Mortality from Gastrointestinal Congenital Anomalies at 264 Hospitals in 74 Low-, Middle- and High-Income Countries: A Multicentre, International, Prospective Cohort Study

Global PaedSurg Research Collaboration*

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Summary

Background
Congenital anomalies are the 5th leading cause of under-5 mortality, globally. Many gastrointestinal congenital anomalies are fatal without timely access to neonatal surgical care. Limited literature exists on these conditions in low- and middle-income countries (LMICs). We compared the outcomes of the seven commonest gastrointestinal congenital anomalies in low-, middle- and high-income countries (LICs, MICs, and HICs), globally, and identified factors associated with mortality.

Methods
The Global PaedSurg Research Collaboration, consisting of healthcare professionals who provide surgical care for neonates and children with congenital anomalies, performed a multicentre, international prospective cohort study of consecutive patients, under 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 for a minimum of 1-month between October 2018 and April 2019. We collected data on patient demographics, clinical status, interventions, and outcomes using REDCap. Follow-up was to 30 days post-primary intervention. The primary outcome was all-cause, in-hospital mortality for all conditions combined and each condition individually, stratified by country income status. We used chi-squared to compare mortality between country income strata, and penalised regression to identify factors associated with mortality (Risk Ratio [RR], 95% Confidence Interval [CI], p value).

Findings
We included 3849 patients with 3975 study conditions (560 oesophageal atresia, 448 congenital diaphragmatic hernia, 681 intestinal atresia, 453 gastroschisis, 325 exomphalos, 991 anorectal malformation, and 517 Hirschsprung's Disease) from 264 hospitals (89 HICs, 166 MICs, 9 LICs) in 74 countries. Mortality amongst all patients was 39·8% (37/93) in LICs, 20·4% (583/2860) in MICs, and 5·6% (50/896) in HICs (p<0·001 between all country income groups). Gastroschisis had the greatest difference in mortality between country income strata (90·0% [9/10] LICs, 31·9% [97/304] MICs, 1·4% [2/139] HICs, p<0·001 between all country income groups). Factors significantly associated with higher mortality for all patients combined included: country income status (LIC [RR 2·78, CI 1·88-4·11, p<0·001], MIC [RR 2·11, CI 1·59-2·79, p<0·001] vs HIC), sepsis at presentation (RR 1·20, CI 1·04-1·40, p=0·016), higher American Society of Anesthesiologists score (ASA) at primary intervention (ASA 4-5 [RR 1·82, CI 1·40-2·35, p<0·001], ASA 3 [RR 1·58, CI 1·30-1·92, p<0·001] vs ASA 1-2), surgical safety checklist not used (RR 1·39, CI 1·02-1·90, p=0·035), and ventilation or parenteral nutrition unavailable when needed (RR 1·96, CI 1·41-2·71, p<0·001, or RR 1·35, CI 1·05-1·74, p=0·018, respectively). Administration of parenteral nutrition (RR 0·61, CI 0·47-0·79, p<0·001), and use of a peripherally inserted central catheter (RR 0·65, CI 0·5-0·86, p=0·002), or percutaneous central line (RR 0·69, CI 0·48-1·00, p=0·049) were associated with lower mortality.

Interpretation
Unacceptable differences in mortality exist for gastrointestinal congenital anomalies between low-, middle- and high-income countries. Improving access to quality neonatal surgical care in LMICs is vital to achieve Sustainable Development Goal 3·2 to 'end preventable deaths in neonates and children under five by 2030'.

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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 January 1, 2000 to October 10, 2020. Three search strings were used: 1) the seven gastrointestinal congenital anomalies included in our study, 2) all-cause in-hospital or 30-day post-operative mortality, 3) patients aged under 16 years. Studies were limited to those of primary surgical intervention and cohorts above 100 patients. We found no previous studies that have prospectively compared outcomes from gastrointestinal congenital anomalies between low-, middle-, and high-income countries (LICs, MICs, and HICs), globally. Research on the individual conditions was mainly from HICs (79 studies), with a few in MICs (n=14), and one in a LIC. Due to the heterogeneity of the studies, it is not possible to accurately compare outcomes between income strata. Information regarding leading causes of death or factors associated with mortality for these conditions in low- and middle-income countries (LMICs) is limited.

Added value of this study

This study provides validated, prospectively collected data on patients with gastrointestinal congenital anomalies in 74 low, middle and high-income countries across the globe. The results highlight huge disparities in mortality between income settings. Moreover, the extremely high mortality rates identified for these conditions in LMICs far exceed surgical mortality rates amongst 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 to ‘end preventable deaths in neonates and children under five by 2030’ is unachievable without an urgent focus on improving access to quality neonatal surgical care in LMICs. Indicators of clinical deterioration prior to surgical intervention were significantly associated with higher mortality for all conditions. Delivery at a paediatric surgery centre (enabled by antenatal diagnosis) can help to prevent this and reduce mortality as demonstrated in patients with gastroschisis and congenital diaphragmatic hernia. However, most patients currently 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 hence help to further reduce global neonatal mortality.

Introduction

In the last 30 years, major strides have been made in reducing childhood mortality globally, with a fall in under-5 deaths from 12·5 million in 1990 to 5·3 million in 2018.[1] Neonatal mortality however has fallen at a slower rate, levelling off at 2·4 million deaths in 2019.[1,2] Consequently the proportion of under-5 deaths occurring in the neonatal period has risen to 46%.[2] Concurrently, as the number of deaths from infectious diseases has fallen, the proportion of deaths attributed to congenital anomalies (birth defects) has risen, accounting for an estimated 303,000 neonatal deaths and half a million under-5 deaths annually.[3-5] Congenital anomalies are now the 5th leading cause of under-5 mortality and 11th leading cause of years of life lost for the global population.[6,7]

Congenital anomalies are defined by the World Health Organisation (WHO) as structural or functional anomalies that occur during intrauterine life.[4] They affect 3-6% of global live births.[4] Low- and middle-income countries (LMICs) have the highest prevalence due to greater maternal exposure to micronutrient deficiencies, teratogens, and intra-uterine infections, and lower termination rates resulting from limited antenatal diagnosis.[4,8] It is estimated that LMICs account for over 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 has 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, often fatal without access to emergency neonatal surgical care, may contribute to a large proportion of the preventable congenital anomaly deaths in LMICs and hence form the focus of this study.

Sustainable Development Goal (SDG) 3·2 aims to 'end preventable deaths in neonates and under-5s by 2030'.[15] It is therefore imperative to identify and quantify preventable deaths from gastrointestinal congenital anomalies globally, and gain insight into how to improve their survival. The aim of this study was to prospectively compare the outcomes of the seven most common gastrointestinal congenital anomalies in low-, middle- and high-income countries, and identify factors associated with mortality.

Methods

The study protocol was registered with ClinicalTrials.gov (NCT03666767) and published.[16] STROBE guidelines have been followed.

Study design, setting and participants

We performed 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 [CDH], intestinal atresia, gastroschisis, exomphalos [also known as omphalocele], anorectal malformation [ARM], and Hirschsprung's Disease). Data were collected by their healthcare 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 from across the world as possible. 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; there was no payment for data collection. Hospital teams chose one calendar month (commencing on the 1st of the month), or multiple one-month study periods (depending on local capacity), between October 2018 to April 2019 to recruit consecutive patients to the study (by date of presentation).

Patients included any neonate, infant, or child under 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 been previously operated on for their condition, were returning with a postoperative complication, were presenting electively, or were being transferred elsewhere for surgical intervention.

A sample size calculation was undertaken using Bonferroni correction for multiple testing, assuming 80% power and an overall type 1 error of 5% (See appendix p 13 for details). To determine a significant difference in mortality between high-income countries (HICs) and LMICs, the minimum sample size per country income group was estimated at 21 for oesophageal atresia, 63 for CDH, 24 for intestinal atresia, 15 for gastroschisis, 115 for exomphalos, 85 for ARM, and 79 for Hirschsprung's Disease (804 patients in total). Comparison of mortality between HICs, middle-income countries (MICs), and low-income countries (LICs) was planned if a sufficient cohort was collected.

At the host institution, the study was classified as a clinical audit exempt from research ethical clearance. Ethical and institutional approval was sought and obtained by each contributing hospital as per local regulations. Consent forms were completed by all patients in hospitals requiring them.

