c-statistic = 0.790
OR odds ratio, CI confidence interval, HDI human development index, ASA American Association of Anesthesiologists risk score, SD standard deviation
| Surgical site infection | No | Yes | Univariable logistic regression OR (95% CI, \( p \) value) | Multilevel logistic regression OR (95% CI, \( p \) value) |
|-------------------------|----|-----|--------------------------------------------------------|--------------------------------------------------|
| **HDI tertile**         |    |     |                                                        |                                                  |
| High                    | 2389 (57.4) | 109 (29.7) | 2.99 (2.34–3.84, \( p < 0.001 \)) | 1.38 (0.76–2.52, \( p = 0.291 \)) |
| Middle                  | 1340 (32.2) | 183 (49.9)  | 3.81 (2.78–5.19, \( p < 0.001 \)) | 2.57 (1.33–4.99, \( p = 0.005 \)) |
| Low                     | 432 (10.4)  | 75 (20.4)   | 2.99 (2.34–3.84, \( p < 0.001 \)) | 1.38 (0.76–2.52, \( p = 0.291 \)) |
| **Age in completed years** |    |     |                                                        |                                                  |
| Mean (SD)               | 28.6 (16.4) | 32.8 (18.9) | 1.01 (1.01–1.02, \( p < 0.001 \)) | 1.01 (1.01–1.02, \( p = 0.001 \)) |
| **Gender**              |    |     |                                                        |                                                  |
| Male                    | 2205 (53.0) | 208 (56.7)  | 0.86 (0.69–1.07, \( p = 0.175 \)) | 0.95 (0.74–1.22, \( p = 0.666 \)) |
| Female                  | 1956 (47.0) | 159 (43.3)  | 3.00 (1.89–4.61, \( p < 0.001 \)) | 1.45 (0.83–2.52, \( p = 0.189 \)) |
| **Diabetes history**    |    |     |                                                        |                                                  |
| No                      | 4058 (97.5) | 341 (92.9)  | 1.64 (1.28–2.08, \( p < 0.001 \)) | 1.42 (1.05–1.94, \( p = 0.025 \)) |
| Yes                     | 103 (2.5)   | 26 (7.1)    | 3.00 (1.89–4.61, \( p < 0.001 \)) | 1.45 (0.83–2.52, \( p = 0.189 \)) |
| **Smoking currently**   |    |     |                                                        |                                                  |
| No                      | 3415 (82.1) | 287 (78.2)  | 1.28 (0.98–1.65, \( p = 0.062 \)) | 1.05 (0.77–1.45, \( p = 0.751 \)) |
| Yes                     | 743 (17.9)  | 80 (21.8)   | 0.53 (0.42–0.68, \( p < 0.001 \)) | 1.00 (0.64–1.54, \( p = 0.987 \)) |
| **ASA score**           |    |     |                                                        |                                                  |
| 1                       | 2937 (72.6) | 213 (58.7)  | 1.21 (0.93–1.56, \( p = 0.144 \)) | 1.08 (0.83–1.40, \( p = 0.562 \)) |
| 2                       | 934 (23.1)  | 111 (30.6)  | 1.64 (1.28–2.08, \( p < 0.001 \)) | 1.42 (1.05–1.94, \( p = 0.025 \)) |
| ≥ 3                     | 172 (4.3)   | 39 (10.7)   | 3.13 (2.13–4.50, \( p < 0.001 \)) | 1.82 (1.10–3.00, \( p = 0.020 \)) |
| **Procedure start time**|    |     |                                                        |                                                  |
| 0800–1800 (daytime)     | 1975 (47.5) | 162 (44.1)  | 1.08 (0.83–1.40, \( p = 0.562 \)) |                                             |
| 1800–2200 (evening)     | 1057 (25.4) | 105 (28.6)  | 1.21 (0.93–1.56, \( p = 0.144 \)) |                                             |
| 2200–0800 (night-time)  | 1129 (27.1) | 100 (27.2)  | 1.08 (0.83–1.40, \( p = 0.562 \)) |                                             |
| **Surgical safety checklist used** |    |     |                                                        |                                                  |
| No, not available in this hospital | 826 (19.9)  | 108 (29.4)  | 0.92 (0.51–1.65, \( p = 0.771 \)) |                                             |
| No, but available in this hospital | 253 (6.1)   | 45 (12.3)   | 1.36 (0.93–1.97, \( p = 0.108 \)) |                                             |
| Yes                     | 3082 (74.1) | 214 (58.3)  | 0.53 (0.42–0.68, \( p < 0.001 \)) | 1.00 (0.64–1.54, \( p = 0.987 \)) |
| **Prophylactic antibiotics** |    |     |                                                        |                                                  |
| No                      | 445 (10.7)  | 43 (11.7)   | 0.90 (0.65–1.27, \( p = 0.545 \)) | 0.99 (0.66–1.50, \( p = 0.976 \)) |
| Yes                     | 3716 (89.3) | 324 (88.3)  | 0.90 (0.65–1.27, \( p = 0.545 \)) | 0.99 (0.66–1.50, \( p = 0.976 \)) |
| **Senior surgeon > 5 years training** |    |     |                                                        |                                                  |
| No                      | 943 (22.7)  | 138 (37.6)  | 0.49 (0.39–0.61, \( p < 0.001 \)) | 0.86 (0.60–1.23, \( p = 0.395 \)) |
| Yes                     | 3217 (77.3) | 229 (62.4)  | 0.49 (0.39–0.61, \( p < 0.001 \)) | 0.86 (0.60–1.23, \( p = 0.395 \)) |
| **Senior anesthetist > 5 years training** |    |     |                                                        |                                                  |
| No                      | 1006 (24.2) | 154 (42.0)  | 0.44 (0.35–0.55, \( p < 0.001 \)) | 0.86 (0.60–1.24, \( p = 0.428 \)) |
| Yes                     | 3155 (75.8) | 213 (58.0)  | 0.44 (0.35–0.55, \( p < 0.001 \)) | 0.86 (0.60–1.24, \( p = 0.428 \)) |
| **Laparoscopic approach** |    |     |                                                        |                                                  |
| No                      | 2338 (56.2) | 326 (88.8)  | 0.16 (0.11–0.22, \( p < 0.001 \)) | 0.22 (0.14–0.33, \( p < 0.001 \)) |
| Yes                     | 1823 (43.8) | 41 (11.2)   | 0.22 (0.14–0.33, \( p < 0.001 \)) |                                             |
| **Perforated viscus**   |    |     |                                                        |                                                  |
| No                      | 3654 (87.9) | 258 (70.5)  | 3.05 (2.38–3.88, \( p < 0.001 \)) | 3.36 (2.47–4.59, \( p < 0.001 \)) |
| Yes                     | 502 (12.1)  | 108 (29.5)  | 3.36 (2.47–4.59, \( p < 0.001 \)) |                                             |

