

Mortality from gastrointestinal congenital anomalies at 264 hospitals in 74 low-income, middle-income, and high-income countries: a multicentre, international, prospective cohort study

Global PaedSurg Research Collaboration*



Summary

Background Congenital anomalies are the fifth leading cause of mortality in children younger than 5 years globally. Many gastrointestinal congenital anomalies are fatal without timely access to neonatal surgical care, but few studies have been done on these conditions in low-income and middle-income countries (LMICs). We compared outcomes of the seven most common gastrointestinal congenital anomalies in low-income, middle-income, and high-income countries globally, and identified factors associated with mortality.

Methods We did a multicentre, international prospective cohort study of patients younger than 16 years, presenting to hospital for the first time with oesophageal atresia, congenital diaphragmatic hernia, intestinal atresia, gastroschisis, exomphalos, anorectal malformation, and Hirschsprung's disease. Recruitment was of consecutive patients for a minimum of 1 month between October, 2018, and April, 2019. We collected data on patient demographics, clinical status, interventions, and outcomes using the REDCap platform. Patients were followed up for 30 days after primary intervention, or 30 days after admission if they did not receive an intervention. The primary outcome was all-cause, in-hospital mortality for all conditions combined and each condition individually, stratified by country income status. We did a complete case analysis.

Findings We included 3849 patients with 3975 study conditions (560 with oesophageal atresia, 448 with congenital diaphragmatic hernia, 681 with intestinal atresia, 453 with gastroschisis, 325 with exomphalos, 991 with anorectal malformation, and 517 with Hirschsprung's disease) from 264 hospitals (89 in high-income countries, 166 in middle-income countries, and nine in low-income countries) in 74 countries. Of the 3849 patients, 2231 (58.0%) were male. Median gestational age at birth was 38 weeks (IQR 36–39) and median bodyweight at presentation was 2.8 kg (2.3–3.3). Mortality among all patients was 37 (39.8%) of 93 in low-income countries, 583 (20.4%) of 2860 in middle-income countries, and 50 (5.6%) of 896 in high-income countries ($p < 0.0001$ between all country income groups). Gastroschisis had the greatest difference in mortality between country income strata (nine [90.0%] of ten in low-income countries, 97 [31.9%] of 304 in middle-income countries, and two [1.4%] of 139 in high-income countries; $p \leq 0.0001$ between all country income groups). Factors significantly associated with higher mortality for all patients combined included country income status (low-income vs high-income countries, risk ratio 2.78 [95% CI 1.88–4.11], $p < 0.0001$; middle-income vs high-income countries, 2.11 [1.59–2.79], $p < 0.0001$), sepsis at presentation (1.20 [1.04–1.40], $p = 0.016$), higher American Society of Anesthesiologists (ASA) score at primary intervention (ASA 4–5 vs ASA 1–2, 1.82 [1.40–2.35], $p < 0.0001$; ASA 3 vs ASA 1–2, 1.58, [1.30–1.92], $p < 0.0001$), surgical safety checklist not used (1.39 [1.02–1.90], $p = 0.035$), and ventilation or parenteral nutrition unavailable when needed (ventilation 1.96, [1.41–2.71], $p = 0.0001$; parenteral nutrition 1.35, [1.05–1.74], $p = 0.018$). Administration of parenteral nutrition (0.61, [0.47–0.79], $p = 0.0002$) and use of a peripherally inserted central catheter (0.65 [0.50–0.86], $p = 0.0024$) or percutaneous central line (0.69 [0.48–1.00], $p = 0.049$) were associated with lower mortality.

Interpretation Unacceptable differences in mortality exist for gastrointestinal congenital anomalies between low-income, middle-income, and high-income countries. Improving access to quality neonatal surgical care in LMICs will be vital to achieve Sustainable Development Goal 3.2 of ending preventable deaths in neonates and children younger than 5 years by 2030.

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Introduction

In the past 30 years, major strides have been made in reducing childhood mortality globally, with a decrease

in deaths in children younger than 5 years from 12.6 million in 1990 to 5.2 million in 2019.^{1,2} However, neonatal mortality has fallen at a slower rate, from

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See [Comment](#) page 280

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See [Online](#) for appendix

Research in context

Evidence before this study

We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for observational or randomised studies published in English from Jan 1, 2000, to Oct 10, 2020. Three search strings were used: the seven gastrointestinal congenital anomalies included in our study; all-cause in-hospital or 30-day postoperative mortality; and patients aged under 16 years. Studies were limited to those of primary surgical intervention and cohorts of more than 100 patients. We found no previous studies that have prospectively compared outcomes from gastrointestinal congenital anomalies between low-income, middle-income, and high-income countries globally. Research on the individual conditions was mainly from high-income countries (79 studies), with a smaller number of studies from middle-income countries (14 studies), and one from a low-income country. Due to the heterogeneity of the studies, an accurate comparison of outcomes between income strata was not possible. Information regarding leading causes of death or factors associated with mortality for these conditions in low-income and middle-income countries (LMICs) is scarce.

Added value of this study

This study provides validated, prospectively collected data on patients with gastrointestinal congenital anomalies in 74 low-income, middle-income, and high-income countries across the globe. The results highlight large disparities in mortality between income settings. Moreover, the high mortality rates identified for these conditions in LMICs far

exceed surgical mortality rates among older children and adults reported in previous international surgical outcomes studies. The large study cohort has enabled robust multivariable analysis and identification of numerous factors substantially and significantly associated with mortality. These results, along with the detailed data on patient management in each setting, provide a foundation from which interventions, guidelines, and policies can be established with the aim of reducing the vast inequities in care provision and outcomes that currently exist.

Implications of all the available evidence

Sustainable Development Goal 3.2, which is to end preventable deaths of neonates and children under 5 years of age by 2030, is unachievable without an urgent focus on improving access to quality neonatal surgical care in LMICs. Indicators of clinical deterioration before surgical intervention were significantly associated with higher mortality for all conditions. Birth at a paediatric surgery centre (enabled by antenatal diagnosis) can help to prevent this and reduce mortality, as shown in patients with gastroschisis and congenital diaphragmatic hernia. However, most patients present from district hospitals, highlighting the importance of improved diagnosis, resuscitation, and timely transfer at this level. At paediatric surgery centres, improved provision of basic neonatal intensive care facilities, including ventilation, parenteral nutrition, and central intravenous access, for neonates could reduce mortality further. These interventions would also benefit sick neonates more broadly, and therefore would help to further reduce global neonatal mortality.

4.7 million deaths in 1990 to 2.4 million in 2019.^{1,2} Consequently, the proportion of deaths in children younger than 5 years occurring in the neonatal period has risen from 37% in 1990 to 46% in 2019.² As the number of deaths from infectious diseases has decreased, the proportion of deaths attributed to congenital anomalies (birth defects) has concurrently increased, accounting for an estimated 303 000 neonatal deaths and half a million deaths in children younger than 5 years annually.^{3–5} Congenital anomalies are now the fifth leading cause of mortality in children younger than 5 years and the 11th leading cause of years of life lost for the global population.^{6,7}

Congenital anomalies are defined by WHO as structural or functional anomalies that occur during intrauterine life.⁴ They affect 3–6% of global live births.⁴ Low-income and middle-income countries (LMICs) have the highest prevalence due to greater maternal exposure to micronutrient deficiencies, teratogens, and intrauterine infections, and lower termination rates resulting from limited antenatal diagnosis.^{4,8} LMICs are estimated to account for more than 95% of congenital anomaly deaths, two-thirds of which could be prevented through surgical care. However, these estimates are based on sparse data.⁵

Data on congenital anomaly outcomes and associated factors in LMICs are limited due to a lack of congenital anomaly registries, research, and inclusion of these conditions within national health surveys.^{9,10} Through international charitable organisations, data have been collected on some congenital anomalies, including cleft lip and palate, club foot, neural tube defects, and congenital heart disease.^{11–14} However, gastrointestinal congenital anomalies, which are also very prevalent, have received little attention. These anomalies, which are often fatal without access to emergency neonatal surgical care, could contribute to a large proportion of the preventable congenital anomaly deaths in LMICs.