Data collection and variables

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

Generic variables collected for all patients included: demographics, antenatal care (maternal ultrasound) and diagnosis, delivery type (vaginal or caesarean section), transportation (ambulance, patients own or born at study hospital), referral site if applicable (district hospital, community clinic, home or other), clinical condition on arrival (sepsis, hypovolaemia, hypothermia), resuscitation on arrival (antibiotics, intravenous [IV] fluid, warming), clinical condition at surgery (American Society of Anesthesiologists [ASA] score), intraoperative care (surgical safety checklist used, anaesthetist and surgeon grade/position, anaesthetic administered), perioperative care (ventilation, IV access, parenteral nutrition, blood transfusion, antibiotics), and outcomes (detailed below). C*ondition-specific variables* included: condition type/classification, surgical intervention, and complications. Follow-up was to 30 days post-primary intervention, or 30 days following admission in patients who did not receive an intervention. Presence and type of follow-up was collected for patients discharged prior to 30 days.

Clear definitions are provided for all variables in the published protocol.[16] Internationally utilised and validated definitions were used where available. Cause of death was decided by the clinical team using 16 pre-determined and one free-text category. From the latter, one additional category was added ('syndrome incompatible with life').

Participating country name was collected and World Bank 2018 country income status classification used to categorise data into low-, middle- and high-income countries.[19]

Data validation was done in 10% of randomly selected participating hospitals using an independent 'validating local investigator' to retrospectively collect a selection of the data again for a one-month study period. Validation data collected included: number of eligible patients; *generic variables* (month of presentation, study condition, sex, unplanned interventions, survival to discharge); *condition-specific variables* (condition type, 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 income strata (LIC, MIC or HIC). Patients were categorised as alive if they were either discharged alive or were still in hospital 30 days following primary intervention or 30 days following admission for patients who did not receive an intervention. Patients were categorised as dead if they died in hospital within 30-days of primary intervention or 30-days following admission for patients who did not receive an intervention.

Secondary outcomes were presence of surgical site infection, wound dehiscence, and/or need for unplanned re-intervention, within 30 days of surgery, and 30-day post-primary intervention mortality. Length of hospital stay

was collected 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 a selection of the seven commonest gastrointestinal congenital anomalies between low-, middle- and high-income countries, globally.

Statistical analysis

We did a complete case analysis. Duplicate entries were identified and excluded. Patients missing the study condition or primary outcome were excluded. If over 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 mean (standard deviation) if normally distributed and median (interquartile range, IQR) if skewed; count data are presented as number (%). 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 Chi-squared analysis or Fisher's exact test if less than 5 patients per group, presented as p values ($p<0{\cdot}05$ was deemed statistically significant). Mortality is presented by country income status for all patients, and each condition separately, with 95% confidence intervals ([CI], calculated using the Wald CI for a proportion formula when $n>5$ or exact binomial confidence intervals when $n\leq5$).

Continuous variables were used as collected, i.e. not categorised. Categorical variables were collapsed to include at least 15 patients per group where clinically and statistically appropriate (appendix pg 47-62). We combined hypovolaemia and/or hypothermia on admission into one variable due to collinearity.

Three multi-level, multivariable models were used to identify factors associated with mortality in all study patients (including income status as a covariable), and in LMIC and HIC settings separately. All models excluded duration of hospital stay due to missing data (n=308) and variable sub-groups (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 HIC model were excluded due to low or no patients in a group: anaesthetic type, operator grade/position, and wound dehiscence (appendix pg 47-48). All variables included within the models had ≤0.2% missing data (Tables 1 and 2, appendix pg 47-62). In the multivariable models, patients with missing data for one or more entries were excluded, resulting from a small group of patients being excluded from each model (detailed in the footnote of each forest plot). 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 does not affect the multivariable outcomes. There are 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 are no significant differences in the proportion of patients from HICs, MICs and LICs in the patients included in the models and the small groups excluded due to missing data. Hence missing data imputation was not undertaken.

All models were adjusted for hospital level clustering and included potential confounders (gestational age at birth, weight and age at presentation, presence of additional anomalies, and ASA score at primary intervention) and effect modifiers (receipt of ventilation, central IV access, and parenteral nutrition). Patients who had no surgical intervention, and therefore had no data on ASA score, anaesthetic, anaesthetist, operator, surgical safety checklist, or secondary outcome complications were included in the models (categorised as 'not applicable' within each variable) to avoid bias, as these patients were either palliated or well enough to be managed without emergency intervention. We used penalised Lasso regression to determine the risk ratio (95% CI, p value) of mortality for each variable within the models. This 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 for each condition separately, were done with income status as a covariable, and adjustments for hospital-level clustering, confounders, and effect modifiers as described above. Models included both generic and condition-specific variables. Variables excluded due to no or low counts are detailed in the appendix (pg 49-62). All multivariable results are presented as forest plots.

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

We analysed the data using STATA 15.

Role of the funding source

The funder had no role in the study design, data collection, analysis, interpretation, manuscript writing or decision to submit for publication. The corresponding author (NW) and statisticians (AD and ME) had full access to all the study data. All authors approved the manuscript and had final responsibility for the decision to submit for publication.

Results

Patient characteristics

We included 3849 patients with 3975 study conditions from 264 hospitals in 74 countries (Fig. 1 and 2) over 961 one-month study periods (median 3 months per hospital).

Of the 3849 patients, 2231 (58·0%) were male (Table 1). Median gestational age at birth was 38 weeks, and weight at presentation 2·8kg - both 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 CDH and gastroschisis in LMICs, and proportionally more with ARM. Fewer patients in LICs (n=24, 25·8%) had an additional anomaly diagnosed compared to MICs (n=1306, 45·7%) and HICs (n=448, 50·0%).

Median age at presentation varied from 3 days in LICs, to 1 day in MICs, and 3 hours in HICs. Neonates accounted for 90% (n=3464) of the study participants at presentation; the remaining 10% ranged from 29 days to 15.8 years of age. Patients travelled further from home to the study hospital in LICs (55km) compared to MICs (30km) and HICs (11km). A higher proportion of patients presented with sepsis, hypovolaemia, and hypothermia, in LICs or MICs compared to HICs. A higher proportion of patients did not receive a surgical intervention in LICs (n=26, 28·0%) compared to MICs (n=307, 10·7%) and HICs (n=62, 6·9%); consequently, these patients lacked an ASA score ('not applicable' ASA category). Among patients who received an intervention, ASA 1 was most prevalent in LICs, ASA 2 in MICs, and ASA 3 in HICs.

Table 1: Patient characteristics

Patient characteristics	Total (n=3849)	HIC (n=896)	MIC (n=2860)	LIC (n=93)	P value*
Sex:					
Male	2231 (58·0%)	528 (58·9%)	1655 (57·9%)	48 (51·6%)	0·393
Female	1596 (41·5%)	367 (41·0%)	1185 (41·4%)	44 (47·3%)	-
Ambiguous	21 (0·5%)	1 (0·1%)	19 (0·7%)	1 (1·1%)	-
Unknown	1 (0·0%)	0 (0·0%)	1 (0·0%)	0 (0·0%)	-
Median gestational age at birth (IQR), weeks	38 (3)	38 (3)	38 (3)	37 (3)	0·756
Median weight at presentation (IQR), kg	2·8 (1)	2·9 (1)	2·8 (1)	2·8 (1·35)	0·128
What study condition(s) does the patient have?					
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%)	**<0·001**
Intestinal atresia	681 (17·7%)	152 (17·0%)	509 (17·8%)	20 (21·5%)	0·528
Gastroschisis	453 (11·8%)	139 (15·5%)	304 (10·6%)	10 (10·8%)	**<0·001**
Exomphalos/Omphalocele	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%)	**<0·001**
Hirschsprung's Disease	517 (13·4%)	107 (11·9%)	393 (13·7%)	17 (18·3%)	0·148
Additional anomaly or study condition diagnosed?					
Yes	1778 (46·2%)	448 (50·0%)	1306 (45·7%)	24 (25·8%)	**<0·001**
Median age at presentation (IQR), hours	22 (85·5)	3 (28)	24 (93)	72 (176)	**<0·001**
Median distance from patient's home to study hospital (IQR), km	25 (98)	11 (63·5)	30 (105)	55 (122·5)	**<0·001**
Septic on arrival to the study centre?					
Yes	660 (17·1%)	38 (4·2%)	598 (21·0%)	24 (25·8%)	**<0·001**
Missing	3 (0·1%)	1 (0·1%)	2 (0·1%)	0 (0·0%)	-
Hypovolaemia on arrival to the study centre?					
Yes	564 (14·7%)	75 (8·4%)	478 (16·7%)	11 (11·8%)	**<0·001**
Missing	4 (0·1%)	1 (0·1%)	2 (0·1%)	1 (1·1%)	-
Hypothermic on arrival to the study centre?					
Yes	403 (10·5%)	32 (3·6%)	358 (12·5%)	13 (14·0%)	**<0·001**
Missing	6 (0·2%)	1 (0·1%)	4 (0·1%)	1 (1·1%)	-

ASA Score at the time of primary intervention:					
1. Healthy person	678 (17·6%)	115 (12·8%)	534 (18·7%)	29 (31·2%)	**<0·001**
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. A moribund patient who is not expected to survive without the operation	151 (3·9%)	15 (1·7%)	136 (4·8%)	0 (0·0%)	-
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 (0·0%)	-

*P values represent univariable testing between income country strata. †These patients were either palliated, managed conservatively or discharged without intervention with planned future intervention (details in appendix pg 16-44). ASA: American Society of Anesthesiologists. HIC: High-income country. IQR: Interquartile range. LIC: Low-income country. MIC: Middle-income country.