Data are \( n \) (%) unless otherwise stated. Hospitals = 339, countries = 52. AIC = 2164. c-statistic = 0.849

\( OR \) odds ratio, \( CI \) confidence interval, \( HDI \) human development index, \( ASA \) American Association of Anesthesiologists risk score, \( SD \) standard deviation
rate associated with laparoscopy of around 6% [number-needed-to-treat (NNT) = 16] in the absence of perforation and 17% (NNT = 8) when the appendix is perforated across HDI groups. For SSI, the analysis implies a greater potential benefit of laparoscopy in low-HDI (ARR 18.6%, 95% CI 11.4–27.7 with perforation) and middle-income countries (ARR 12.2%, 95% CI 6.6–19.6% with perforation), which is expected given the association of HDI and SSI seen in the multilevel model.

To further explore these relationships, a propensity-score-based matching analysis was performed. Patients were first subset into low-/middle-HDI and high-HDI groups. Using all available independent baseline variables and a nearest neighbor approach, 167 patients in the laparoscopic group were matched to 167 in the open group in the low-/middle-HDI subset (Fig. 1, Tables S3 and S4, Supplemental Digital Content) and 783 matched in the high-HDI group. Balance was more easily achieved in the low-/middle-HDI group, with persistent imbalance only seen for seniority of anesthetist and surgical safety checklist use. Balance using nearest neighbor matching was difficult to achieve in the high-HDI group, reflecting de facto differences in the characteristics of patients offered laparoscopic compared with those undergoing open procedures in practice. Alternative matching procedures were successfully explored, but have not been included for space and clarity. Adjusted logistic regression models were applied to the matched sets to address any residual confounding. In the low-/middle-HDI group, a laparoscopic approach was still associated with fewer overall complications (OR 0.23 95% CI 0.11–0.44, \( p < 0.001 \)), minor complications (OR 0.16 95% CI 0.06–0.35, \( p < 0.001 \)), and episodes of SSI (OR 0.21 95% CI 0.09–0.45, \( p < 0.001 \)) (Table S5, Supplemental Digital Content, Fig. 1). Similar results were observed within the matched high-HDI group (Table S6, Supplemental Digital Content).

**Discussion**

This is the first patient-level prospective study to describe the surgical approach to appendectomy and the frequency of postoperative complications on a global scale. Our findings reveal clear differences in the management of appendicitis and disparities in complication frequency between different HDI groups, with significantly more wound infections (SSI) in low-HDI versus high-HDI countries. A laparoscopic approach was common in the high-HDI group (1693/2499, 67.7%) but infrequent in low- (41/507, 8.1%) and middle-HDI (132/1540, 8.6%) groups. In analyses that attempted as far as it is possible to account for the inherent selection bias in these observational data, laparoscopy in low-/middle-HDI countries was significantly associated with fewer complications and lower SSI rates.

We have previously shown differences in outcomes after emergency surgery by HDI, with mortality found to be higher in low- and middle-HDI countries compared with high-HDI countries both in adults [4] and children [17]. In the present study, unadjusted analyses show a similar picture. However, in the multivariable analysis for overall

| HDI group | 1 Low No | 2 Low Yes | 3 Middle No | 4 Middle Yes | 5 High No | 6 High Yes |
|----------|---------|---------|---------|---------|---------|---------|
| Overall complications | Complication (%) with open approach | 14.7 (9.7–20.9) | 37.0 (26.8–48.3) | 13.0 (9.1–17.7) | 33.7 (24.8–43.9) | 13.6 (9.6–18.3) | 35.0 (26.3–44.5) |
| | Complication (%) with lap approach | 8.5 (5.1–12.8) | 24.0 (15.5–34.5) | 7.4 (4.7–10.9) | 21.5 (14.1–30.9) | 7.8 (5.3–10.7) | 22.4 (15.7–30.1) |
| | Absolute risk reduction (%) open versus laparoscopic | 6.3 (3.5–9.6) | 13.0 (7.7–18.5) | 5.6 (3.3–8.2) | 12.3 (7.5–17.1) | 5.9 (3.3–8.8) | 12.6 (7.5–18.1) |
| | Number-needed-to-treat | 16 (11–29) | 8 (6–13) | 18 (13–31) | 9 (6–14) | 17(12–31) | 8 (6–14) |
| Surgical site infection (SSI) | SSI (%) with open approach | 9.8 (5.5–15.9) | 26.1 (15.8–39.2) | 5.7 (2.9–9.7) | 16.6 (8.9–26.8) | 5.1 (2.8–8.0) | 15.0 (8.7–23.3) |
| | SSI (%) with lap approach | 2.4 (1.1–4.5) | 7.5 (3.5–13.6) | 1.4 (0.6–2.6) | 4.4 (1.9–8.5) | 1.2 (0.6–2.1) | 3.9 (1.9–6.9) |
| | Absolute risk reduction (%) open versus laparoscopic | 7.4 (4.1–12.1) | 18.6 (11.4–27.7) | 4.8 (2.2–7.4) | 12.2 (6.6–19.6) | 3.9 (2.1–6.4) | 11.2 (6.3–17.4) |
| | Number-needed-to-treat | 14 (9–25) | 6 (4–9) | 21 (14–46) | 9 (6–16) | 26 (16–48) | 9 (6–16) |
complications, no persistent association was seen with HDI after accounting for case-mix and structural differences. There were persistent differences seen in SSI rates after adjustment. SSI is therefore a phenomenon in which factors not accounted for in our models play an important role. More studies are needed to understand how this can be intervened upon.

It is well established in high-income settings that laparoscopic appendectomy is associated with better outcomes; however, little information exists in low-resource settings [18–21]. Wei et al. undertook a randomized comparison of open and laparoscopic appendectomy and concluded that a laparoscopic approach was associated with lower SSI rates and fewer complications,[18] a finding similar to that observed in the current study. Further advantages include reduced postoperative stay, less postoperative pain, and lower oxidative stress [19, 20]. In our study, the presence of a perforated appendix was associated with a 3- to 4-fold increase in adverse outcomes in multivariable models, including an increased surgical site and organ space (abscess) infection, findings similar to previous studies [21]. It has been debated whether a laparoscopic approach is always appropriate for patients with more advanced disease and peritonitis; however, evidence does exist supporting a laparoscopy even in complicated cases where reduced infection rates and postoperative length of stay can be achieved [22, 23].