Sustainable Development Goal 3.2 aims to “end preventable deaths of newborns and children under 5 years of age”.¹⁵ Therefore, preventable deaths from gastrointestinal congenital anomalies need to be identified and quantified globally, and insight must be gained into how to improve survival. The aim of this study was to prospectively compare the outcomes of the seven most common gastrointestinal congenital anomalies in low-income, middle-income, and high-income countries, and to identify factors associated with mortality.

Methods

Study design and participants

We did a global, multicentre, international, prospective cohort study of patients presenting to hospital for surgical care with seven gastrointestinal congenital anomalies (oesophageal atresia, congenital diaphragmatic hernia, intestinal atresia, gastroschisis, exomphalos [also known as omphalocele], anorectal malformation, and Hirschsprung's disease). STROBE guidelines were followed for this study.

Data were collected by patients' health-care providers, including a consultant or senior physician with overall clinical responsibility, who also oversaw patient recruitment, data completeness, and accuracy. We aimed to recruit as many participating hospitals as possible from across the world. Local investigators were invited to participate through international conference presentations, professional organisations, social media, and via a network of national and regional study leads. Participation was voluntary; no payment was made for data collection. Hospital teams chose one calendar month (commencing on the first day of the month) or multiple 1-month study periods (depending on local capacity), between October, 2018, and April, 2019, inclusive, to recruit consecutive patients to the study (by date of presentation).

Patients included any child younger than 16 years presenting acutely, for the first time, with one or more of the study conditions, and who received primary surgical intervention, conservative treatment, or palliative care. Patients were excluded if they had previously had surgery for their condition, were returning with a postoperative complication, were presenting electively, or were being transferred elsewhere for surgical intervention.

This study was classified as a clinical audit, with written confirmation from King's College London Ethics Committee that it, therefore, does not require ethical approval. All participating centres gained local study approval to participate according to their institutional ethical regulations. Consent forms were completed by all patients in hospitals requiring them. Data transfer agreements were legally signed between institutions where required.

Procedures

The study protocol, data collection forms, and all supporting documentation were produced in 12 languages.¹⁶ Anonymous, de-identified data were collected using the secure online platform REDCap.¹⁷ A pilot study to optimise data collection procedures was done in 16 hospitals (in 13 countries). Variables were chosen based on published core outcome sets and commonly collected outcomes in systematic reviews from high-income countries, as well as important variables identified in LMIC literature.¹⁸

Generic variables collected for all patients included: demographics, antenatal care (maternal ultrasound) and

diagnosis, delivery type (vaginal or caesarean section), transportation (ambulance, patient's own, or born at study hospital), referral site if applicable (district hospital, community clinic, home, or other), clinical condition on arrival (sepsis, hypovolaemia, or hypothermia), resuscitation on arrival (antibiotics, intravenous fluid, or warming), clinical condition at surgery (American Society of Anesthesiologists [ASA] score), intraoperative care (surgical safety checklist used, anaesthetist and surgeon grade or position, and anaesthetic administered), perioperative care (ventilation, intravenous access, parenteral nutrition, blood transfusion, and antibiotics), and outcomes (detailed later). Condition-specific variables included: condition type or classification, surgical intervention, and complications. Patients were followed up until 30 days after the primary intervention, or 30 days after admission in patients who did not receive an intervention. The presence and type of follow-up was collected for patients discharged before 30 days.

Clear definitions are provided for all variables in the published protocol.¹⁸ Internationally utilised and validated definitions were used where available. Cause of death was decided by the clinical team using 16 predetermined categories and one free-text category. From the free-text responses, one additional category was added (syndrome incompatible with life). Participating country name was collected, and World Bank 2018 country income status classification was used to categorise countries as low-income, middle-income, or high-income.¹⁹

Data validation was done in 10% of randomly selected participating hospitals with use of an independent validating local investigator, who retrospectively collected a selection of the data again for a 1-month study period. The validation data collected included the number of eligible patients, generic variables (month of presentation, study condition, sex, unplanned interventions, and survival to discharge), and condition-specific variables (condition type and surgical intervention). All local investigators at validation hospitals completed a data accuracy questionnaire to help identify potential errors and aid data interpretation.

Outcomes

The primary outcome was all-cause, in-hospital mortality for all conditions combined and each condition individually, stratified by country income (low-income, middle-income, or high-income). Patients were categorised as alive if they were either discharged alive or were still in hospital 30 days after primary intervention or 30 days after admission for patients who did not receive an intervention. Patients were categorised as dead if they died in hospital within 30 days of the primary intervention or 30 days after admission for patients who did not receive an intervention.

Secondary outcomes were the presence of one or more of surgical site infection, wound dehiscence, or a need

for unplanned reintervention, within 30 days of surgery, and 30-day post-primary intervention mortality. Length of hospital stay was recorded for all patients (including admission and discharge day, up to a 30-day maximum). Cause of death was an exploratory outcome.

The study aimed to test our hypothesis that there is a significant difference in mortality from the seven most common gastrointestinal congenital anomalies between low-income, middle-income, and high-income countries globally.

Statistical analysis

A sample size calculation was done using Bonferroni correction for multiple testing, assuming 80% power and an overall type 1 error of 5% (appendix p 13). To determine a significant difference in mortality between high-income countries and LMICs, the minimum sample size per country income group was estimated to be 21 for oesophageal atresia, 63 for congenital diaphragmatic hernia, 24 for intestinal atresia, 15 for gastroschisis, 115 for exomphalos, 85 for anorectal malformation, and 79 for Hirschsprung's disease (804 patients in total). A comparison of mortality between high-income countries, middle-income countries, and low-income countries was planned if a sufficient cohort was collected.

We did a complete case analysis. Duplicate entries were identified and excluded. Patients missing the study condition or primary outcome were excluded. If more than 20% of patients were missing the primary outcome in any given month at a participating hospital, all patients in that month were excluded. Data are presented as means with SDs if normally distributed and medians with IQRs if skewed; count data are presented as numbers and percentages. Data are summarised for all patients and by country income status. We calculated differences in patient demographics, care received, and primary and secondary outcomes, between country income strata using χ^2 analysis or Fisher's exact test if a group had less than five patients. $p < 0.05$ was deemed statistically significant. Mortality is presented by country income status for all patients and for each condition separately, with 95% CIs (calculated using the Wald CI for a proportion formula when $n > 5$ or exact binomial confidence intervals when $n \leq 5$).

Continuous variables were used as collected (ie, they were not categorised). Categorical variables were collapsed to include at least 15 patients per group if clinically and statistically appropriate (appendix pp 47–62). We combined hypovolaemia, hypothermia, or both on admission into one variable due to collinearity.

Three multilevel, multivariable models were used to identify factors associated with mortality in all study patients (including income status as a covariable), and in LMIC and high-income country settings separately. All models excluded duration of hospital stay due to missing data ($n=308$) and variable subgroups (time to primary intervention; and time to first and full enteral

feeding, and antibiotic duration, following primary intervention). The models containing all patients and those from LMICs included all other generic variables. Three additional variables from the high-income countries model were excluded due to low or no patients in a group: anaesthetic type, surgeon grade or position, and wound dehiscence (appendix pp 47–48). All variables included within the models had a maximum of 0.2% missing data (appendix pp 47–62). In the multivariable models, patients with missing data for one or more entries were excluded. Through the use of dummy variables that indicate when a data point is missing, we tested and concluded that the small amount of missing data did not affect the multivariable outcomes. There were no significant differences in the mortality between the patients included in the models and the small groups that were excluded due to missing data. Similarly, there were no significant differences in the proportion of patients from high-income, middle-income, and low-income countries in the patients included in the models and the small groups excluded due to missing data. Therefore, missing data imputation was not done.

All models were adjusted for hospital-level clustering and included potential confounders (gestational age at birth, bodyweight and age at presentation, presence of additional anomalies, and ASA score at primary intervention) and effect modifiers (receipt of ventilation, central intravenous access, and parenteral nutrition). Patients who had no surgical intervention, and therefore had no data on ASA score, anaesthetic, anaesthetist, surgeon, surgical safety checklist, or secondary outcome complications were included in the models (categorised as not applicable within each variable) to avoid bias, because these patients were either palliated or well enough to be managed without emergency intervention. We used penalised Lasso regression to determine the risk ratio (RR; 95% CI, p value) of mortality for each variable within the models. This method was chosen over the originally planned logistic regression with backwards stepwise elimination to enable more variables to be included in the models, with greater robustness. Our large cohort size made this technique feasible.