Care received

Only 9 (9·7%) patients had their condition diagnosed or a problem identified antenatally in LICs compared to 813 (28·8%) in MICs and 506 (56·5%) in HICs (Table 2). In LICs, most patients (n=75, 80·7%) were born via vaginal delivery and few (n=15, 16·1%) via caesarean section. In contrast, 1421 (49·7%) patients were born via caesarean section in MICs and 411 (45·8%) in HICs. Only 2 LIC patients (2·2%) were inborn at the paediatric surgery centre, compared to 618 (21·6%) in MICs and 391 (43·6%) in HICs. In all settings, the majority of outborn patients (born outside the paediatric surgery centre) presented from district hospitals. In LICs, 41 (45·1%) patients travelled to the study centre using non-hospital transport, compared to 1041 (46·4%) in MICs and 74 (14·7%) in HICs.

Some septic and hypovolaemic patients did not receive IV antibiotics (LIC n=9 [37.5%]; MIC n=144 [24.1%]; HIC n=7 [18.4%]) or IV fluids (LIC n=5 [45.5%]; MIC n=84 [17.6%]; HIC n=34 [45.3%]) within one hour of presentation, and some hypothermic patients were not warmed (MIC n=27 [7.6%]; HIC n=4 [12.5%]). Only 55 (59·1%) LIC patients received a general anaesthetic (because n=32 (34·4%) were not operated), compared to 2327 (81·3%) in MICs and 772 (86·2%) in HICs. Anaesthesia was more frequently provided by a nurse in LICs (n=17, 18·3%) than in MICs (n=17, 0·6%) and HICs (n=1, 0·1%), and surgery was more frequently performed by a general surgeon or unsupervised trainee (LICs n=13 [14·0%]; MICs n=54 [1·9%]; HICs n=14 [1·6%]). A surgical safety checklist was used less frequently in LICs (n=31, 33·3%) than in MICs (n=1791, 62·6%) and HICs (n=747, 83·4%).

In LICs, only 10 (10·8%) patients received ventilation, 3 (3·2%) parenteral nutrition, and 6 (6·5%) central IV access. This compares to 1363 (47·7%), 1416 (49·5%), and 1263 (44·2%) patients, respectively, in MICs, and 637 (71·1%), 683 (76·2%), and 670 (74·8%), respectively, in HICs.

Table 2: Care received

Care received	Total (n=3849)	HIC (n=896)	MIC (n=2860)	LIC (n=93)	P value*
Antenatal care, delivery, transportation to the paediatric surgery centre, and referral site:					
Antenatal ultrasound undertaken?					
Yes: study condition diagnosed	881 (22·9%)	368 (41·1%)	512 (17·9%)	1 (1·1%)	**<0·001**
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%)	-
Median gestational age of study condition diagnosis if antenatal: (IQR), weeks	25 (11)	21 (11)	28 (11)	-	**<0·001**
Type of delivery:					
Vaginal (spontaneous)	1767 (45·9%)	373 (41·6%)	1324 (46·3%)	70 (75·3%)	**<0·001**
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/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 within the study hospital:					
Yes	1011 (26·3%)	391 (43·6%)	618 (21·6%)	2 (2·2%)	**<0·001**
Missing	5 (0·1%)	1 (0·1%)	4 (0·1%)	0 (0·0%)	-
If born outside the study centre, mode of transport to hospital:					
Ambulance or other transport provided by the health service	1677 (59·1%)	430 (85·1%)	1197 (53·4%)	50 (54·9%)	**<0·001**
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 (0·0%)	-
If born outside the study centre, where did the patient present from?					
District Hospital	1835 (64·7%)	401 (79·4%)	1377 (61·4%)	57 (62·6%)	**<0·001**
Home	504 (17·8%)	51 (10·1%)	445 (19·8%)	8 (8·8%)	-
Community Clinic/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 (0·0%)	-
From a different speciality within the hospital	5 (0·2%)	4 (0·8%)	0 (0·0%)	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 (0·0%)	
Care at the paediatric surgery centre:					
Resuscitation on arrival					
If septic, were appropriate antibiotics administered?					
Yes within 1 hour of arrival	500 (75·8%)	31 (81·6%)	454 (75·9%)	15 (62·5%)	0·417
Yes within the first day of arrival	150 (22·7%)	7 (18·4%)	135 (22·6%)	8 (33·3%)	-
No	10 (1·5%)	0 (0·0%)	9 (1·5%)	1 (4·2%)	-
If hypovolaemic, was an intravenous fluid bolus given?					
Yes within 1 hour of arrival	440 (78·0%)	40 (53·3%)	394 (82·4%)	6 (54·5%)	**<0·001**
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 (0·0%)	0 (0·0%)	
If hypovolaemic, how much intravenous fluid was given?					
10 - 20mls/kg	408 (72·3%)	36 (48·0%)	363 (75·9%)	9 (81·8%)	**<0·001**
Above 20mls/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%)	
If hypothermic, was the patient warmed to within normal range on arrival?					
Yes	371 (92·3%)	28 (87·5%)	330 (92·4%)	13 (100·0%)	0·345
Primary intervention					
Median time from arrival at study hospital to primary intervention: (IQR), hours	24 (59)	22 (43)	24 (64)	34 (86)	**<0·001**
What type of anaesthesia was used for the primary intervention?					
General anaesthesia with endotracheal tube or laryngeal airway	3154 (81·9%)	772 (86·2%)	2327 (81·3%)	55 (59·1%)	**<0·001**
Intervention without anaesthesia +/- 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 (0·0%)	-
Spinal/caudal anaesthesia	19 (0·5%)	0 (0·0%)	19 (0·7%)	0 (0·0%)	-
Ketamine anaesthesia	9 (0·2%)	1 (0·1%)	5 (0·2%)	3 (3·2%)	-
Not applicable: no surgery or primary intervention undertaken.	392 (10·2%)	55 (6·1%)	305 (10·7%)	32 (34·4%)	-
Missing	2 (0·1%)	0 (0·0%)	2 (0·1%)	0 (0·0%)	-
Who undertook the anaesthetic for the primary intervention?					
Anaesthetic doctor	3115 (80·9%)	741 (82·7%)	2336 (81·7%)	38 (40·9%)	**<0·001**
Medical officer, surgeon or other healthcare 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 undertaken	610 (15·8%)	112 (12·5%)	463 (16·2%)	35 (37·6%)	-
Missing	3 (0·1%)	0 (0·0%)	3 (0·1%)	0 (0·0%)	-
Who undertook the primary intervention?					
Paediatric surgeon (or junior with paediatric surgeon assisting/in the room)	3345 (86·9%)	825 (92·1%)	2474 (86·5%)	46 (49·5%)	**<0·001**
Junior doctor or other (without a paediatric/general surgeon assisting/in the room)	59 (1·5%)	7 (0·8%)	49 (1·7%)	3 (3·2%)	-
Trainee surgeon (without a paediatric/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/in the room)	32 (0·8%)	7 (0·8%)	18 (0·6%)	7 (7·5%)	-
Not applicable - no surgery or primary intervention undertaken.	361 (9·4%)	49 (5·5%)	281 (9·8%)	31 (33·3%)	-
Missing	3 (0·1%)	1 (0·1%)	2 (0·1%)	0 (0·0%)	-
Was a surgical safety checklist used at the time of primary intervention?					
Yes	2569 (66·7%)	747 (83·4%)	1791 (62·6%)	31 (33·3%)	**<0·001**
No	693 (18·0%)	39 (4·4%)	626 (21·9%)	28 (30·1%)	
Not applicable: no surgical intervention undertaken	584 (15·1%)	109 (12·1%)	441 (15·4%)	34 (36·5%)	
Missing	3 (0·1%)	1 (0·1%)	2 (0·1%)	0 (0·0%)	-
Perioperative care					
Did the patient receive central venous access?					
Yes: peripherally inserted central catheter (PICC)	1120 (29·1%)	436 (48·7%)	678 (23·7%)	6 (6·5%)	**<0·001**
Yes: percutaneously inserted central line	415 (10·8%)	187 (20·9%)	228 (8·0%)	0 (0·0%)	**<0·001**
Yes: umbilical catheter	402 (10·4%)	153 (17·1%)	249 (8·7%)	0 (0·0%)	**<0·001**
Yes: surgically placed central line (open insertion)	254 (6·6%)	27 (3·0%)	227 (7·9%)	0 (0·0%)	**<0·001**
No	1910 (49·6%)	226 (25·2%)	1597 (55·8%)	87 (93·5%)	**<0·001**
Median total duration of antibiotics following primary intervention: (IQR), days	7 (8)	3 (6)	7 (10)	3 (7)	**<0·001**
Did the patient receive a blood transfusion?					
No: not required.	2448 (63·6%)	671 (74·9%)	1708 (59·7%)	69 (74·2%)	**<0·001**
Yes	1348 (35·0%)	213 (23·8%)	1114 (38·9%)	21 (22·6%)	-
No: it was 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 (0·0%)	-
Did the patient require ventilation?					
No	1755 (45·6%)	258 (28·8%)	1422 (49·7%)	75 (80·6%)	**<0·001**
Yes and it was given	2008 (52·2%)	637 (71·1%)	1363 (47·7%)	8 (8·6%)	**-**
Yes, but it was not available	85 (2·2%)	1 (0·1%)	74 (2·6%)	10 (10·8%)	-
Missing	1 (0·0%)	0 (0·0%)	1 (0·0%)	0 (0·0%)	-
Median time patient remained on ventilation if given: (IQR), days	4 (6)	4 (7)	4 (6)	1·5 (1·5)	**0·003**
Median time to first enteral feed: (post-primary intervention) (IQR), days	4 (6)	4 (6)	4 (6)	1 (2)	**<0·001**
Median time to full enteral feeds: (post-primary intervention) (IQR), days	8 (12)	11 (16)	7 (12)	3 (5)	**<0·001**
Did the patient require parenteral nutrition?					
No	1476 (38·3%)	212 (23·7%)	1196 (41·8%)	68 (73·1%)	**<0·001**
Yes and it was given	2102 (54·6%)	683 (76·2%)	1416 (49·5%)	3 (3·2%)	**-**
Yes and it was sometimes available, but less than required	143 (3·7%)	0 (0·0%)	143 (5·0%)	0 (0·0%)	-
Yes, but it was not available	125 (3·2%)	0 (0·0%)	103 (3·6%)	22 (23·7%)	-
Missing	3 (0·1%)	1 (0·1%)	2 (0·1%)	0 (0·0%)	-
Median time patient received parenteral nutrition if received: (IQR), days	11 (14)	14 (16)	10 (13)	30 (20)	**<0·001**