Appendicitis is common in low-resource settings but its incidence varies greatly by country. It is the fourth-most common procedure performed by training surgeons in the College of Surgeons of East, Central and Southern Africa (COSECSA) region [24]. Appendicitis also presents differently in the poorest countries,[25] which is supported in the current study by the higher perforation rate seen in the low-HDI group (21.5%) compared with high-HDI group (13.9%). Given traditional assumptions around treatment delay and progression to perforation, this may be due to the well-described first-delay in seeking medical attention in low-HDI settings, compounded by a second-delay in reaching a medical facility that may be many days’ travel away [3]. Alternatively, this may represent a pathophysiological distinction between perforated and non-perforated appendicitis,[26] with selection exaggerated in low-resource settings by delays in seeking medical attention arising from

| High HDI countries   | Matched multivariable OR 95% CI | p−value |
|----------------------|---------------------------------|---------|
| Overall complications (CD I to V) | 1.00 (Reference) | − |
| Laparoscopic | 0.64 (0.43 to 0.95) | 0.027 |
| Open | 143 / 783 |
| Minor complication (Clavien Dindo I/II) | 1.00 (Reference) | − |
| Laparoscopic | 0.69 (0.46 to 1.05) | 0.082 |
| Open | 128 / 783 |
| Reintervention (Clavien Dindo III) | 1.00 (Reference) | − |
| Laparoscopic | 0.63 (0.30 to 1.29) | 0.213 |
| Open | 13 / 783 |
| Major complication (Clavien Dindo IV) | 1.00 (Reference) | − |
| Laparoscopic | 0.11 (0.01 to 0.59) | 0.037 |
| Open | 13 / 783 |
| Surgical site infection (SSI) | 1.00 (Reference) | − |
| Laparoscopic | 0.21 (0.10 to 0.41) | <0.001 |
| Open | 77 / 783 |
| Organ space infection (OSI) | 1.00 (Reference) | − |
| Laparoscopic | 0.61 (0.30 to 1.21) | 0.154 |
| Open | 19 / 783 |
| 30−day mortality | 1.00 (Reference) | − 0.998 |
| Laparoscopic | 1 / 783 |

| Low-/middle-HDI countries   | Matched multivariable OR 95% CI | p−value |
|-----------------------------|---------------------------------|---------|
| Overall complications (CD I to V) | 1.00 (Reference) | − |
| Laparoscopic | 0.29 (0.11 to 0.44) | <0.001 |
| Open | 42 / 167 |
| Minor complication (CD I/II) | 1.00 (Reference) | − |
| Laparoscopic | 0.16 (0.06 to 0.35) | <0.001 |
| Open | 36 / 167 |
| Reintervention (CD III) | 1.00 (Reference) | − |
| Laparoscopic | 0.76 (0.22 to 2.48) | 0.654 |
| Open | 8 / 167 |
| Major complication (CD IV) | 1.00 (Reference) | − |
| Laparoscopic | 0.42 (0.06 to 1.98) | 0.302 |
| Open | 5 / 167 |
| Surgical site infection (SSI) | 1.00 (Reference) | − |
| Laparoscopic | 0.21 (0.09 to 0.45) | <0.001 |
| Open | 31 / 167 |
| Organ space infection (OSI) | 1.00 (Reference) | − |
| Laparoscopic | 1.80 (0.57 to 6.29) | 0.326 |
| Open | 9 / 167 |
| 30−day mortality | 1.00 (Reference) | − 0.957 |
| Laparoscopic | 1 / 167 |

Fig. 1 Odds ratio plot for all outcome measures after propensity score matching by HDI group. OR odds ratio, CD Clavien–Dindo grade, CI confidence interval. Note there was an insufficient number of events to specify models for 30-day mortality.
geographic barriers to access, cultural differences, and the potential out-of-pocket impoverishing or catastrophic costs of surgery discouraging all but the sickest in attending hospital [27, 28].

The increased use of laparoscopy in low-income settings is controversial. In the poorest regions, the provision of any surgical service is extremely difficult and current high-technology, resource intensive laparoscopy is not feasible. However, our results raise the possibility of a benefit for patients and the healthcare system more widely. Given the higher rates of SSI in some low-income settings, the absolute benefit of laparoscopy is likely to be greater as shown by the simulation results [ARR of SSI in low-HDI countries (18.6%) compared with high-HDI countries (11.2%)]. This translates to a NNT with laparoscopic rather than open surgery of 6 to prevent one SSI in low-HDI countries managing perforated appendicitis. Moreover, in the absence of CT imaging, diagnostic laparoscopy can provide an effective way to investigate patients with acute abdominal pain short of the requirement for a full laparotomy.

The major strength of this study is the collection of patient-level prospective data from 52 countries. This unique dataset allows comparison across the HDI spectrum which is rarely possible. A published, detailed protocol translated into major languages ensured consistent data collection across varying regions without the burden of communication barriers. Local validation by leads ensured data accuracy and completeness was high. The interpretation of observational data is always difficult due to the inherent bias implicit in treatment allocation of patients. We have explored both multilevel models accounting for clustering patients in hospitals and countries, and propensity-score-matched models. In the latter, patients within low-/middle-HDI countries undergoing open or laparoscopic approaches were matched using available baseline variables, thus attempting to compare only “similar” patients who had undergone alternative treatments. Good balance was achieved and benefits of laparoscopy continue to be seen.

There are a number of weaknesses associated with our approach. Denominator data at a country level cannot easily be collected using this methodology. The “snapshot” may not accurately reflect overall practice, particularly where there are prominent seasonal effects [29]. We were not able to capture the degree of sepsis beyond the ASA and perforation rates, which may result in residual confounding. Within low-income, rural settings, collection of 30-day follow-up data can be challenging as patients are often discharged to remote regions and therefore cannot return to attend follow-up clinics. This was minimized by liberal use of telephone follow-up where feasible. A subsequent validation study of this methodology suggests that telephone follow-up is possible in upwards of one-third of included patients. Validation of data entry is challenging particularly where patient record keeping is limited. Collaborators frequently commented that the collected study data were of higher quality than existing hospital data. At each participating center, a lead was appointed to perform data validation and ensure accurate data-entry.