Exploratory penalised Lasso regression analyses were done for each condition separately, with income status as a covariable, adjustments for hospital-level clustering, and with the aforementioned confounders and effect modifiers included. Models included both generic and condition-specific variables. Variables excluded due to no or low counts are detailed in the appendix (pp 49–62). All multivariable results are presented as forest plots.

We compared the validation data with the original study data collected using a weighted κ statistic to determine level of agreement; observed agreement was also reported. We analysed the data using STATA 15.

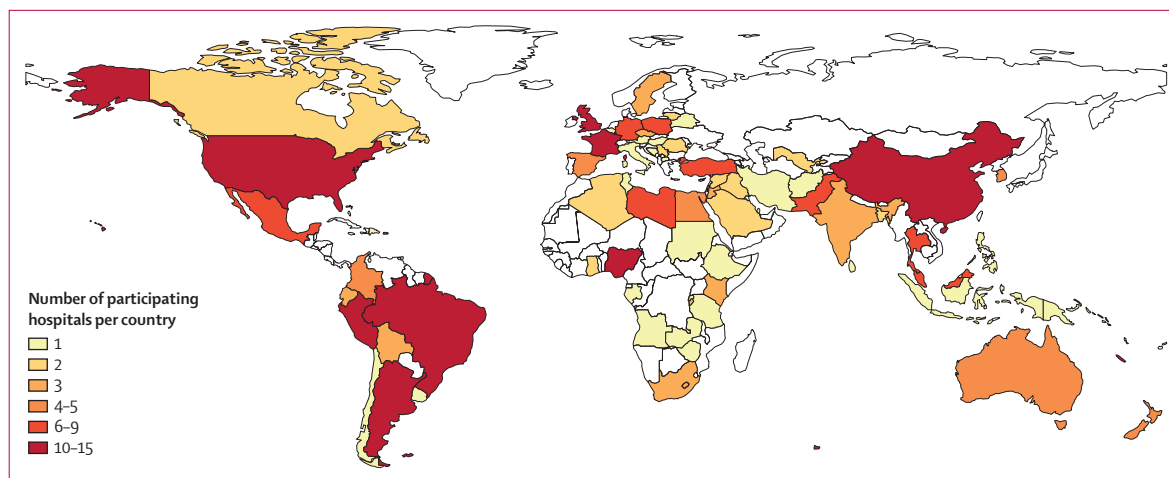


Figure 1: Global distribution of participating hospitals

The study protocol was registered with ClinicalTrials.gov, NCT03666767, and was published previously.¹⁸

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We included 3849 patients with 3975 study conditions from 264 hospitals in 74 countries (figures 1, 2) over 962 1-month study periods (median 3 months per hospital [IQR 2–5]). Of the 3849 patients, 2231 (58.0%) were male (table 1). Median gestational age at birth was 38 weeks (36–39) and median bodyweight at presentation was 2.8 kg (2.3–3.3); both characteristics were similar across income groups. Similar proportions of patients presented with oesophageal atresia, intestinal atresia, exomphalos, and Hirschsprung's disease across all income settings, but significantly fewer patients presented with congenital diaphragmatic hernia and gastroschisis in LMICs compared with high-income countries, and significantly more presented with anorectal malformation. Fewer patients in low-income countries ($n=24$, 25.8%) had an additional anomaly diagnosed compared with middle-income countries ($n=1306$, 45.7%) and high-income countries ($n=448$, 50.0%).

Median age at presentation was 72 h (IQR 16–192) in low-income countries, 24 h (3–96) in middle-income countries, and 3 h (0–28) in high-income countries. Neonates accounted for 90% ($n=3464$) of the study participants at presentation; the other 10% ranged from 29 days to 15.8 years of age. Patients travelled further from home to the study hospital in low-income countries (median distance of 55 km [10–133]) compared with middle-income countries (30 km [5–110]) and high-income countries (11 km [0–64]). Higher proportions of patients presented with sepsis, hypovolaemia, and hypothermia in low-income countries and middle-income countries

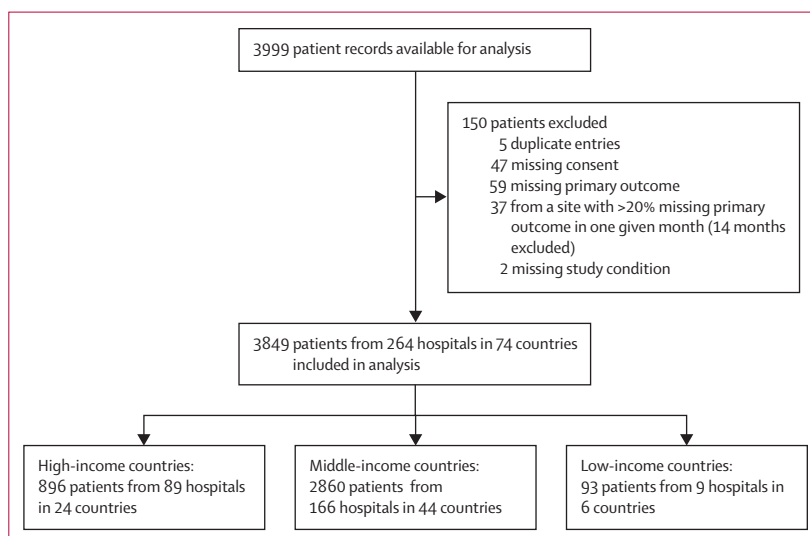


Figure 2: Flow diagram of patient inclusion in the study

compared with high-income countries. A higher proportion of patients did not receive a surgical intervention in low-income countries ($n=26$, 28.0%) compared with middle-income countries ($n=307$, 10.7%) and high-income countries ($n=62$, 6.9%); consequently, these patients did not have an ASA score. Among patients who received an intervention, an ASA score of 1 was most prevalent in low-income countries, an ASA score of 2 was most prevalent in middle-income countries, and an ASA score of 3 was most prevalent in high-income countries.

Nine (9.7%) of 93 patients had their condition diagnosed or a problem identified antenatally in low-income countries compared with 823 (28.8%) of 2860 in middle-income countries and 506 (56.5%) of 896 in high-income countries (table 2). In low-income countries, most patients ($n=75$, 80.7%) were born via vaginal delivery and few ($n=15$, 16.1%) via caesarean section.

	Total (n=3849)	High-income countries (n=896)	Middle-income countries (n=2860)	Low-income countries (n=93)	p value*
Sex					
Male	2231 (58.0%)	528 (58.9%)	1655 (57.9%)	48 (51.6%)	0.39
Female	1596 (41.5%)	367 (41.0%)	1185 (41.4%)	44 (47.3%)	..
Ambiguous genitalia	21 (0.5%)	1 (0.1%)	19 (0.7%)	1 (1.1%)	..
Unknown	1 (<0.1%)	0	1 (<0.1%)	0	..
Gestational age at birth, weeks	38 (36–39)	38 (36–39)	38 (36–39)	37 (36–39)	0.76
Bodyweight at presentation, kg	2.8 (2.3–3.3)	2.9 (2.4–3.4)	2.8 (2.3–3.3)	2.8 (2.2–3.5)	0.13
Study condition					
Oesophageal atresia	560 (14.5%)	141 (15.7%)	412 (14.4%)	7 (7.5%)	0.093
Congenital diaphragmatic hernia	448 (11.6%)	148 (16.5%)	299 (10.5%)	1 (1.1%)	<0.0001
Intestinal atresia	681 (17.7%)	152 (17.0%)	509 (17.8%)	20 (21.5%)	0.53
Gastroschisis	453 (11.8%)	139 (15.5%)	304 (10.6%)	10 (10.8%)	0.0004
Exomphalos	325 (8.4%)	70 (7.8%)	241 (8.4%)	14 (15.1%)	0.057
Anorectal malformation	991 (25.7%)	178 (19.9%)	788 (27.6%)	25 (26.9%)	0.0003
Hirschsprung's disease	517 (13.4%)	107 (11.9%)	393 (13.7%)	17 (18.3%)	0.15
Additional anomaly or study condition diagnosed	1778 (46.2%)	448 (50.0%)	1306 (45.7%)	24 (25.8%)	<0.0001
Age at presentation, h	22 (1–85)	3 (0–28)	24 (3–96)	72 (16–192)	0.0001
Distance from patient's home to study hospital, km	25 (2–100)	11 (0–64)	30 (5–110)	55 (10–133)	<0.0001
Sepsis status on arrival to study centre					
Yes	660 (17.1%)	38 (4.2%)	598 (20.9%)	24 (25.8%)	<0.0001
Missing	3 (0.1%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	..
Hypovolaemia status on arrival to study centre					
Yes	564 (14.7%)	75 (8.4%)	478 (16.7%)	11 (11.8%)	<0.0001
Missing	4 (0.1%)	1 (0.1%)	2 (0.1%)	1 (1.1%)	..
Hypothermia status on arrival to study centre					
Yes	403 (10.5%)	32 (3.6%)	358 (12.5%)	13 (14.0%)	<0.0001
Missing	6 (0.2%)	1 (0.1%)	4 (0.1%)	1 (1.1%)	..
ASA score at time of primary intervention					
1 (healthy person)	678 (17.6%)	115 (12.8%)	534 (18.7%)	29 (31.2%)	<0.0001
2 (mild systemic disease)	1195 (31.0%)	260 (29.0%)	914 (32.0%)	21 (22.6%)	..
3 (severe systemic disease)	1046 (27.2%)	316 (35.3%)	717 (25.1%)	13 (14.0%)	..
4 (severe systemic disease that is a constant threat to life)	375 (9.7%)	122 (13.6%)	249 (8.7%)	4 (4.3%)	..
5 (moribund patient who is not expected to survive without the operation)	151 (3.9%)	15 (1.7%)	136 (4.8%)	0	..
Not applicable (no surgical intervention)†	395 (10.3%)	62 (6.9%)	307 (10.7%)	26 (28.0%)	..
Missing	9 (0.2%)	6 (0.7%)	3 (0.1%)	0	..