*p values represent univariable testing between income country strata. HIC: High-income country. IQR: Interquartile range. LIC: Low-income country. MIC: Middle-income country.

Condition-specific patient characteristics, antenatal care, perioperative care, surgical intervention, and outcomes, are detailed in the appendix (pg 16-44). Of note, in HICs, where 94·8% (849/896) women received an antenatal ultrasound, antenatal detection rates (problem identified +/- condition diagnosed) were: gastroschisis 96·4% (134/139), exomphalos 92·9% (65/70), intestinal atresia 71·1% (108/152), CDH 64·9% (96/148), oesophageal atresia 51·1% (72/141), ARM 27·5% (49/178), and Hirschsprung's disease 11·2% (12/107).

The proportion of patients followed up to 30 days post-primary intervention to assess survival status and presence of complications is detailed in the appendix (pg 45). Of the 3849 study patients, 418 (10.9%) were still in hospital at 30-days post-intervention. Of the 2761 (71.7%) patients discharged home prior to 30-days, 2495 (90.4%) were followed-up to 30-days.

Primary Outcome

Overall all-cause, in-hospital mortality was 39·8% (37/93) in LICs, 20·4% (583/2860) in MICs and 5·6% (50/896) in HICs, p<0·0001 between all country income groups (Figure 3, appendix pg 46). For each condition considered individually, gastroschisis, oesophageal atresia, and intestinal atresia also showed a significant difference between all income groups; CDH showed a significant difference between HICs and MICs (there were too few patients from LICs to compare); ARM had a significant difference between HICs and LICs, and HICs and MICs, but not between MICs and LICs; Hirschsprung's disease and exomphalos showed no significant difference between country income groups (appendix pg 46). Gastroschisis had the greatest difference in mortality (LIC 90·0% [9/10], MIC 31·9% [97/304], HIC 1·4% [2/139], p<0.001 between all country income groups), followed by CDH, oesophageal atresia and intestinal atresia (Figure 3, appendix pg 46). Neonates accounted for 98% of 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.

Multivariable analysis of factors affecting mortality

On multivariable analysis of all study patients, country income status was associated with the highest risk of mortality (LIC vs HIC, Risk Ratio [RR] 2·78 [CI 1·88-4·11]; MIC vs HIC RR 2·11 [CI 1·59-2·79]) (Figure 4). CDH had the highest risk of mortality and Hirschsprung's disease the lowest.

Antenatal diagnosis and presence of an additional anomaly were associated with a higher mortality; higher gestational age and weight, and delivery via induced vaginal delivery, 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, there was a higher mortality for patients with a higher ASA score, no physician anaesthetist present, and surgical safety checklist not used. In the perioperative period, not having ventilation or parenteral nutrition when required, needing/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 (PICC), or percutaneous central line, were associated with lower mortality.

The multivariable analysis results of patients in LMICs reflect those for all patients, except that gastroschisis was also significantly associated with higher mortality alongside CDH, and Hirschsprung's disease was no longer significantly lower (Figure 5). In the HIC multivariable model, no individual condition had a significantly higher or lower risk of mortality compared to the study patients without that condition (Figure 6). Delivery type, sepsis at presentation, ASA score, use of a surgical safety checklist, ventilation, parenteral nutrition, and central IV access were no longer significant. In contrast, hypothermia and/or hypovolaemia at presentation were associated with a 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 [CI 0·12-0·54]). For CDH (RR 0·63 [CI 0·43-0·93]) and gastroschisis (RR 0·58 [0·35-0·95]), birth at the study centre was associated with lower mortality compared to outborn patients (appendix pg 63-69).

Secondary Outcomes

Thirty-day post-intervention mortality was similar to all-cause in-hospital mortality, except an additional 11 patients died following discharge prior to 30 days in MICs (Table 3). In operated patients, surgical site infection rates did not differ across income settings, while wound dehiscence and further unplanned intervention differed statistically, though not substantially. Median hospital stay amongst survivors was lowest in LICs (9 days),

followed by MICs (14 days), and HICs (20 days); time to death amongst non-survivors was similar across settings (LICs and MICs 6 days, HICs 9 days).

Table 3: Secondary outcomes

Variable	Total (n=3849) n, % (95% CI)	HIC (n=896) n, % (95% CI)	MIC (n=2860) n, % (95% CI)	LIC (n=93) n, % (95% CI)	P value*
30-day post-intervention mortality:	681, **17·7%** (16·5, 18·9)	50, **5·6%** (4·3, 7·3)	594, **20·8%** (19·3, 22·3)	37, **39·8%** (30·4, 50·0)	**<0·001**
Surgical site infection:					
Yes	335, **10·2%** (9·2, 11·3)	76, **9·5%** (7·6, 11·7)	253, **10·5%** (9·3, 11·8)	6, **9·4%** (4·2, 19·7)	0·407
No	2942, **89·8%** (88·7, 90·8)	728, **90·6%** (88·3, 92·4)	2156, **89·5%** (88·2, 90·7)	58, **90·6%** (80·3, 95·6)	-
Not applicable, no superficial wound	569	92	448	29	-
Full thickness wound dehiscence:					
Yes	102, **3·1%** (2·6, 3·8)	12, **1·5%** (0·8, 2·6)	89, **3·7%** (3·0, 4·5)	1, **1·6%** (0·2, 11·1)	**0·003**
No	3178, **96·9%** (96·2, 97·4)	792, **98·5%** (97·4, 99·2)	2325, **96·3%** (95·5, 97·0)	61, **98·4%** (88·9, 99·8)	-
Not applicable, no full thickness wound	566	92	443	31	-
Further unplanned intervention:					
Yes - percutaneous intervention	53, **1·5%** (1·2, 2·0)	25, **3·0%** (2·0, 4·3)	28, **1·1%** (0·7, 1·6)	0, **0·0%**	**0·047**
Yes - surgical intervention	400, **11·4%** (10·4, 12·5)	92, **10·9%** (9·0, 13·2)	298, **11·5%** (10·3, 13·0)	10, **15·6%** (8·5, 27·0)	-
No	3045, **87·1%** (85·9, 88·1)	728, **86·2%** (83·7, 88·3)	2263, **87·4%** (86·1, 88·6)	54, **84·4%** (73·0, 91·5)	-
Not applicable, no primary intervention	347	51	267	29	-
Hospital stay amongst survivors (days), median (IQR):†	15 (8, 25)	20 (12, 30)	14 (8, 23)	9 (5, 18)	**<0·001**
Hospital stay amongst non-survivors (days), median (IQR):†	6 (2, 13)	9 (3, 15)	6 (2, 13)	6 (3, 12)	0·280

*p values represent univariable testing between income country strata. †patients still in hospital at 30-days following admission (n=560) were included as 30. HIC: High-income country. IQR: Interquartile range. LIC: Low-income country. MIC: Middle-income country.