These results have significant implications for policy makers. Variation exists in outcomes after appendectomy across the world, but at least some of that variation may be explained by local surgical infrastructure such as the availability of laparoscopic surgery. Health services are faced with competing priorities and must balance a desire to improve surgical care with the costs of treating, say, malaria. The introduction of any new technology in a resource-poor setting must also be done with care. Recommendations include ensuring the existence of sufficient financial support and organizational systems to address staff training, including biomedical engineering staff to undertake equipment maintenance, and to establish robust, affordable, and sustainable supply chains [10]. A successful implementation of laparoscopic surgery has already been demonstrated at scale in low-resource settings [30].

Future research must focus on identifying innovative, affordable, and safe strategies to implement and scale laparoscopic surgery in low-resource settings. Such adaptive techniques may include gasless laparoscopy, room air insufflation, and development of affordable, reusable instrumentation. In addition, there is an ongoing need to establish robust systems for the continuous measurement of surgical outcomes across the world. High-quality clinical trials relevant to low-HDI countries must be performed to ensure the identification of the most effective treatments, such as how to reduce SSI. Outcomes in surgery will only improve with system-wide improvements across the pre-hospital, hospital, and post-hospital sectors.

This study has shown significant variation in the management and outcomes following appendectomy worldwide. The availability of laparoscopy differs by country HDI, and appears to be significantly associated with better outcomes. There are profound clinical, operational, and financial barriers to the introduction of laparoscopy that if overcome could result in significantly improved outcomes for patients and the wider health system in low-resource environments.

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Writing group Thomas M Drake*, Julian Camilleri-Brennan*, Stephen Tabiri, Stuart J Fergusson, Richard Spence, J Edward F Fitzgerald, Aneel Bhangu, Ewen M Harrison (Guatemala), Cutting Edge Manipul, Midhun Mohan (India), Radhian Amandito (Indonesia), Marwan Shawki (Iraq), Michael Hanrahan (Ireland), Francesco Pata (Italy), Justas Zilinskas (Lithuania), Alfredo Roslani, Cheng Chun Goh (Malaysia), Aneel Bhangu, Ewen M Harrison, Chetan Khatri, Midhun Mohan, Dmitri Nepogodiev, Kjetil Søreide.

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Austria Clemens Nawara, Dietmar Öfner, Florian Primavesi (Department Of Surgery, Paracelsus Medical University Salzburg).

Bangladesh Asharur Rahman Mitul, Khalid Mahmud (Dhaka Shishu Children Hospital), Margub Hussain, Hafiz Hakim, Tapan Kumar (Dhaka Medical College Hospital), Antje Oosterkamp (Lambada Hospital).

Benin Pamphile A Assouto, Ismail Lawani, Yacoubou Isouboou (Centre National Hospitalier Et Universitaire Hubert Coutouou, Ouagadougou).

Brunei Aung Khyaw Tun, Chean Leong Chong, (Pmmpmhamb Hospital) Giridhar H Devadasar, Chean Leong Chong, Mahmoud Rashid Minhas Qadir, (Ssb Hospital), Kyaw Phyo Aung, Lee Shi Yeo, Chean Leong Chong (Ripas Hospital).

Brazil Vanessa Dina Palomino Castillo, Monique Moron Munhoz, Gisele Moreira (Conjunto Hospitalar De Sorocabra), Luiz Carlos Barros De Castro Segundo, Salim Anderson Khouri Ferreira, Maïra Cassa Careta (Hospital Da Santa Casa De Misericórdia De Vitória), Stella Binna Kim, Alexandre Vanencion De Sousa, Alyne Dalitzer Lazzarin (Hospital De Caridade São De Paula), Gustavo Peixoto Soares Miguel, Ana Vega Carreiro De Freitas, Barbara Pereira Silvestre (Hospital Luis Lagomaggiore).

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Colombia Irene Montes, Sebastian Sierra, Manuela Mendez (Clinica Cesar), Maria Isabel Villegas, Maria Clara Mendoza Arango, Ivan Mendoza, (Clinica Las Vegas), Fred Alexander Naranjo Aristizábal, Jaime Andres Montoya Botero, Victor Manuel Quintero Riazo (Hospital Pablo Tobon Uribe), Jadeline Restrepo, Carlos Morales, Maria Clara Mendoza Arango (Hospital Universitario San Vicente Fundacion), Herman Cruz, Alejandro Munera, Maria Clara Mendoza Arango (Ips Universitaria Clinica Leon Xii).

Croatia Robert Karlo, Edgar Domini, Jakov Mihanovic (Zadar General Hospital), Mihael Radic, Kresimir Zamarin, Nikica Pezelj (General Hospital Sibenik).

Dominican Republic Manuel Hache-Marliere, Sylvia Batista Lemaire, Ruben Rivas (Cedimat - Centro De Diagnostico Medicina Avanzada, Laboratorio Y Telemedicina).