Data are n (%) or median (IQR). ASA=American Society of Anesthesiologists. *p values represent univariable testing between country income strata. †These patients were either palliated, managed conservatively, or discharged without intervention with planned future intervention (appendix pp 16–44).

Table 1: Patient characteristics

By contrast, 1421 (49.7%) patients in middle-income countries and 411 (45.8%) in high-income countries were born via caesarean section. Only two (2.2%) patients from low-income countries were born at the paediatric surgery centre, compared with 618 (21.6%) in middle-income countries and 391 (43.6%) in high-income countries. In all settings, the majority of outborn patients (born outside the paediatric surgery centre) presented from district hospitals. In low-income countries, 41 (45.1%) patients travelled to the study centre using non-hospital transport, compared with 1041 (46.4%) in middle-income countries and 74 (14.7%) in high-income countries.

Some septic and hypovolaemic patients did not receive intravenous antibiotics (nine [37.5%] of 24 in low-income countries; 144 [24.1%] of 598 in middle-income countries; seven [18.4%] of 38 in high-income countries) or intravenous fluids (five [45.5%] of 11 in low-income countries; 84 [17.6%] of 478 in middle-income countries; 34 [45.3%] of 75 in high-income countries) within 1 h of presentation, and some hypothermic patients were not warmed (28 [7.8%] in middle-income countries; four [12.5%] in high-income countries). Only 55 (59.1%) of 93 patients in low-income countries received a general anaesthetic (of which 32 [34.4%] did not receive a general anaesthetic because they did not have surgery), compared with 2327 (81.3%) of 2860 in middle-income countries and 772 (86.2%) of 896 in high-income countries. Anaesthesia was more frequently provided by a nurse in low-income countries (n=17, 18.3%) than in middle-income countries (n=17, 0.6%) and high-income countries (n=1, 0.1%), and surgery was more frequently performed by a general surgeon or unsupervised trainee (low-income countries, n=13 [14.0%]; middle-income countries, n=54 [1.9%]; high-income countries, n=14 [1.6%]). A surgical safety checklist was used less frequently in low-income countries (n=31, 33.3%) than in middle-income countries (n=1791, 62.6%) and high-income countries (n=747, 83.4%).

In low-income countries, only eight (8.6%) patients received ventilation, three (3.2%) received parenteral nutrition, and six (6.5%) had central intravenous access, compared with much higher proportions in middle-income countries (1363 [47.7%] received ventilation, 1416 [49.5%] received parenteral nutrition, and 1263 [44.2%] had central venous access) and high-income countries (637 [71.1%], 683 [76.2%], and 670 [74.8%]).

Condition-specific patient characteristics, antenatal care, perioperative care, surgical intervention, and outcomes are detailed in the appendix (pp 16–44). In high-income countries, where 849 (94.8%) of 896 women received an antenatal ultrasound, antenatal detection rates (problem identified with or without diagnosis of condition) were: 134 (96.4%) of 139 for gastroschisis, 65 (92.9%) of 70 for exomphalos, 108 (71.1%) of 152 for intestinal atresia, 96 (64.9%) of 148 for congenital

	Total (n=3849)	High-income countries (n=896)	Middle-income countries (n=2860)	Low-income countries (n=93)	p value*
Antenatal care, delivery, transportation to the paediatric surgery centre, and referral site					
Antenatal ultrasound					
Yes, study condition diagnosed	881 (22.9%)	368 (41.1%)	512 (17.9%)	1 (1.1%)	<0.0001
Yes, problem identified but study condition not diagnosed	457 (11.9%)	138 (15.4%)	311 (10.9%)	8 (8.6%)	..
Yes, no problem identified	1945 (50.5%)	343 (38.3%)	1551 (54.2%)	51 (54.8%)	..
No	558 (14.5%)	44 (4.9%)	482 (16.9%)	32 (34.4%)	..
Missing	8 (0.2%)	3 (0.3%)	4 (0.1%)	1 (1.1%)	..
Gestational age of study condition diagnosis if antenatal, weeks	25 (20–31)	21 (16–27)	28 (21–32)	..	0.0002
Type of delivery					
Vaginal (spontaneous)	1767 (45.9%)	373 (41.6%)	1324 (46.3%)	70 (75.3%)	<0.0001
Vaginal (induced)	194 (5.0%)	97 (10.8%)	92 (3.2%)	5 (5.4%)	..
Caesarean section (elective)	1022 (26.6%)	185 (20.6%)	830 (29.0%)	7 (7.5%)	..
Caesarean section (urgent or non-elective)	825 (21.4%)	226 (25.2%)	591 (20.7%)	8 (8.6%)	..
Unknown	37 (1.0%)	14 (1.6%)	21 (0.7%)	2 (2.2%)	..
Missing	4 (0.1%)	1 (0.1%)	2 (0.1%)	1 (1.1%)	..
Born at the study hospital					
Yes	1011 (26.3%)	391 (43.6%)	618 (21.6%)	2 (2.2%)	<0.0001
Missing	5 (0.1%)	1 (0.1%)	4 (0.1%)	0 (0.0%)	..
Mode of transport to hospital if born elsewhere					
Ambulance or other transport provided by the health service	1677 (59.1%)	430 (85.1%)	1197 (53.4%)	50 (54.9%)	<0.0001
Patient's own transport	1156 (40.7%)	74 (14.7%)	1041 (46.4%)	41 (45.1%)	..
Missing	5 (0.2%)	1 (0.2%)	4 (0.2%)	0	..
Location from which patient presented if born elsewhere					
District hospital	1835 (64.7%)	401 (79.4%)	1377 (61.4%)	57 (62.6%)	<0.0001
Home	504 (17.8%)	51 (10.1%)	445 (19.8%)	8 (8.8%)	..
Community clinic or general practice	446 (15.7%)	44 (8.7%)	379 (16.9%)	23 (25.3%)	..
From another country	7 (0.2%)	3 (0.6%)	4 (0.2%)	0	..
From a different specialty within the hospital	5 (0.2%)	4 (0.8%)	0	1 (1.1%)	..
Unknown	33 (1.2%)	1 (0.2%)	30 (1.3%)	2 (2.2%)	..
Missing	8 (0.3%)	1 (0.2%)	7 (0.3%)	0	..
Care at the paediatric surgery centre					
Resuscitation on arrival					
Administration of appropriate antibiotics if septic					
n	660	38	598	24	..
Yes, within 1 h of arrival	500 (75.8%)	31 (81.6%)	454 (75.9%)	15 (62.5%)	0.42
Yes, within the first day of arrival	150 (22.7%)	7 (18.4%)	135 (22.6%)	8 (33.3%)	..
No	10 (1.5%)	0	9 (1.5%)	1 (4.2%)	..
Administration of intravenous fluid if hypovolaemic					
n	564	75	478	11	..
Yes, within 1 h of arrival	440 (78.0%)	40 (53.3%)	394 (82.4%)	6 (54.5%)	<0.0001
Yes, within the first day of arrival	104 (18.4%)	24 (32.0%)	76 (15.9%)	4 (36.4%)	..
No	19 (3.4%)	10 (13.3%)	8 (1.7%)	1 (9.1%)	..
Missing	1 (0.2%)	1 (1.3%)	0	0	..
Quantity of intravenous fluid given if hypovolaemic					
n	564	75	478	11	..
10–20 mL/kg	408 (72.3%)	36 (48.0%)	363 (75.9%)	9 (81.8%)	<0.0001
>20 mL/kg	135 (23.9%)	28 (37.3%)	106 (22.2%)	1 (9.1%)	..
Missing	21 (3.7%)	11 (14.7%)	9 (1.9%)	1 (9.1%)	..