Exploratory outcomes

Overall, the leading causes of death were sepsis (n=235, 35·1%) and respiratory failure (n=189, 28·2%) (Figure 7). Proportionally, sepsis caused more deaths in LMICs than in HICs.

Data Validation

Median observed agreement between the study and validation data was 100% (IQR 88-100%); kappa statistic 0·96 (IQR 0·57-1·00) (appendix pg 70-71). Variables deemed potentially inaccurate were: gestational age at birth, distance from home to study centre, and time from birth to presentation (appendix 72-75). Validators identified eight patients missed from study inclusion (appendix pg 76).

Discussion

This international, prospective, cohort study has provided information on outcomes for nearly 4000 patients with gastrointestinal congenital anomalies in 74 countries across the globe. It highlights substantial differences in mortality between low-, middle- and high-income countries. The chance of dying from a gastrointestinal congenital anomaly if born in a LIC is two in five, compared to one in five in a MIC, and one in twenty in a HIC. Neonates born with gastroschisis have the greatest mortality difference; 90% in LICs and 32% in MICs, compared to just 1% in HICs. Thus, conditions associated with a normal life span for most in HICs 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 others who have shown far better surgical outcomes in high- than in lower- or middle-income countries.[20-22] However, the remarkably high surgical mortality rates amongst neonates in our study far exceed those reported in LMICs for older children and adults requiring surgery (which is between 1-4% mortality, depending on the study).[20-22] The inequities that we have found highlights 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 children's surgery, particularly neonatal surgery, has been almost non-existent.[8]

Our study is the first comprehensive global outcomes study of gastrointestinal congenital anomalies that we are aware of. It confirms previous findings from smaller, mostly single-centre, retrospective studies. A systematic review of neonatal surgery in sub-Saharan Africa reported over 50% mortality for emergency gastrointestinal surgery compared to 3% mortality for spina bifida and cleft surgery.[9] A hospital in Northern Ghana reported that

96% of their 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 lack components of neonatal surgical care considered essential in high income settings. These include antenatal diagnosis, birth at a paediatric surgery centre, effective resuscitation and timely ambulance transfer for patients born in or referred to district hospitals, use of a surgical safety checklist, physician anaesthetist at primary intervention, and basic neonatal intensive care unit (NICU) resources such as ventilation, central IV 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 a 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 CDH, and caesarean section for exomphalos, both enabled by antenatal diagnosis. Antenatal diagnosis enables delivery at a paediatric surgery centre, avoiding clinical deterioration prior to 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 need for blood transfusion and ventilation. Although proportionally more patients who had an operation had better ASA scores in LICs and MICs, compared to HICs, this may reflect that the sickest 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, may 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 HICs, highlighting the need for both increased access to and improved quality of antenatal ultrasound. A randomised controlled trial in five LMICs demonstrated this is possible.[27] However, they found 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]

This study highlights that currently most patients with gastrointestinal congenital anomalies in LMICs are not born at the paediatric surgery centre - most are referred from district hospitals. Even in HICs, where 95% of the women received an antenatal ultrasound, not all anomalies were detected. Hence, upskilling staff at district hospitals to deal with births at, or referrals to, these facilities is vital to prevent clinical deterioration prior to surgical intervention. Such an initiative in India showed successful knowledge and skills transfer by multi-disciplinary paediatric surgical teams to district hospitals.[29] Unfortunately, the current WHO 'Recommendations on Newborn Health' includes a section on 'management of other severe conditions', but has no mention of congenital anomalies.[30] Hence, upgrading this document is 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 prevention of sepsis, hypothermia and hypovolaemia.[31] Our study also showed that patients in LMICs travel further and present later, frequently without hospital transport. While not independently significantly associated with mortality, these factors likely also impact patients' clinical condition 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 independently associated with mortality in the preoperative, intraoperative, and perioperative periods. Poorer clinical condition was associated with higher mortality – potentially addressed through improved resuscitation on arrival. Our results show that not all septic and hypovolaemic patients received IV antibiotics and fluids within an hour of arrival, and some hypothermic patients were not warmed. Absence of a physician anaesthetist at the primary intervention and neglect of the surgical safety checklist were associated with a higher mortality. To address the former, KidsOR charity have recently pledged funds to train paediatric anaesthetists alongside paediatric surgeons across Africa.[32] Efforts are required to broaden surgical safety checklist use in LMICs; utilisation of implementation science techniques may facilitate this.[33] In the perioperative period, lack of availability of ventilation and parenteral nutrition when required were significantly associated with high mortality in LMICs, while receipt of parenteral nutrition, and peripheral or percutaneous central IV access, were protective.

Incorporation of basic neonatal intensive care facilities has been omitted from previous global neonatal care recommendations, as they are deemed expensive.[1] These resources however are essential, not only for surgical neonates, but also for many low-birthweight and sick neonates due to other causes; 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.[34] 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 need for ventilation.[35] This is currently being trialled in a multicentre, multinational interventional study in sub-Saharan Africa, alongside locally sourced, affordable, peripherally administered, partial parenteral nutrition, which could benefit neonatal outcomes more broadly.[36]

This study has several limitations. For feasibility, the study focused on a selection of common, high-mortality, gastrointestinal congenital anomalies on which limited data was available, rather than the full complement of anomalies. Despite intentional study design to minimise reporting burden for high-volume, low-resource centres, the proportion of patients included from LICs (2%) was lower than in the global population (9%).[37] The proportion of MIC study patients (74%) however reflects the global MIC population (75%).[37] Although the number of patients included from LICs was relatively low, the mortality rates that we found reflect what has previously been reported in the limited data available from these regions. For example, two of the largest single institution observational studies on gastroschisis in LICs report a mortality of 90% (136/151) in Uganda and 84% (80/95) in Zimbabwe, respectively.[38,39] The Gastroschisis Interventional Study across seven tertiary paediatric surgery centres in Ghana, Zambia, Malawi and Tanzania (LICs and lower-middle income countries) reported an overall baseline mortality of 95%.[36] Mortality rates for the other study conditions also mirror those reported from Uganda.[39]

Despite the higher mortality rates in LMICs compared with HICs, there are a number of reasons why the reported mortality may be an under-estimation. Data collection was done at paediatric surgery centres; some patients may have died without reaching such care in LMICs.[40] This is evidenced by the 'missing' patients with CDH, particularly within the LIC cohort, and the under-representation of gastroschisis within the LMIC cohorts – similarly reported in HICs in the 1970s.[41] Cases with more advanced disease severity (i.e severe CDH) or multiple anomalies (i.e co-existing cardiac anomaly) may be more likely to die prior to presentation in LMICs (or not get referred). This may partly account for the higher proportion of patients with ASA 1 and 2 in LICs and MICs, respectively, compared to HICs and also the lower proportion of patients with associated anomalies in LICs. The latter, however, may also result from underdiagnosis due to lower diagnostic expertise and resources in LICs. If over 20% of patients were missing the primary outcome in any given month at a participating hospital, all patients in that month were excluded. Although included to help optimise the accuracy of mortality rates, this could inadvertently introduce 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 due to this compared to the 961 months of data (3849 patients) included in the study and therefore the effect is likely to be minimal. Thirty-day post-intervention follow-up was missing in 37·5% LIC patients, 9·0% MIC patients, and 7·5% HIC patients, therefore potentially missing some post-discharge deaths and complications.