Egypt Ahmed Khylrahl, Ahmed Hassan, Gamal Shmy, Mohamed A Baky Fahmy (Al-Azher University Hospital); Ayman Nabawi, Mohamed Elhilil, Mohamed Ghoneem, Muhammad El-Saied Ahmad, Mahmoud Gohar, Mohamed Asal, Mostafa Abdelkader, Mahmoud Gomah, Hayssam Rashwan, Mohamed Karkeet, Ahmed Gomaa (Alexandria Main University Hospital); Amr Hassan, Ahmed Elgebaly, Ahmed Saleh, Abdel Fattah, Abdullah Gouda, Abd Elrahman Elshafy, Abdalla Gharib, Ahmed Menshawy, Mohammed Hanafy, Ahmed Al-Mallah, Mahmoud Abdulgawad, Mohamad Baheeg, Mohammed Alhendy, Ibrahim Abdelfattah, Abdalla Kenbar, Omar Osman, Mostafa Gemadeh, Ahmed Mohamed, Abdalrahman Adel, Abdalla Gharib, Abdalrahman Mohammed, Abdalrahman Sayed, Mohamed Abozaid (Al-Hussein Hospital); Ahmed Hafez El-Badri, Ali Amin Ahmad Ata, Mohamed Nasr, Abdalrahman Alkamash, Mohamed Saeed, Nader Abd El Hamid, Attia Mohamed Attia, Ahmed Abd El Galeel, Eslem Elbany, Khalid Salah El-Dien, Usama Hantour, Omar Alhady, Billil Mansour, Amr Muhammad Elkoraby, (Bab El-Shareia Hospital); Emad Mohamed Saeed Taha, Kholod Tarek Assem, Soliman Magdy Ahmed, Nermeen Soubhy El-Shahat, Mehrabash Alkhrayh, (Manouba Hospital), Mostafa Abozaid, (Al-Hussein Hospital); Mahmoud Fathi Abozayed, Ahmed Adel, Abdalrahman Saeed, Gehad Samir El Sayed, Jaben Hassan Youssif (Bapna University Hospital); Soliman Magdy Ahmed, Nermeev Soubhy El-Shahat, Abd El-Rahman Hegazy Khedr (Bolhas Central Hospital); Abdelrahman Osama Elsebaaye, Mohamed Elzayat, Mohamed Abdelraheim, Ibrahim Elzayat, Mahmoud Warda, Khaled Naser El Dene, Abdelrahman Essam Elmenn, Omar Salah, Mohamed Abbas, Mona Rashid, Ibrahim Elzayat, Daifa Hemeda, Gehad Tawfik, Mai Salama, Hazem Khaled, Mohamed Seisa, (El Dawly Hospital - Mansoura); Kareem Elshier, Abdelfatah Hussein, Mahmoud Elkhdrawi (El Mahalla General Hospital); Ahmed Mohamed Alfli, Osama Saadeldeen Ebrahim, Mahmoud Mohamed Metwally (El - Mataria Educational Hospital); Rowida Elmelegy, Diaa Moustafa Elbendary Elsawyabi, Hisham Safa, Eman Nofal, Mohamed Elbarmawy, Ahmed Abdelmotaleb Ghazy, Hisham Samih, Asmaa Abdelgelil, Sarah Abdelghany, Ahmed El Koly, Metwally Abaraya, Fatma Elkady, Mahmoud Salma, Sarah Samy, Reem Fakher, Aya Aboarab, Ahmed Samir, Ahmed Sakr, Abdalrahman Haroun, Asmaa Abdalrahman Al-Araag, Ahmed Elkholy, Sally Elshinwaney (El-Menshawy Hospital); Esraa Ghanem (Elshehada Central Hospital); Ahmed Tamam, Ali Mohamed Hammad,
Hospital), Simon George Gosling, Michelle McCarthy, Amoudthia Rasendran, Ciara Fahy, Jiheon Song, Michael Hanrahan, Diana Duarte Cadogan, Anna Powell, Richard Gilbert, Caroline Clifford, Coimhe Normile, Aoife Driscoll (Mercy University Hospital), Stassen Paul, Chris Lee, Ross Bow (Midlands Regional Hospital Mullingar), William Hutch, Michael Hanrahan (University College Cork), Helen Mohan, Maeve O’neill, Kenneth Mealy (Wexford General Hospital).

Italy Piergiorgio Danelli, Andrea Bondurri, Anna Maffioli (Azienda Ospedaliera Luigi Sacco - Polo Universitario), Mario Pasini, Giacomo Pata, Stefano Roncali (Azienda Ospedaliera Spedali Civili Di Brescia - Chirurgia Generale), Paolo Silvani, Michele Carlucci, Roberto Faccinanni (IRCCS Ospedale San Raffaele), Luigi Bonavida, Yumi Machitabella, Chiara Ceriani (University of Milan, IRCCS Policlinico San Donato), Gregorio Tognoni, Salomone Di Saverio, Khaled Khattab (Maggiore Hospital), Miguel Angel Paludo, Domenica Pata, Luigi Maria Cloro (Nicola G Gianettasio Hospital), Andrea Allegri, Luca Ansaloni, Federico Coccolini (Papa Giovanni Xxiii Hospital), Ezio Veronese, Luca Bortolasi, Alireza Hasheminia, (San Bonifacio Hospital), Giacomo Nasti, Massimiliano Dal Canto, Stefano Cucumazzo (Santa Croce Hospital), Francesco Pata, Angelo Benevento, Gaetano Teserta (Sant'Antonio Abate Hospital, Gallarate), Pier Paolo Grandinetti, Alessio Mansicalco, Giovanni Luca Lamanna (Santi Benvenuto E Rocco Hospital Asur), Luca Turati, Giovanni Sgori, Emanuele Rausa (Treviso Hospital), Roberta Villa, Michela Monteleone, David Merlini (Unita’ Di Chirurgia D’urgenza Azienda Ospedaliera Salvini), Federico Coccolini, Luca Ansaloni, Andrea Allegri (Unit Of General Surgery I, Papa Giovanni Xxiii Hospital), Veronica Grassi, Roberto Cirocchi, Alban Cacurri (University Of Perugia).

Libya Hamza Waleed, Ahmed Diab, Fathi Elzowawi (Misurata Central Hospital).

Lithuania Mantas Jokubauskas, Karolis Varkalys, Donatas Venskutonis (Kaunas Clinical Hospital), Robertas Pranevicius, Viktorijos Ambrozieviciute (Klaipedas Seaman Hospital), Simona Jucute, Austė Skardžiukaitė (Lietuvos Sveikatos Mokslų Universitetas), Donatas Venskutonis, Saulius Bradulskis, Linas Urbanavicius, Aiste Austruote, Romualdas Riaukai, Justas Zilinskiis, Zilvinas Dambrauskas (Lithuanian University Of Health Sciences), Paulius Karumnas, Zigmantas Urniezius, Reda Zilinskienė (Republic Hospital Of Kaunas), Anele Rudzenskaite (Republic Hospital Of Panevezys), Ausrine Usaityte, Margarita Montrimaita, Nerius Kaselis (Republic Klaipeda Hospital), Andrius Strazdas, Kristijonas Jokubonis (Stasys Kudriska Regional Hospital Of Alytus), Kornelija Maceviciute, Jonavos Ligonine, Marija Agius, Elaine Borg, Maureen Bezzina, Roberta Carina, Christian Hinojosa, Melanie Zapata Ponze De Leon, Susan Limache, Arenas, Crislee López, Clara Milagros Herrera Puma, Wilfredo Pino, Zelada Alvarez, Juan Marcelo Delgado, Gustavo Miguel Machain Vega, Helmut Alfredo Segovia Lohse (Hospital De Clinicas).

Malaysia Dineshwyar Periasamy, Afizah Salleh, Andre Das (Hospital Kajang), Reuben Goh Ern Tze, Milaksh Nirural Kumara, Nik Azim Nik Abdullah (Sarawak General Hospital), Nik Ritza Kosai, Mustafa Taher, Reynu Rajan (University Kebugasaan Malaysia Medical Centre), Hoong Yin Chong, April Camilla Roslani, Cheng Chun Goh (University Malaya Medical Centre).