(Table 2 continues on next page)

	Total (n=3849)	High-income countries (n=896)	Middle-income countries (n=2860)	Low-income countries (n=93)	p value*
(Continued from previous page)					
Warming of patient to within normal range on arrival if hypothermic					
n	403	32	358	13	..
Yes	371 (92.1%)	28 (87.5%)	330 (92.2%)	13 (100.0%)	0.35
Primary intervention					
Time from arrival at study hospital to primary intervention, h	24 (7-66)	22 (5-48)	24 (8-72)	34 (10-96)	0.0001
Type of anaesthesia used for primary intervention					
General anaesthesia with endotracheal tube or laryngeal airway	3154 (81.9%)	772 (86.2%)	2327 (81.3%)	55 (59.1%)	<0.0001
Intervention without anaesthesia and with or without analgesia	248 (6.4%)	67 (7.5%)	178 (6.2%)	3 (3.2%)	..
Local anaesthesia only	25 (0.6%)	1 (0.1%)	24 (0.8%)	0	..
Spinal or caudal anaesthesia	19 (0.5%)	0	19 (0.7%)	0	..
Ketamine anaesthesia	9 (0.2%)	1 (0.1%)	5 (0.2%)	3 (3.2%)	..
Not applicable (no surgery or primary intervention)	392 (10.2%)	55 (6.1%)	305 (10.7%)	32 (34.4%)	..
Missing	2 (0.1%)	0	2 (0.1%)	0	..
Person delivering anaesthetic for primary intervention					
Anaesthetic doctor	3115 (80.9%)	741 (82.7%)	2336 (81.7%)	38 (40.9%)	<0.0001
Medical officer, surgeon, or other health-care professional	86 (2.3%)	42 (4.7%)	41 (1.5%)	3 (3.2%)	..
Anaesthetic nurse	35 (0.9%)	1 (0.1%)	17 (0.6%)	17 (18.3%)	..
No anaesthetic	610 (15.8%)	112 (12.5%)	463 (16.2%)	35 (37.6%)	..
Missing	3 (0.1%)	0	3 (0.1%)	0	..
Person delivering primary intervention					
Paediatric surgeon (or junior with paediatric surgeon assisting or in the room)	3345 (86.9%)	825 (92.1%)	2474 (86.5%)	46 (49.5%)	<0.0001
Junior doctor or other (without a paediatric or general surgeon assisting or in the room)	59 (1.5%)	7 (0.8%)	49 (1.7%)	3 (3.2%)	..
Trainee surgeon (without a paediatric or general surgeon assisting or in the room)	49 (1.3%)	7 (0.8%)	36 (1.3%)	6 (6.5%)	..
General surgeon (or junior with general surgeon assisting or in the room)	32 (0.8%)	7 (0.8%)	18 (0.6%)	7 (7.5%)	..
Not applicable (no surgery or primary intervention)	361 (9.4%)	49 (5.5%)	281 (9.8%)	31 (33.3%)	..
Missing	3 (0.1%)	1 (0.1%)	2 (0.1%)	0	..
Surgical safety checklist used at the time of primary intervention					
Yes	2569 (66.7%)	747 (83.4%)	1791 (62.6%)	31 (33.3%)	<0.0001
No	693 (18.0%)	39 (4.4%)	626 (21.9%)	28 (30.1%)	..
Not applicable (no surgical intervention)	584 (15.1%)	109 (12.1%)	441 (15.4%)	34 (36.5%)	..
Missing	3 (0.1%)	1 (0.1%)	2 (0.1%)	0	..
Perioperative care					
Patient received central venous access					
Yes, peripherally inserted central catheter	1120 (29.1%)	436 (48.7%)	678 (23.7%)	6 (6.5%)	<0.0001
Yes, percutaneously inserted central line	415 (10.8%)	187 (20.9%)	228 (8.0%)	0	<0.0001
Yes, umbilical catheter	402 (10.4%)	153 (17.1%)	249 (8.7%)	0	<0.0001
Yes, surgically placed central line (open insertion)	254 (6.6%)	27 (3.0%)	227 (7.9%)	0	<0.0001
No	1910 (49.6%)	226 (25.2%)	1597 (55.8%)	87 (93.5%)	<0.0001
Total duration of antibiotics after primary intervention, days	7 (3-11)	3 (1-7)	7 (3-13)	3 (0-7)	0.0001
Blood transfusion					
Not required	2448 (63.6%)	671 (74.9%)	1708 (59.7%)	69 (74.2%)	<0.0001
Yes	1348 (35.0%)	213 (23.8%)	1114 (38.9%)	21 (22.6%)	..
Required but not available	47 (1.2%)	9 (1.0%)	35 (1.2%)	3 (3.2%)	..
Missing	6 (0.1%)	3 (0.3%)	3 (0.1%)	0	..

(Table 2 continues on next page)

	Total (n=3849)	High-income countries (n=896)	Middle-income countries (n=2860)	Low-income countries (n=93)	p value*
(Continued from previous page)					
Ventilation					
No	1755 (45.6%)	258 (28.8%)	1422 (49.7%)	75 (80.6%)	<0.0001
Yes	2008 (52.2%)	637 (71.1%)	1363 (47.7%)	8 (8.6%)	..
Required but not available	85 (2.2%)	1 (0.1%)	74 (2.6%)	10 (10.8%)	..
Missing	1 (<0.1%)	0	1 (<0.1%)	0	..
Duration of ventilation if given, days	4 (2–8)	4 (2–9)	4 (2–8)	2 (1–3)	0.0025
Time to first enteral feed post-primary intervention, days	4 (2–8)	4 (2–8)	4 (2–8)	1 (1–3)	<0.0001
Time to full enteral feeds post-primary intervention, days	8 (4–16)	11 (6–22)	7 (3–15)	3 (2–7)	<0.0001
Parenteral nutrition					
No	1476 (38.3%)	212 (23.7%)	1196 (41.8%)	68 (73.1%)	<0.0001
Yes	2102 (54.6%)	683 (76.2%)	1416 (49.5%)	3 (3.2%)	..
Yes, but less was available than required	143 (3.7%)	0	143 (5.0%)	0	..
Required but not available	125 (3.2%)	0	103 (3.6%)	22 (23.7%)	..
Missing	3 (0.1%)	1 (0.1%)	2 (0.1%)	0	..
Duration of parenteral nutrition if received, days	11 (6–20)	14 (8–24)	10 (5–18)	30 (10–30)	0.0001

Data are n (%), median (IQR), or n. *p values represent univariable testing between country income strata.