There are some additional factors to consider when interpreting the study data. Although we have 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 the latter. In LICs, most cases of Hirschsprung's disease were diagnosed clinically without biopsy confirmation; 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 multi-disciplinary team care have played a key role in optimising outcomes in HICs, but have not been captured within this study. In HICs, and some MICs, where antenatal detection is higher, potentially some foetus' with more severe or multiple anomalies may have been terminated contributing to the lower mortality. However, this is not reflected in the data since HICs had the highest proportion of patients with additional anomalies, followed by MICs. 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 SDG 3·2 to 'end preventable deaths in neonates and children under five 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 (GICS), provides such a platform, and the newly formed 'Congenital Anomalies Working Group' focusses on bringing these teams together for collective action.[42,43] 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.[44] Improving access to quality neonatal surgical care in LMICs holds the potential to re-accelerate global neonatal mortality reduction.

Article Information

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Contributors
NW conceived the idea for the study, gained study funding, wrote the study protocol, designed the data collection forms, established the Global PaedSurg Research Collaboration, co-ordinated the data collection and validation, undertook the data analysis and wrote/revised the manuscript. The steering committee (AJML, NAA, NS, JD, DP, EA, AA, KL, ES) contributed input and revisions to the funding application, study design, protocol, and manuscript. The writing committee (NW, steering committee plus BML, MS, CR, MA, ST, ARM, DAAA, CGF, AN, BML, MA, AD, ME) contributed to the data interpretation, manuscript content and revisions. Statistical analysis was undertaken by NW, AD, ME, MFD, FI, and NM. Lead organisers (detailed in appendix) assisted with recruitment of and communication with local investigators, helped translate all study documentation and the REDCap data collection tool into 12 languages, helped co-ordinate the pilot study, main study and validation process, revised the data collection tools following feedback from the pilot study, contributed to the study design, chased missing data and contributed to the manuscript content. Lead investigators (detailed in appendix) contributed to the study design and content of the data collection forms through feedback following participation in the pilot study. Continent, Regional and Country leads (detailed in appendix) helped to recruit and communicate with local investigators from within their region and co-ordinate local study activities including assistance with questions related to data collection and gaining study approval. Local investigators (detailed in appendix) developed mini-teams at their hospital, gained local study approval, utilised 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.

Patient and Public Involvement
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.

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

Ethics Approval
This study was classified as a clinical audit with written confirmation from King's College London Ethics Committee that it does not therefore require ethical approval. All participating centres gained local study approval to participate according to their institutional ethical regulations. Data transfer agreements were legally signed between institutions were required.

Data Availability
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: https://osf.io/e4uvh/.