Mali Marija Agius, Elaine Borg, Maureen Bezzina, Roberta Bugeja, Martinique Vella-Baldacchino, Andrew Spina, Josephine Psaila (Mater Dei Hospital, Malta).

Martinique Helene Francois-Coridon, Cecilia Tolg, Jean-Francois Martinique (Department Of Pediatric Surgery, Mother And Children’s Hospital, University Hospital Of Martinique).

Mexico Carmina Diaz-Zorrilla, Antonio Ramos-De La Medina, Samantha Corro-Diaz Gonzalez (Hospital Español de Veracruz).

Mozambique Mário Jacobe, Domingos Mapasse, Elizabeth Snyder (Hospital Central Maputo).

New Zealand Ramadan Omer, Mohammed Osman (Whangarei Hospital, Northland District Health Board).

Nigeria Aminu Mohammad, Lofty-John Anyanwu, Abdulrahman Sheshe (Aminu Kano Teaching Hospital), Alaba Adesina, Olubukola Faturoti, Ogechukwu Taiwo (Babcock University Teaching Hospital), Muhammad Habib Ibrahim, Abdulrasheed A Nasir, Siyaka Itopa Suleiman (Federal Medical Centre, Birnin Kebbi), Adewale Adeniyi, Opeoluwa Adesanya, Ademola Adebanjo (Federal Medical Centre), Roland Osuji, Kazeem Atobatele, Ayokunle Ogunyemi, Omolara Williams, Mobolaji Oluudara, Obabode Oshodi (Lagos State University Teaching Hospital), Adesoji Ademuyiwa, Abdullah Razzaq Sulavangbemiga Lawal, Felix Alakaloko, Olumide Elebute, Adeedapo Osisowo, Christopher Bode (Lagos University Teaching Hospital), Abidemi Adesuyi (National Hospital Abuja), Adesoji Tade, Adeleke Adekoya, Collins Nwokoro (Okabisi Onabah University Teaching Hospital), Omosolaja Oyewole, James Adeniran (University Of Ilorin Teaching Hospital).

Norway William J. Lossius (Department Of Gastrointestinal Surgery, St. Olavs Hospital, Trondheim University Hospital), Ingemar Havemann (Sørlandet Hospital Kristiansand), Kenneth Thorsen, Jon Kristian Nagarveid, Kjetil Smareide (Stavanger University Hospital), Trude Beate Wold, Linn Nyno (University Hospital Of North Norway, Troms).

Oman Mohamed Elsiddig, Manzoor Dar (Sohar Hospital).

Pakistan Kamran Faisal Bhopal, Zainab Utkitar, Muhammad Mohsin Furqan (Bawabah Victoria Hospital), Bakhtiar Nighat, Masood Jawaid, Abdul Khalique (Dow University Hospital), Ahsan Zil-E-Ali, Anam Rashid (Fatima Memorial Hospital), Hasnain Abbas Dhamashmi, Tahira Naqvi, Ahmad Faraz (Karachi Medical And Dental College, Abbas Shaheed Hospital), Abdul Wahid Anwar, Tahir Muhammad Yaseen, Ghina Shamim Shamsi, Ghina Shamsi, Tahir Yaseen, Wahid Anwer (The Inus Hospital).

Paraguay Horacio Paredes Decoud, Omar Aguiler, Ismael Saul Selada Alvarez, Juan Marcelo Delgado, Gustavo Miguel Machain Vega, Helmut Alfredo Segovia Lohse (Hospital De Clinicas).

Peru Wendy Leslie Messa Aguilar, Jose Antonio Cabala Chong, Ana Cecilia Manchego Bautista (Carlos Alberto Segun Escobedo National Hospital, Essalud), Eduardo Huaman, Sergio Zegarra, Rony Camacho (Hospital Nacional Guillermo Almenara), Jose Maria Vergara Celis, Diego Alonso Romanzi Pozo (Hospital De Emergencias Pediatricas), Jose Hamasaki, Edilberto Temohce, Jaime Herrera-Matta (Hospital De Policia), Carla Pierina Garcia Torres, Luis Miguel Alvarez Barreda, Ronal Renato Barrionuevo Ojeda (Hospital Goyeneche), Octavio Garaycochea (Hospital Ifi - 1 Minsa Mombamba), Melina Castro Mollo, Michelle Solange De Fari Timae Linas Delgado, Francisco Fujii (Hospital Maria Auxiliadora), Ana Cecilia Manchego Bautista, Wendy Leslie Messa Aguilar, Jose Antonio Cabala Chiong (Hospital Nacional Carlos Alberto Seguin), Susana Yrma Aranzabal Durand, Carlos Alejandro Arroyo Basto, Nelson Manuel Urbina Rojas (Hospital Nacional Edgardo Rebagliati Martins-Essalud), Sebastian Bernardo Shu Yip, Ana Lucia Conteras Vergara, Andrea Echevarria Rosas Moran, Giulianno Borda Luque, Manuel Rodriguez Castro, Ramon Alvarado Jaramillo (Hospital Nacional Cayetano Heredia), George Manrique Sila, Criselle Elizabeth Lopez, Mandelangel Zapata Ponze De Leon, Massiel Machaca, Ronald Coasaca Huaraya, Andy Arenas, Criselle Lopez, Clara Milagros Herrera Puma, Wilfredo Pino, Christian Hinojosa, Melanie Zapata Ponze De Leon, Susan Limache, George Manrique Sila, Layza-Alejandra Mercado Rodriguez (Hospital Regional Honorio Delgado Espinosa).

Portugal Renato Melo, Jose Costa-Maia, Nuno Murhalho (Servico De Cirurgia Geral - Centro Hospitalar Sao Joao - Porto).
Romania Ionase Dan, Mircea Hoga, Pandi Eduard (Emergency Clinical Hospital Brasov), Razvan-Matei Bratu, Mircea Beuran, Ionut-Bogdan Diaconescu, Bogdan-Valeriu Martian, Florin-Mihail Iordache, Mihaela Vartic (Emergency Clinical Hospital Bucharest), Lucian Cornelii Vida, Liviu Iuliu Muntean, Aurel Sandu Mironescu (Spitalul Clinic De Copii Brasov).