Table 2: Care received by patients

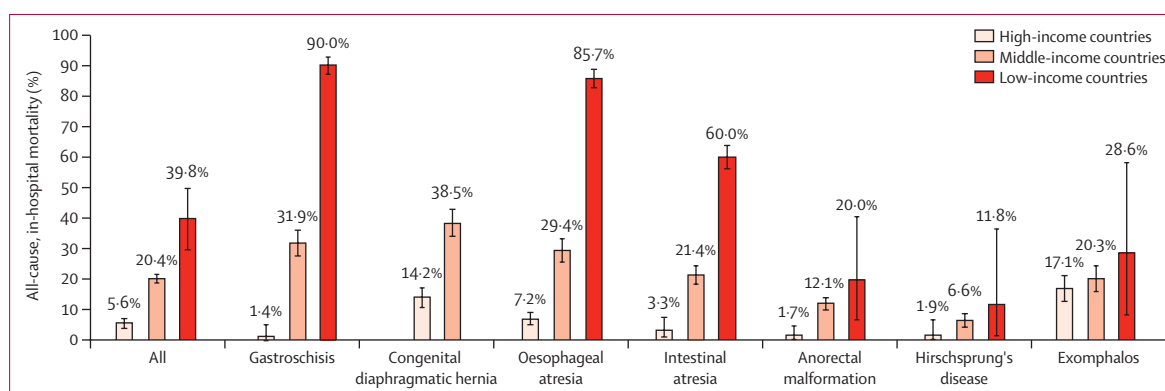


Figure 3: All-cause, in-hospital mortality

Data are shown as percentages (95% CIs). Numbers of patients are shown in the appendix (p 46). Only one patient with congenital diaphragmatic hernia presented in a low-income country during the study period.

diaphragmatic hernia, 72 (51.1%) of 141 for oesophageal atresia, 49 (27.5%) of 178 for anorectal malformation, and 12 (11.2%) of 107 for Hirschsprung's disease.

The proportions of patients followed up to 30 days post primary intervention to assess survival status and presence of complications are described in the appendix (p 45). Of 3849 study patients, 418 (10.9%) were still in hospital at 30 days post intervention. Of the 2761 (71.7%) patients discharged home before 30 days, 2495 (90.4%) were followed up to 30 days.

Overall all-cause, in-hospital mortality was 37 (39.8%) of 93 in low-income countries, 583 (20.4%) of 2860 in middle-income countries, and 50 (5.6%) of 896 in high-income countries, ($p < 0.0001$ between all country income groups; figure 3, appendix p 46). For each condition considered individually, gastroschisis, oesophageal

atresia, and intestinal atresia also showed a significant difference between all income groups; congenital diaphragmatic hernia showed a significant difference between high-income countries and middle-income countries (there were too few patients from low-income countries to make a comparison); anorectal malformation had a significant difference between high-income countries and low-income countries, and high-income countries and middle-income countries, but not between middle-income countries and low-income countries; Hirschsprung's disease and exomphalos showed no significant difference between country income groups (appendix p 46). Gastroschisis had the greatest difference in mortality (nine [90.0%] of ten in low-income countries, 97 [31.9%] of 304 in middle-income countries, two [1.4%] of 139 in high-income countries; $p \leq 0.0001$ between

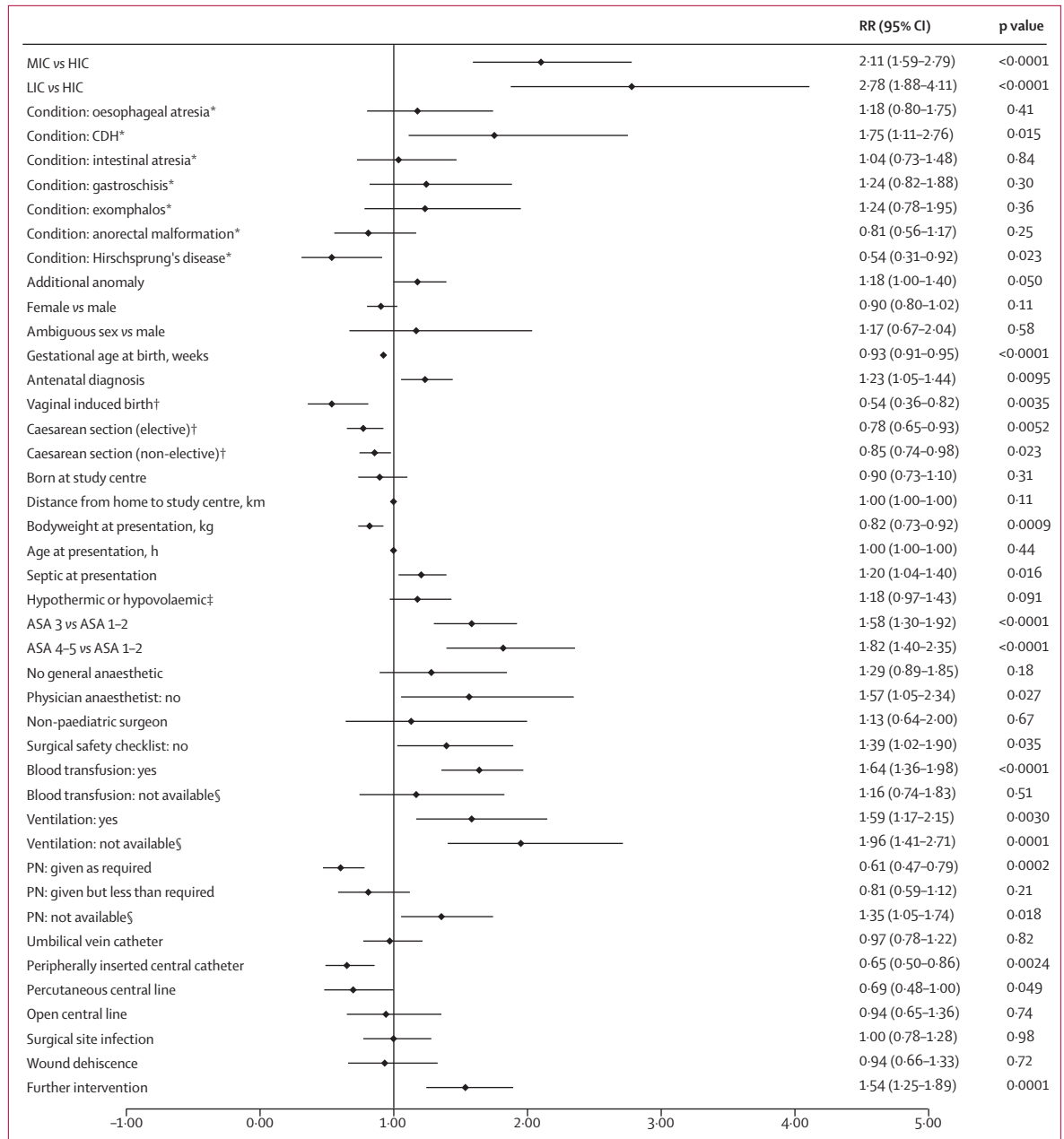


Figure 4: Multivariable analysis of factors affecting mortality (all patients and income settings)

Of 3849 study patients, 3735 were included within this multivariable model (n=114 excluded due to missing data). Additional anomaly includes additional study condition(s) if present. Further intervention refers to the need for unplanned re-intervention within 30 days of surgery. ASA=American Society of Anesthesiologists score at primary intervention. CDH=congenital diaphragmatic hernia. HIC=high-income country. LIC=low-income country. MIC=middle-income country. PN=parenteral nutrition. RR=risk ratio. *Versus not having the specified condition. †Versus spontaneous vaginal delivery. ‡At presentation. §When required.

all country income groups), followed by congenital diaphragmatic hernia, oesophageal atresia, and intestinal atresia (figure 3, appendix p 46). Neonates accounted for 658 (98.2%) of 670 deaths. Of note, all of the patients who did not receive an intervention had either been discharged alive or died within 30 days of admission.

On multivariable analysis of all study patients, country income status was associated with the highest

risk of mortality (low-income vs high-income country, RR 2.78 [95% CI 1.88–4.11]; middle-income vs high-income country, 2.11 [1.59–2.79]; figure 4). Congenital diaphragmatic hernia had the highest risk of mortality and Hirschsprung's disease had the lowest.

Antenatal diagnosis and presence of an additional anomaly were associated with higher mortality; higher gestational age and bodyweight, and delivery via induced

vaginal birth or caesarean section were associated with lower mortality. For outborn patients, sepsis at presentation was associated with a higher mortality. At the time of primary intervention, mortality was higher for patients with a higher ASA score, with no physician anaesthetist present, and with a surgical safety checklist not used. In the perioperative period, not having ventilation or parenteral nutrition when required, needing or receiving ventilation or a blood transfusion, and undergoing a further unplanned intervention were associated with higher mortality. Receiving parenteral nutrition, a peripherally inserted central catheter, or a percutaneous central line were associated with lower mortality.