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Figures

Figure 1: Global distribution of participating hospitals

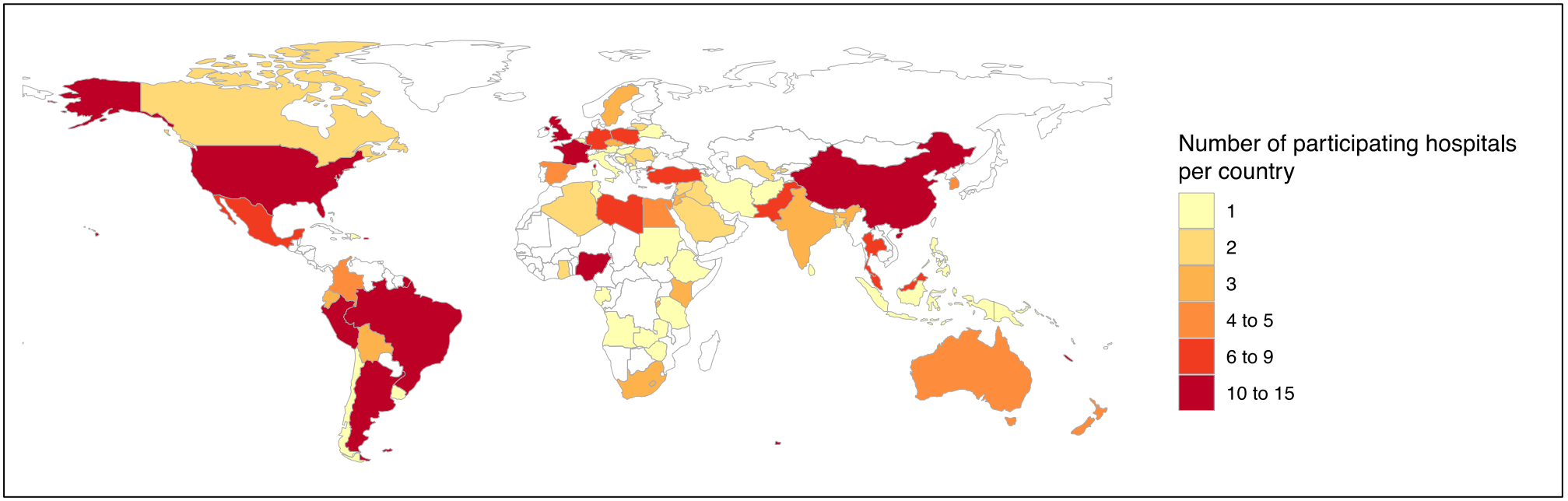


Figure 2: Flow diagram of patient inclusion in the study

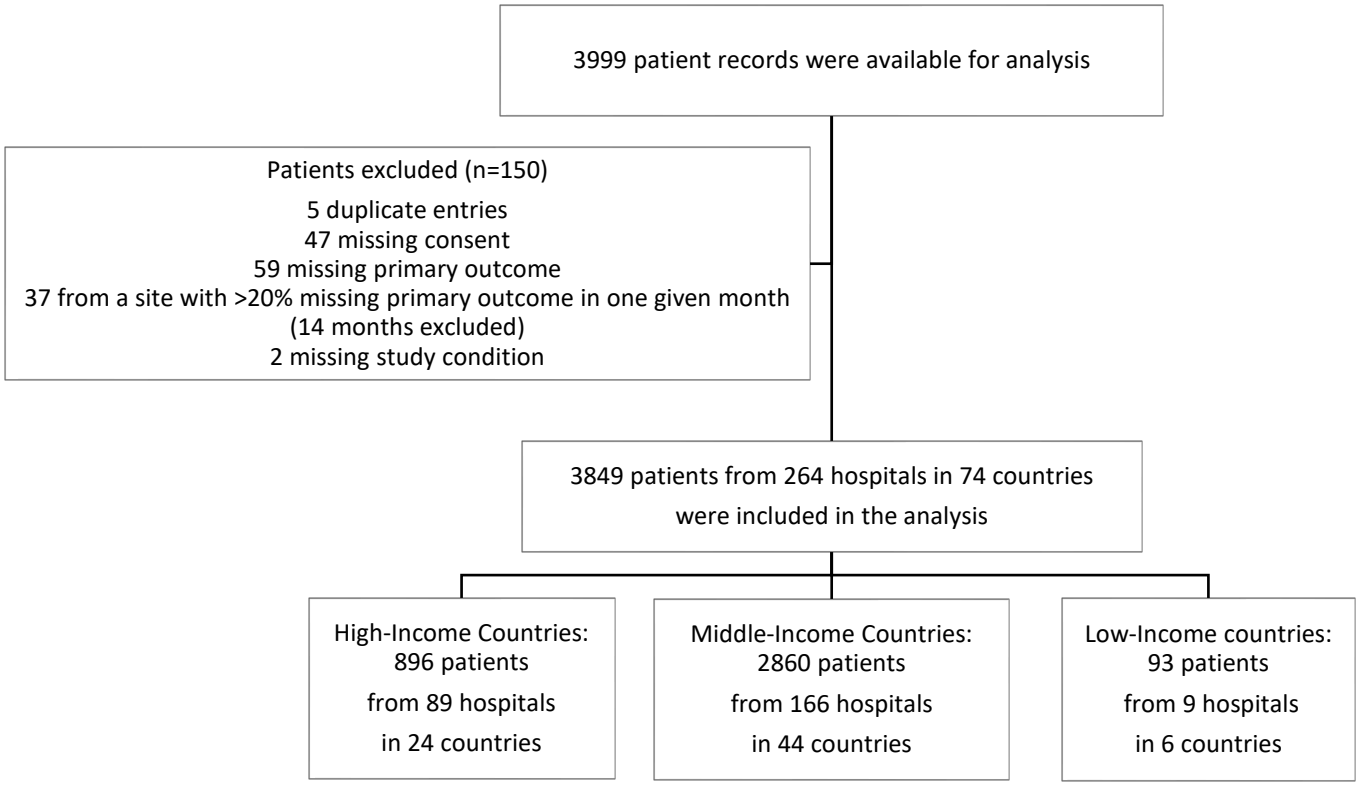
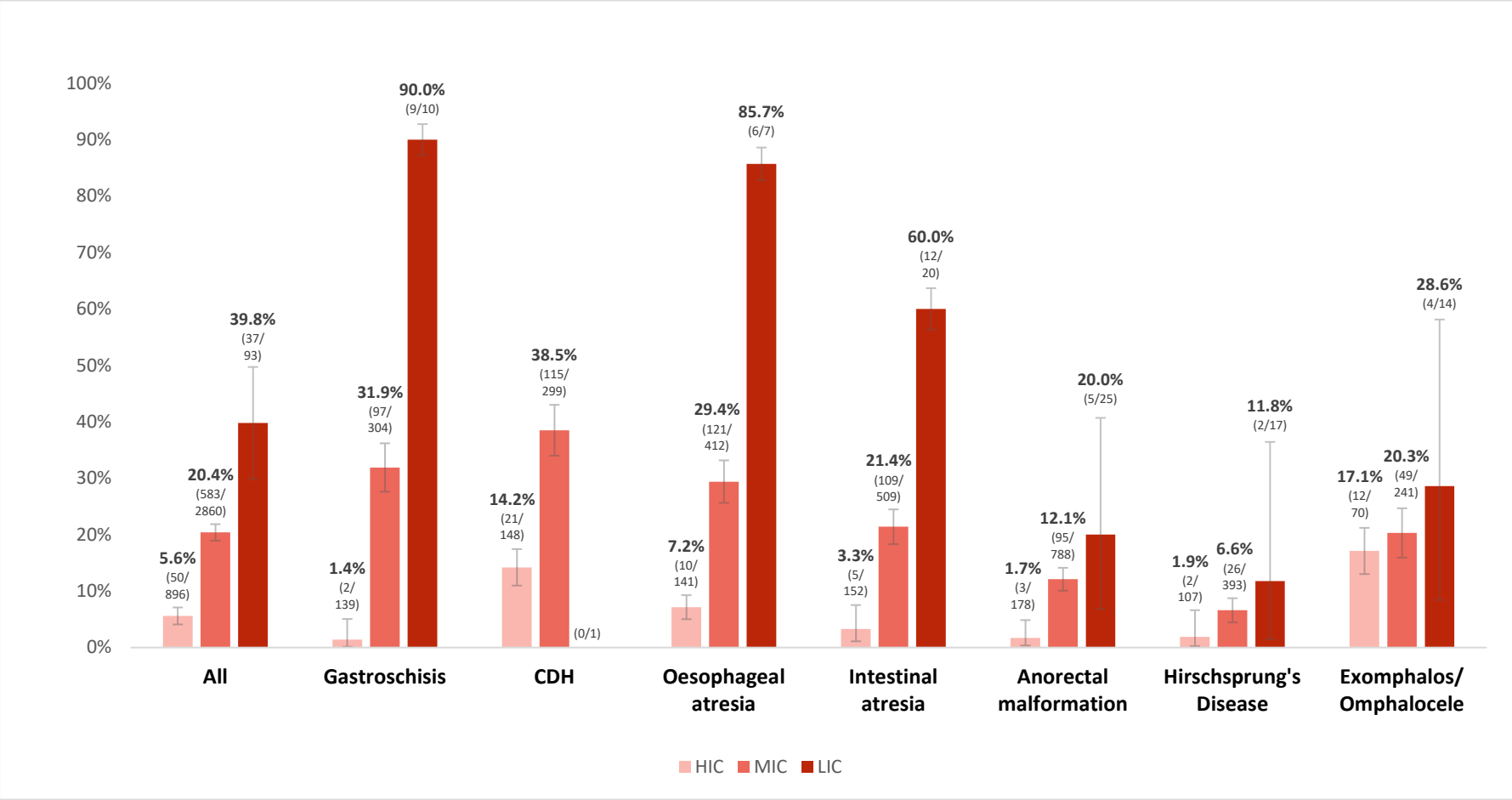
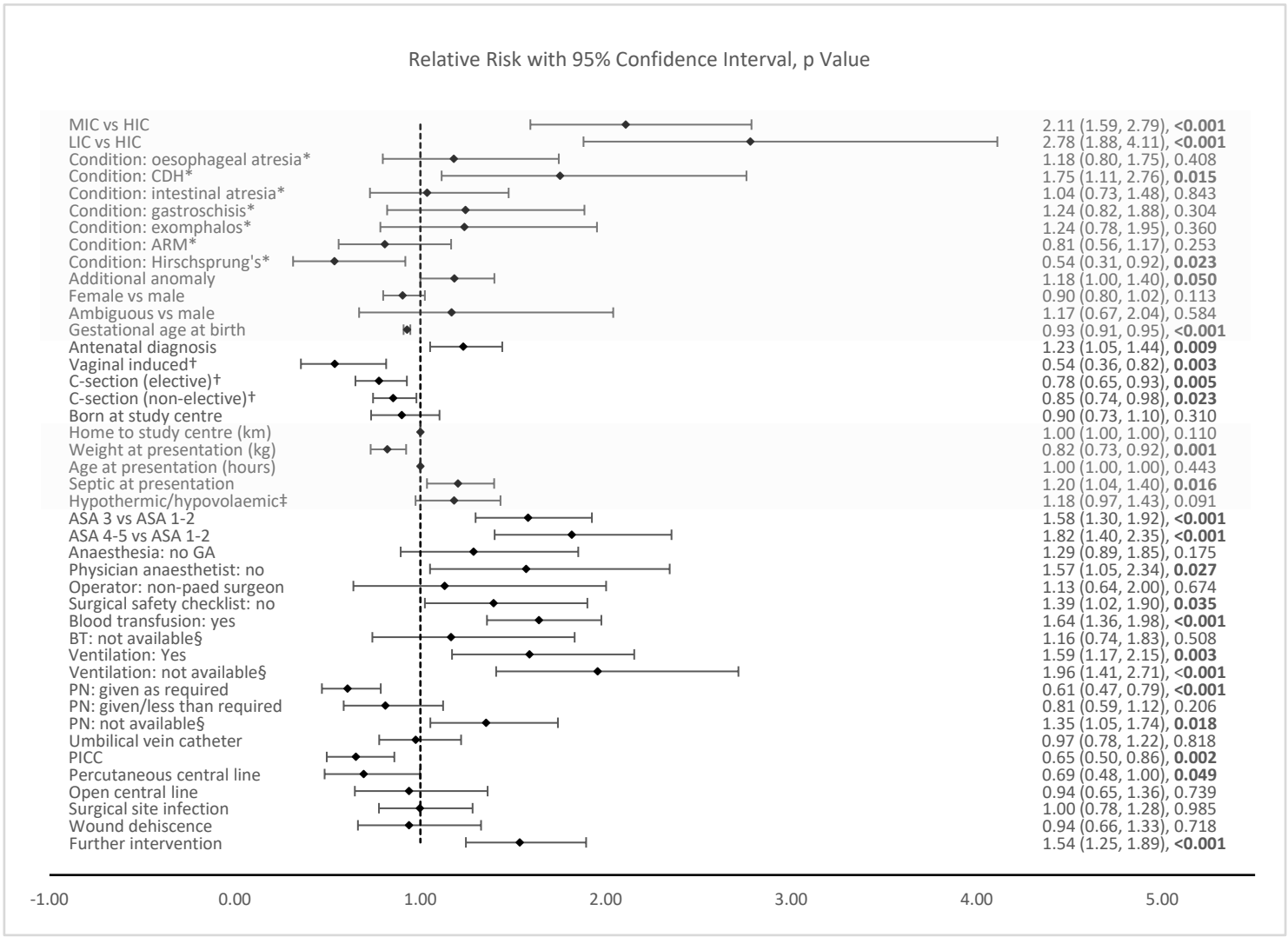


Figure 3: All-cause, in-hospital mortality rates (%, no. of deaths/no. of patients), with 95% confidence intervals