Rwanda Vizir Jean Paul Nsengimana (Chuk), Alice Nairagire, Jean De La Croix Allen Ingabire, Eugene Nyirirwa (University Teaching Hospital Of Kagali).

San Marino Nicola Zanini, Elio Jovine, Giovanni Landolfo (San Marino State Hospital).

Saudi Arabia Ibrahim Al Nolmar, Salem A. Alnuayyan, Abdurahman M. Altawyry (Buraydah Central Hospital), Moayad Othman, Nohad Osman (Imam Abdurrahman Al Faisal Hospital), Enas Alqatahni (King Abdulaziz Hospital Al Ahsa National Guard), Mohammad Alzahrani, Rifaan Alyami, Emad Aljohani (King Abdulaziz Medical City), Ibrahim Alhabli, Zaher Mikwar, Sultan Almualllem (King Abdulaziz Medical City (King Khalid National Guard Hospital), Jeddah), Emad Aljohani, Rifaan Alyami, Mohammad Alzahrani (King Abdulaziz Medical City, Riyadh), Abrar Nawawi, Mohammad Bakhdair, Ashraf A. Maghrabi, Mohammed Alsaqgaf, Murad Aljiffry, Abdulmalik Alfa, Ahmad Khjoa, Alaa Habeebullah, Nofah Akeel (Department of Surgery, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia), Nashat Ghandora, Abdullah Almoflihi, Abdulmalik Huwait (King Fahad General Hospital), Abeer Al-shammari, Mashael Al-Mousa (King Fahad Hospital), Masood Alghamdi, Walid Adham, Bandar Albeladi, Muayad Ahmed Alfarsi, Atif Mahdi, Saad Al Awad (King Fahd Hospital), Afnan Altamimi, Thamer Nouh, Mazen Hasnaan (King Khaled University Hospital, King Saud University), Salim Aldhafeeri, Nawal Sadig, Osama Alghohry (King Khalid General Hospital, Mohammad Alredisy, Ahmad Gudal, Ahmad Alrifai (King Khalid National Guard Hospital), Mohammed AlRowais, Amani Althilawi (Department of Surgery, King Saud University), Alaa Shabak, Uthman Almoudi, Mawadah Alrajaji (National Guard Hospital), Basim Alghamdi, Saud Aljohani, Abdullah Daeqeq (Rycm), Jubran J Al-Faifi (Security Forces Hospital).

South Africa Vicky Jennings, Nyawira Ngayu, Rachel Moore (Chris Hani Baragwanath Academic Hospital), Victor Kong (Edendale Hospital), Hayden Kretzmann, Katie Connor, Daniel Nel (Ferre Hospital), Colleen Sampson, Richard Spence, Eugenio Panieri (Groote Schuur), Sarah Rayne, Nosissa Sishuba (Helen Joseph Hospital, Department Of Surgery, University Of The Witswatersrand), Myint Tun, Albert Mohale (Harran University Research And Treatment Hospital), Mohammed Al Rowais, Amani Althilawi (King Khalid General Hospital, Mohammad Alredisy, Ahmad Gudal, Ahmad Alrifai (King Khalid National Guard Hospital), Mohammed AlRowais, Amani Althilawi (Department of Surgery, King Saud University), Alaa Shabak, Uthman Almoudi, Mawadah Alrajaji (National Guard Hospital), Basim Alghamdi, Saud Aljohani, Abdullah Daeqeq (Rycm), Jubran J Al-Faifi (Security Forces Hospital).

Spain Fernando Fernandez-Bueno (Hospital Central De La Defensa Gomez Ulla), Jose Aguilar-Jimenez, Jose Andres Garcia-Marin (Hospital Morales Meseguer. Sm), Lorena Solar Garcia, Luis Joaquin Garcia Florez, Ruben Dario Arias Pacheco (Hospital San Agustín), Janet Pag-Fon, Nozomi, Jaroslav Jarad Zquebada, Jose Luis Rodicio, Mohammad Mahmood, Mohammad Elsayed, Mohammad Elsayed, Mohamed Mahmoud (Omdurman Teaching Hospital).
Surgical Endoscopy

Wales Hospital), Jonathan R L Wild, Tom AM Malik, Victoria K Proc-

surgical Endoscopy 13 (Princess Alexandra Hospital), Leo Duffy, Elizabeth Mcleer, Eleanor

Williams (Princess Of Wales Hospital), Robin Som, Omar Javed (Queen Elizabeth Hospital Woolwich), Matthew Boal, Nicola Harrison, Habib Tafazal, Omar Javed, Tom Brogden, Dmitri Nepogodiev, Edwin

Griffiths (Queen Elizabeth Hospital Birmingham) Rhalumi Daniel Obute, Thomas E Glover, David J Clark (Queen Elizabeth Hospital King’s Lynn), Mohamed Boshnaq, Mansoor Akhtar, Pascale Capleton, Samer Doughan, Mohamed Rabie, Ismail Mohamed (Queen Elizabeth The Queen Mother Hospital), Duncan Samuel, Lauren Dickson, Matthew Kennedy, Eleanor Dempster, Emma Brown, Natalie Maple, Eimear Monaghan, Bernhard Wolf, Alicia Garland (Raigmore Hospital), Arthur Mcphee, David Anderson, Robert Anderson (Royal Alex-

andria Hospital), Sarah Hassan, Paul Sutton, Dave Smith (Royal Bolton Hospital), Jonathan Lund, Catherine Boereroomb, Jennifer Murphy, Gillian Tierney, Samson Tou (Royal Derby Hospital), Eleanor Fran-

ziska Zimmermann, Neil James Smart, Andrea Marie Warwick (Royal Devon And Exeter National Health Service Foundation Trust), Theo-

dora Stasinou, Ian Daniels, Kim Findlay-Cooper (Royal Devon & Exeter NHS Foundation Trust), Stefan Mitrasinovic, Swayamjyoti Ray, Massimo Varcada, Rovan D’Souza, Sharif Omara (Royal Free Hospital), Matthew Spurr, Lucienne Parkinson, Anthony Hanks (Royal Glamorgan Hospital), Jennifer Ma, Emily Abington, Meera Ramcharn, Gethin Williams (Royal Gwent Hospital), Joseph Winstanley, Ewan D. 