The multivariable analysis results of patients in LMICs were similar to those for all patients, except that gastroschisis was also significantly associated with higher mortality alongside congenital diaphragmatic hernia, and Hirschsprung's disease was no longer significantly lower (appendix p 63). In the high-income country multivariable model, no individual condition had a significantly higher or lower risk of mortality compared with the study patients without that condition (appendix p 64). Delivery type, sepsis at presentation, ASA score, use of a surgical safety checklist, ventilation, parenteral nutrition, and central intravenous access were not significantly associated with mortality. By contrast, hypothermia and hypovolaemia at presentation were associated with higher mortality.

On exploratory analysis of mortality by study condition, exomphalos was the only condition for which delivery method affected mortality risk (elective caesarean section vs spontaneous vaginal delivery, RR 0.25 [95% CI 0.12–0.54]; appendix pp 65–71). For congenital diaphragmatic hernia (0.63 [0.43–0.93]) and gastroschisis (0.58 [0.35–0.95]), birth at the study centre was associated with lower mortality compared with outborn patients.

30-day post-intervention mortality was similar to all-cause in-hospital mortality, with the exception that an additional 11 patients died after discharge before 30 days in middle-income countries (appendix p 72). In patients who had surgery, surgical site infection rates did not differ across income settings, whereas wound dehiscence and further unplanned intervention differed statistically, although not substantially. Median hospital stay among survivors was lowest in low-income countries (9 days [IQR 5–18]), followed by middle-income countries (14 days [8–23]) and high-income countries (20 days [12–30]). Time to death among non-survivors was similar across settings (low-income countries, 6 days [3–12]; middle-income countries, 6 days [2–13]; high-income countries, 9 days [3–15]).

Overall, the leading causes of death were sepsis ($n=235$, 35.1%) and respiratory failure ($n=189$, 28.2%; appendix p 73). Proportionally, sepsis caused more deaths in LMICs than in high-income countries.

Median observed agreement between the study and validation data was 100% (IQR 88–100; κ statistic 0.96 [IQR 0.57–1.00]; appendix pp 74–75). Variables deemed

potentially inaccurate were gestational age at birth, distance from home to study centre, and time from birth to presentation (appendix pp 76–79). Validators identified eight patients missed from study inclusion (appendix p 80).

Discussion

This international, prospective, cohort study has provided information on outcomes for almost 4000 patients with gastrointestinal congenital anomalies in 74 countries across the world. The study highlights substantial differences in mortality between low-income, middle-income, and high-income countries. The chance of dying from a gastrointestinal congenital anomaly if born in a low-income country is two in five, compared with one in five in a middle-income country and one in 20 in a high-income country. Neonates born with gastroschisis have the greatest mortality difference, with mortality of 90% in low-income countries and 32% in middle-income countries, compared with 1% in high-income countries. Thus, conditions associated with a normal lifespan for most individuals in high-income countries are frequently fatal within days of life for neonates born with the same conditions in LMICs. Tackling these inequities has the potential to reduce global neonatal mortality and is essential if preventable deaths in neonates are to be ended by 2030.¹⁵

Gastrointestinal congenital anomalies require surgical care, and our findings are consistent with previous studies that have shown far better surgical outcomes in high-income countries than in low-income or middle-income countries.^{20–22} However, the notably high surgical mortality rates amongst neonates in our study far exceed those reported in LMICs for older children and adults requiring surgery (between 1% and 4%, depending on the study).^{20–22} The inequities that we have found highlight neonatal surgical care as a global health priority. Our findings fit with knowledge that surgery has been neglected in the global health field; indeed, a focus in LMICs on paediatric surgery, particularly neonatal surgery, has been almost non-existent.⁸

To our knowledge, this is the first comprehensive global outcomes study of gastrointestinal congenital anomalies. It confirms previous findings from smaller, mostly single-centre, retrospective studies. A systematic review of neonatal surgery in sub-Saharan Africa reported greater than 50% mortality for emergency gastrointestinal surgery compared with 3% mortality for spina bifida and cleft lip and palate surgery.⁹ A hospital in northern Ghana reported that 96% of neonatal surgical deaths were from congenital anomalies and two-thirds of such deaths involved gastrointestinal anomalies.²³

Our results highlight that many patients in LMICs do not receive components of neonatal surgical care that are considered essential in high-income settings. These include antenatal diagnosis, birth at a paediatric surgery centre, effective resuscitation, timely ambulance transfer

for patients born in or referred to district hospitals, use of a surgical safety checklist, a physician anaesthetist at primary intervention, and basic neonatal intensive care unit resources such as ventilation, central intravenous access, and parenteral nutrition. Our large study cohort, across all income settings, enabled us to calculate the risk of mortality associated with receipt of, or lack of access to, these resources.

Our finding that antenatal diagnosis is associated with higher mortality is potentially misleading, simply reflecting easier antenatal detection of more severe cases.²⁴ Indeed, on exploratory multivariable analyses, lower mortality was associated with birth at the study hospital for gastroschisis and congenital diaphragmatic hernia, and caesarean section for exomphalos, both enabled by antenatal diagnosis. Antenatal diagnosis enables delivery at a paediatric surgery centre, avoiding clinical deterioration before arrival and presentation in a poor clinical condition. Multiple indicators of poor clinical condition were significantly associated with higher mortality on multivariable analysis in LMICs: sepsis at presentation, higher ASA score at primary intervention, and a need for blood transfusion and ventilation. Although proportionally more patients who had an operation had better ASA scores in low-income countries and middle-income countries compared with high-income countries, this finding could reflect that the most sick patients in LMICs do not receive surgical intervention (and therefore an ASA score) and are palliated; competing priorities for limited resources and cost of surgery, which often requires out-of-pocket expenses for families in LMICs, might contribute to such decision making.^{25,26} Our study highlights that fewer women underwent antenatal ultrasound scanning in LMICs, and even when they did, the anomalies were less frequently detected than in high-income countries, highlighting the need for both increased access to and improved quality of antenatal ultrasound. A randomised controlled trial in five LMICs showed that increased antenatal ultrasound scanning is possible (95% of women in the intervention group vs 43% in the control group) and that 9.3% of scanned women were referred for an ultrasound-diagnosed condition (maternal and fetal).²⁷ However, the study authors found that increased antenatal diagnosis rates alone do not translate into increased hospital delivery or neonatal survival, emphasising the need for a systems approach targeting barriers to delivery at a paediatric surgery centre.²⁸

Our study highlights that most patients with gastrointestinal congenital anomalies in LMICs are not born at the paediatric surgery centre; most are referred from district hospitals. Even in high-income countries, where 95% of the women received an antenatal ultrasound, not all anomalies were detected. Therefore, upskilling staff at district hospitals to deal with births at, or referrals to, these facilities is vital to prevent clinical deterioration before surgical intervention. Such an

initiative in India showed successful knowledge and skills transfer by multidisciplinary paediatric surgical teams to district hospitals.²⁹ Unfortunately, the 2017 WHO recommendations on newborn health include a section on management of “other severe conditions”, but do not mention congenital anomalies.³⁰ Therefore, upgrading this document will be an important step for knowledge dissemination. Similarly, management of neonates with congenital anomalies should be incorporated within national WHO Every Newborn Action Plans, with a particular focus on the prevention of sepsis, hypothermia and hypovolaemia.³¹ Our study also showed that patients in LMICs travel further to hospitals and present later, frequently without hospital transport. Although they were not independently significantly associated with mortality, these factors probably also affect the clinical condition of patients on arrival, highlighting the need for improved access to timely and effective inter-hospital transportation.

At paediatric surgery centres, we identified a number of factors that were independently associated with mortality in the preoperative, intraoperative, and perioperative periods. Poorer clinical condition was associated with higher mortality, which could potentially be addressed through improved resuscitation on arrival. Our results show that not all septic and hypovolaemic patients received intravenous antibiotics and fluids within an hour of arrival, and some hypothermic patients were not warmed. The absence of a physician anaesthetist at the primary intervention and not using a surgical safety checklist were associated with a higher mortality. To address the absence of physician anaesthetists, the charity KidsOR has recently pledged funds to train paediatric anaesthetists alongside paediatric surgeons across Africa. Efforts are required to broaden the use of surgical safety checklists in LMICs; the use of implementation science techniques may help to improve this.³² In the perioperative period, non-availability of ventilation and parenteral nutrition when required was significantly associated with high mortality in LMICs, whereas receipt of parenteral nutrition and peripheral or percutaneous central intravenous access were associated with lower mortality.