Kennedy, Emily NW Yeung (Royal Hospital For Sick Children), Stuart J Fergusson, Catrion James, Stephen O’neill, Shujing Jane Lim, Ignatius Liew, Hari Nair, Cameron Fairfield, Julia Oh, Samantha Koh, Andrew

Wilson, Catherine Fairfield (Royal Infirmary Of Edinburgh), Deirfan Anandkumar, Ashok Kirugaparan, Timothy J Jones, Hew D Torrance, Alexander J Fowler. Charmilie Chandrakumar, Priyank Patel, Syed 

Fiaz Ashraf, Somn M. Lakhani, Aaron Lawson Mclean, Sonia Bason (Royal London Hospital), Jeremy Batt, Catriona Bowman, Michael Stoddart, Natasha Benons (Royal United Hospital Bath), Clare Mason, Rebecca

Harrison, John Quayle (Salford Royal NHS Foundation Trust), Tom Barker, Virginia Summerour, Edward Harper (Sandwell And West Birmingham Hospitals NHS Trust), Caroline Smith, Matthew Hampton (Sheffield Children’s Hospital), Sophie K Pitt, Alex E Ward, Timothy O’Connor, Emily G Heywood, Thomas M Drake (Sheffield Teaching Hospitals NHS Foundation Trust), Abee Chowdhury, Sina Hossaini,

Nicholas Fs Watson (Sherwood Forest Hospitals NHS Foundation Trust), Doug Mecknehine, Ayaan Farah, Anita Chun (Southend University Hospital), Hoey Koh, Grace Lim, Graham Sunderland (Southern General Hospital), Laura Gould, Alice Chambers (Southend Hospital), P C Munipalle, H Rooney, D R L Browning (Southend Hospital, North Bristol NHS Trust), Bernadette Pereira, Kristof Nemeth, St Georges Healthcare NHS Trust), Emily Decker, Stefano Giulian, Aly

Shalaby (St.George’s Healthcare NHS Trust And University), Shafaaque Shaikh, Chen Yan Tan, Ebrahim Y A Palkhi (St.James’s University Hospital), Aleksandra Szczap, Swathikan Chidambaram, Chee Yang Chen, Kavian Kulasabanathan, Srishti Chhabra (St Mary’s Hospital), Elisabeth Kostov, Philippe Harbird, James Barnacle (St. Mary’s Hospital), Madan Mohan Palliyil, Mina Zikry, Johnther Lohan, Charief

Raslan, Mohammad Saeed, Shazia Hafiz, Niksa Soltani, Katie Baille (Stockport NHS Foundation Trust), Priyanka Singh, Shailee Sheth, Kishen Patel, Mahry Khalili, Jeesoo Choi, Matthew Benger (St Thomas’ Hospital), Lucy Marples, Alastair Macfarlane, Ramesh Thurairajaja (St. Thomas Hospital), Tamsin Boyce, Harriet Hewell, Elin Jones (The Royal Gwent Hospital), Francesca Th’ng, Nichola Robinson (The Royal Infirmary Of Edinburgh), Ahmad Mirza, Haroon Saeed, Simon Gallows (The University Hospital Of South Manches-

ter), Gia Elena, Mohammad Afzal, Mohamed Zakir (United Lin-

colnshire Hospitals - Pilgrim Hospital), Peter Sadde, Charles Hand, Aiesha Sriram, Tamsyn Clark, Patrick Holton, Amy Livesey (University Hospital Coventry And Warwickshire), Yashashwi Sinha, Fahad Mujtaba Iqbal, Indervir Singh Bhajar (University Hospital Of North Midlands), Adriana Rotundo, Cara Jenvey, Robert Slade (University Hospital Of North Staffordshire NHS Trust), David Golding, Samuel

Haines, Ali Adel Ne’ma Abdullah, Thomas W Tilston, Dafydd
Loughran, Danielle Donoghue, Lorenzo Giacci, Mohamed Ashur Sherif, Peter Harrison, Alethea Tang (University Hospital Of Wales), Deevia Kotecha (University Hospitals Leicester - Leicester Royal Infirmary), Mohamed Elshaer, Tomas Urbonas, Amjid Riaz, Annie Chapman, Parisha Acharya, Joseph Shalhoub (Watford General Hospital), Cathleen Grossart, David McMorrall (Western General Hospital), Makhosini Mlotshwa, William Hawkins, Sofronis Loizides (Western Sussex Hospitals NHS Trust), Kandaswamy Krishna, Melanie Orchard, Chik Wai Ho (Weston General Hospital), Peter Thomson, Shahab Khan, Fiona Taylor, Julak Shukla, Emma Elizabeth Howie (Whipps Cross University Hospital), Linda Macdonald, Olusegun Komolafe, Neil McIntyre (Wishaw General Hospital), James Cragg, Jody Parker, Duncan Stewart (Wrexham Maelor Hospital), Luke Lintin, Julia Tracy, Tahir Farooq (Yevvil District Hospital).

United States George Molina, Haytham Kaafarani, Laura Luque (Massachusetts General Hospital), Robel Beyene, Jack Sava, Mark Scott (Medstar Washington Hospital Center), Mamta Swaroop, Raelene Kennedy (Northwestern Memorial Hospital), Ijeoma A Azodo, Daithi Heffernan, Tristen Chun, Andrew Stephen (The Rhode Island Hospital), Melanie Sion, Michael S. Weinstein, Viren Punja (Thomas Jefferson University Hospital), Nikolay Bugaev, Monica Goodstein, Shadi Razmjou (Tufts Medical Center), Eric Etchill, Juan Carlos Puyana, Matthew Kesinger (University of Pittsburgh Medical Center - Presbyterian Hospital), Lena Napolitano, Kathleen To, Mark Hemmila (University of Michigan).

Zambia Oliver Todd, Edward Jenner, Ellen Hoogakker (St Francis Hospital).

Protocol Translation Jacky Hong Chieh Chen, Lawani Ismail, Dylan Roi, Eugenio Grasset Escobar.

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Compliance with ethical standards

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Appendix

Management and outcome of appendectomy in high, middle and low income countries

| Countries: 52 | Hospitals: 387 | Collaborators: 1532 | Patients: 4546 |
|--------------|--------------|-----------------|---------------|
| Surgical site infection higher in low income countries | Laparoscopic rate low in LMICs | Laparoscopy in LMICs associated with fewer complications |
| ![Graphic](graphic.png) | ![Graphic](graphic.png) | ![Graphic](graphic.png) |
| 4.4% of patients | 12.0% of patients | 14.8% of patients |
| 67.7% of patients | 8.6% of patients | 8.1% of patients |
| Association with surgical site infection | Propensity score matched odds ratio (95% CI) |
| 0.21 (0.09, 0.45) |

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