Basic neonatal intensive care facilities have been omitted from previous global neonatal care recommendations because they are deemed expensive.¹ However, these resources are essential, not only for surgical neonates, but also for many low-birthweight and sick neonates due to other causes, and they should be included in long-term strategies for LMICs. Such interventions lend themselves to innovative solutions, as seen with the rapid development of low-technology, cost-effective ventilation methods during the COVID-19 pandemic.³³ The need for intensive care resources can also be reduced through context-optimised surgical techniques, such as cotside bowel reduction and sutureless closure of gastroschisis using a preformed silo, which reduces the need for ventilation.³⁴ These techniques are currently being trialled in a

For more on KidsOR see
<https://www.kidsor.org>

multicentre, multinational interventional study in sub-Saharan Africa, alongside locally sourced, affordable, peripherally administered, partial parenteral nutrition, which could benefit neonatal outcomes more broadly.³⁵

This study has several limitations. For feasibility, the study focused on a selection of common, high-mortality, gastrointestinal congenital anomalies rather than the full complement of anomalies. Despite the study being intentionally designed to minimise reporting burden for high-volume, low-resource centres, the proportion of patients included from low-income countries (2%) was lower than in the global population (9%).³⁶ However, the proportion of study patients from middle-income countries (74%) reflects the global middle-income country population (75%).³⁶ Although the number of patients included from low-income countries was relatively low, the mortality rates that we found reflect what has previously been reported in the scarce data available from these regions. For example, two of the largest single-centre observational studies on gastroschisis in low-income countries reported a mortality of 90% (136 of 151) in Uganda and 84% (80 of 95) in Zimbabwe.^{37,38} The Gastroschisis Interventional Study across seven tertiary paediatric surgery centres in Ghana, Zambia, Malawi, and Tanzania (low-income countries and lower-middle income countries) reported an overall baseline mortality of 95%.³⁵ Mortality rates for the other study conditions are also similar to those reported from Uganda.³⁸

Despite the higher mortality rates in LMICs compared with high-income countries, the reported mortality could be an underestimation for several reasons. Data collection was done at paediatric surgery centres; some patients might have died without reaching such care in LMICs.³⁹ This is evidenced by the missing patients with congenital diaphragmatic hernia, particularly within the low-income country cohort, and the under-representation of gastroschisis within the LMIC cohorts; such under-reporting also occurred in high-income countries in the 1970s.⁴⁰ Cases with more advanced disease severity (eg, severe congenital diaphragmatic hernia) or multiple anomalies (eg, coexisting cardiac anomaly) might be more likely to die before presentation in LMICs (or not get referred). This situation would account in part for the higher proportion of patients with an ASA score of 1 in low-income countries and of 2 in middle-income countries compared with high-income countries, and also the lower proportion of patients with associated anomalies in low-income countries. However, the lower proportion of associated anomalies might also result from underdiagnosis due to lower diagnostic expertise and resources in low-income countries. If more than 20% of patients were missing the primary outcome in any given month at a participating hospital, all patients in that month were excluded. Although we used this strategy to optimise the accuracy of mortality estimates, it could have inadvertently introduced bias if poorer data collection is associated with poorer outcomes. However,

no participating hospitals were excluded as a result, and only 14 months of data (37 patients) were excluded compared with 962 months of data (3849 patients) included in the study. Therefore, the effect is likely to be small. 30-day post-intervention follow-up was missing in 37.5% of patients in low-income countries, 9.0% of patients in middle-income countries, and 7.5% of patients in high-income countries; therefore, some post-discharge deaths and complications were potentially missed.

There are some additional factors to consider when interpreting the study data. Although we identified multiple factors associated with mortality through robust multivariable analyses, our findings regarding the causes of death are less robust. Cause of death was determined via clinical diagnosis of the treating physician, which is commonly multifactorial and difficult to confirm with certainty. However, our findings are consistent with the *Lancet* Newborn Series, which also reported sepsis to be the leading global cause of death in neonates more broadly.¹ ASA scoring could have inter-rater variability in different regions of the world. Our multivariable model of patients with exomphalos included both minor and major variants; elective caesarean section is commonly confined to major variants. In low-income countries, most cases of Hirschsprung's disease were diagnosed clinically without biopsy confirmation; a lack of diagnostic facilities could result in missed patients and also inclusion of patients without the condition. Centralisation of care within and between paediatric surgery centres and multidisciplinary team care has played a key role in optimising outcomes in high-income countries, but it has not been captured within this study. In high-income countries and some middle-income countries where antenatal detection is higher, some fetuses with more severe or multiple anomalies might have been terminated, contributing to the lower mortality. However, this situation is not reflected in the data because high-income countries had the highest proportion of patients with additional anomalies, followed by middle-income countries. For feasibility and to focus on neonatal mortality, the follow-up period was limited to 30 days; longer-term follow-up is required to determine disability and quality of life.

This study provides evidence that Sustainable Development Goal 3.2 to end preventable deaths in neonates and children younger than 5 years by 2030 is unachievable without urgent action to improve neonatal surgical care in LMICs.¹⁵ The comprehensive study design and large cohort enabled identification of factors associated with mortality that can be addressed through improvements in antenatal and district-level care, and care at paediatric surgery centres. Strong collaboration between obstetric, neonatal, surgical, anaesthetic, and nursing teams is required. The Global Initiative for Children's Surgery provides such a platform, and the newly formed Congenital Anomalies Working Group focuses on

bringing these teams together for collective action.^{41,42} This study provides the necessary data to inform interventions, guidelines, and policies in the field, and to advocate for the inclusion of neonatal surgical care within national surgical, obstetric, and anaesthetic plans being developed in LMICs globally.⁴³ Improving access to quality neonatal surgical care in LMICs holds the potential to reaccelerate global neonatal mortality reduction.

Contributors

NJW conceived the idea for the study, gained study funding, wrote the study protocol, designed the data collection forms, established the Global PaedSurg Research Collaboration, coordinated the data collection and validation, undertook the data analysis, and wrote and revised the manuscript. The steering committee (AJML, NAA, NS, JD, DP, EA, AA, KL, ERS) contributed to the funding application, study design, protocol, and manuscript. The writing committee (NJW, steering committee, plus BML, MS, CR, MA, ST, ARM, DAAA, CGF, AN, MA, AD, ME) contributed to the data interpretation, manuscript content, and revisions. Statistical analysis was done by NJW, AD, ME, MFD, FI, and NM. The corresponding author (NJW) and statisticians (AD and ME) had full access to all the study data and validated the data. All authors approved the manuscript and had final responsibility for the decision to submit for publication. Lead organisers (appendix p 2) assisted with recruitment of and communication with local investigators, helped translate all study documentation and the REDCap data collection tool into 12 languages, helped to coordinate the pilot study, main study, and validation process, revised the data collection tools after feedback from the pilot study, contributed to the study design, followed up missing data, and contributed to the manuscript content. Lead investigators (appendix pp 2–3) contributed to the study design and content of the data collection forms through feedback after participation in the pilot study. Continent, regional, and country leads (appendix pp 3–4) helped to recruit and communicate with local investigators from within their region and coordinate local study activities, including assistance with questions related to data collection and gaining study approval. Local investigators (appendix pp 4–12) developed mini-teams at their hospital, gained local study approval, used the protocol to identify eligible patients, collected data, entered data into REDCap, and checked the data to prevent duplicate entries and ensure accuracy. The study results were shared with all study team members through an online presentation and all had the opportunity to contribute to the data interpretation and manuscript content through discussion at the meeting and written communications. All authors have read and approved the final manuscript. CDH UK, a family-led charity and parent advisory group, provided input into the data collection form, data interpretation, and manuscript content. Their input will be sought to assist with dissemination.

Declaration of interests

NS is the director of the London Safety and Training Solutions, which offers training in patient safety, implementation solutions, and human factors to health-care organisations. All other authors declare no competing interests.

Data sharing

Following publication of the study results, the full, anonymous, de-identified patient dataset will be made publicly available via the Centre for Open Science website.

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