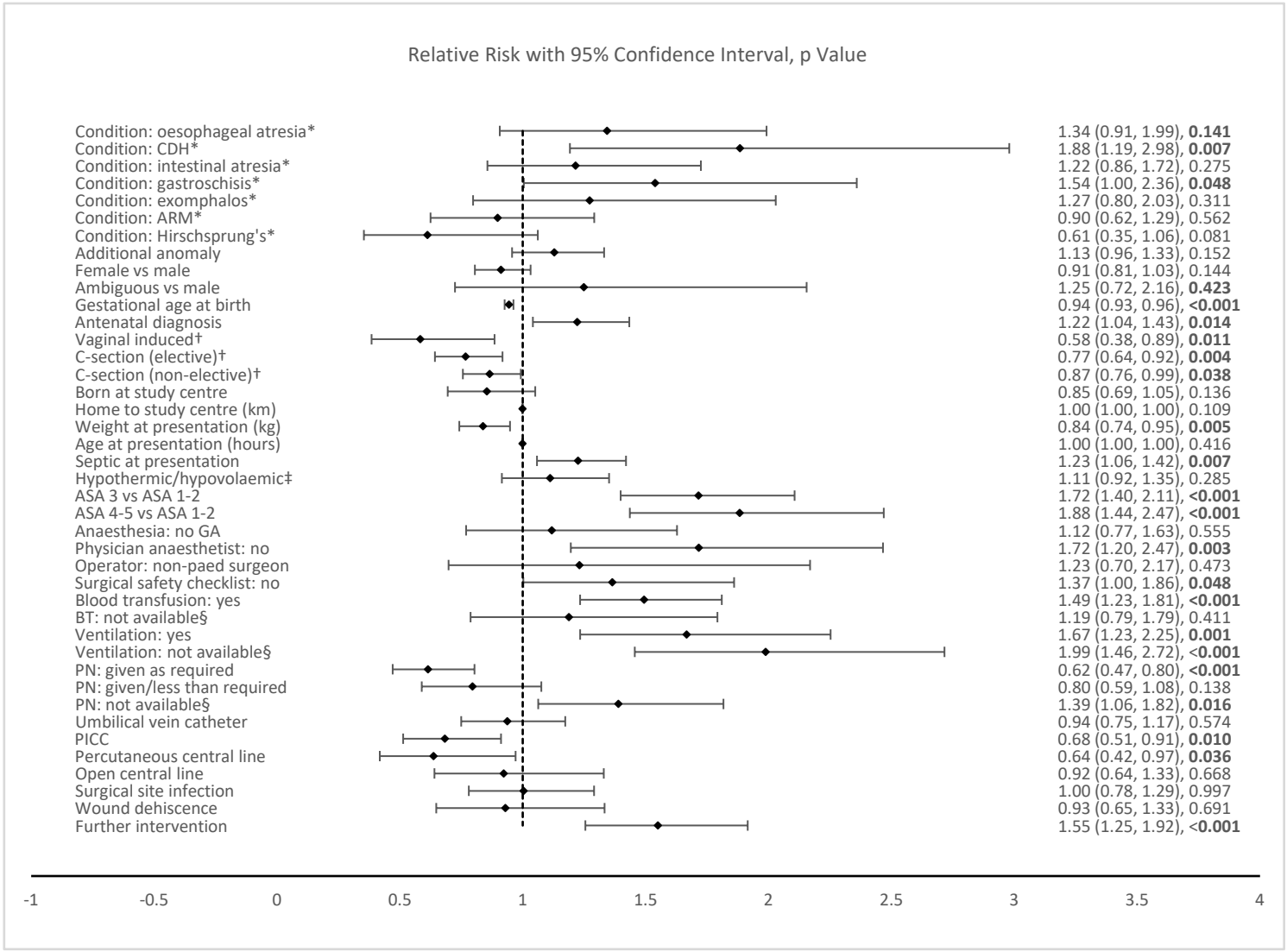
*Some patients had more than one study condition hence the overall number of deaths (n=670) is less than the sum of deaths from each condition. Only one patient with CDH presented in a LIC during the study period. CDH: Congenital diaphragmatic hernia. HIC: High-income countries. LIC: Low-income countries. MIC: Middle-income countries.

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



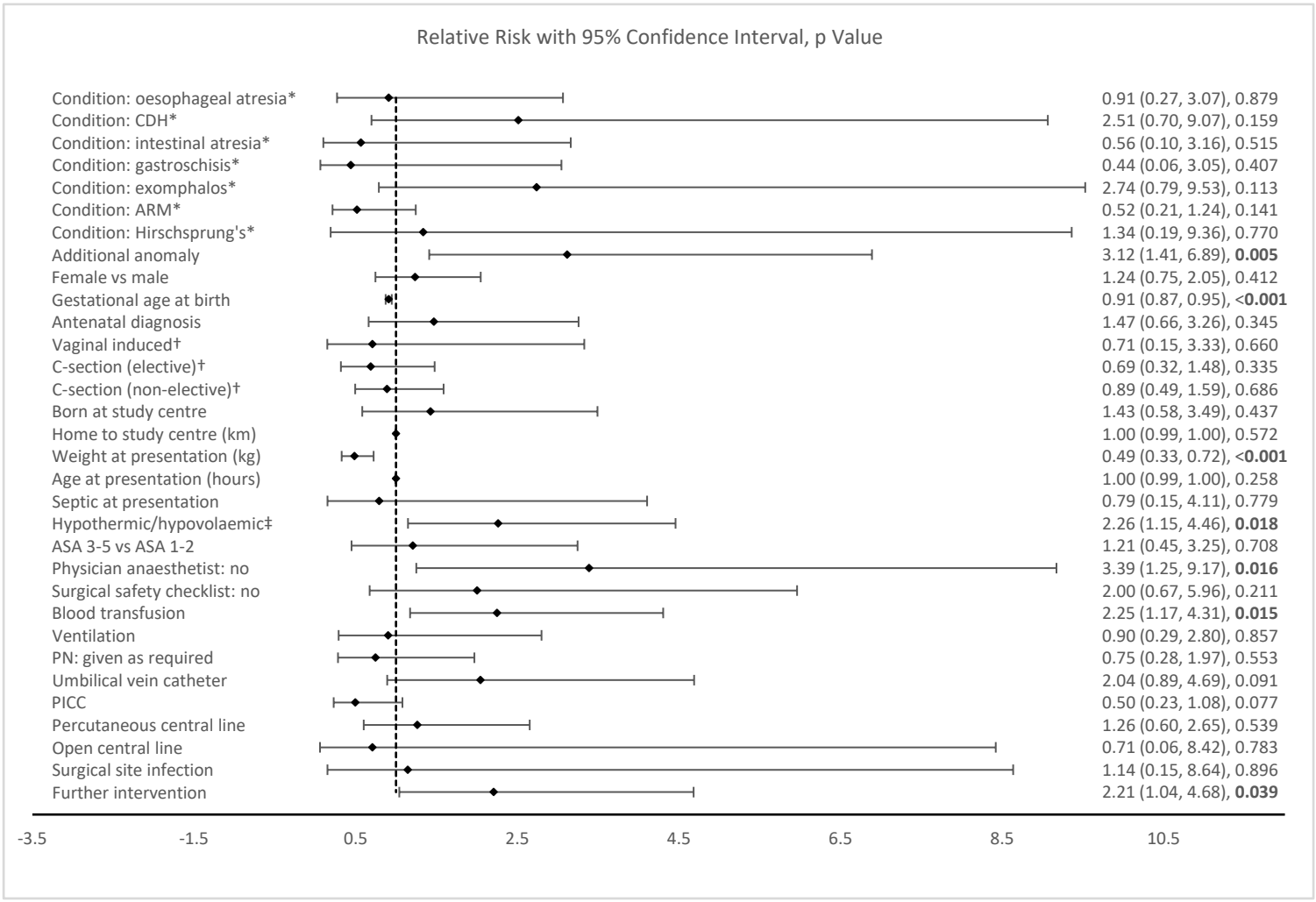
*Vs non-condition (i.e study patients with oesophageal atresia vs study patients without oesophageal atresia). †Vs spontaneous vaginal delivery. ‡At presentation. §When required. ARM: Anorectal malformation. ASA: American Society of Anesthesiologists score at primary intervention. BT: Blood transfusion. CDH: Congenital diaphragmatic hernia. C-section: Caesarean section. GA: General anaesthetic. HIC: High-income country. LIC: Low-income country. MIC: Middle-income country. PICC: Peripherally inserted central catheter. PN: Parenteral nutrition. Non-paed surgeon: Non-paediatric surgeon. Further intervention: Need for unplanned re-intervention within 30 days of surgery. Additional anomaly includes additional study condition(s) if present. Figure shading demarcates the variables into the following groups, respectively: demographics, antenatal care and birth, distance from home to study hospital and clinical condition at presentation, intra-operative factors, perioperative factors, and secondary outcomes. Of the 3849 study patients, 3735 were included within this multivariable model (n=114 excluded due to missing data).

Figure 5: Multivariable analysis of factors affecting mortality in low- and middle-income countries



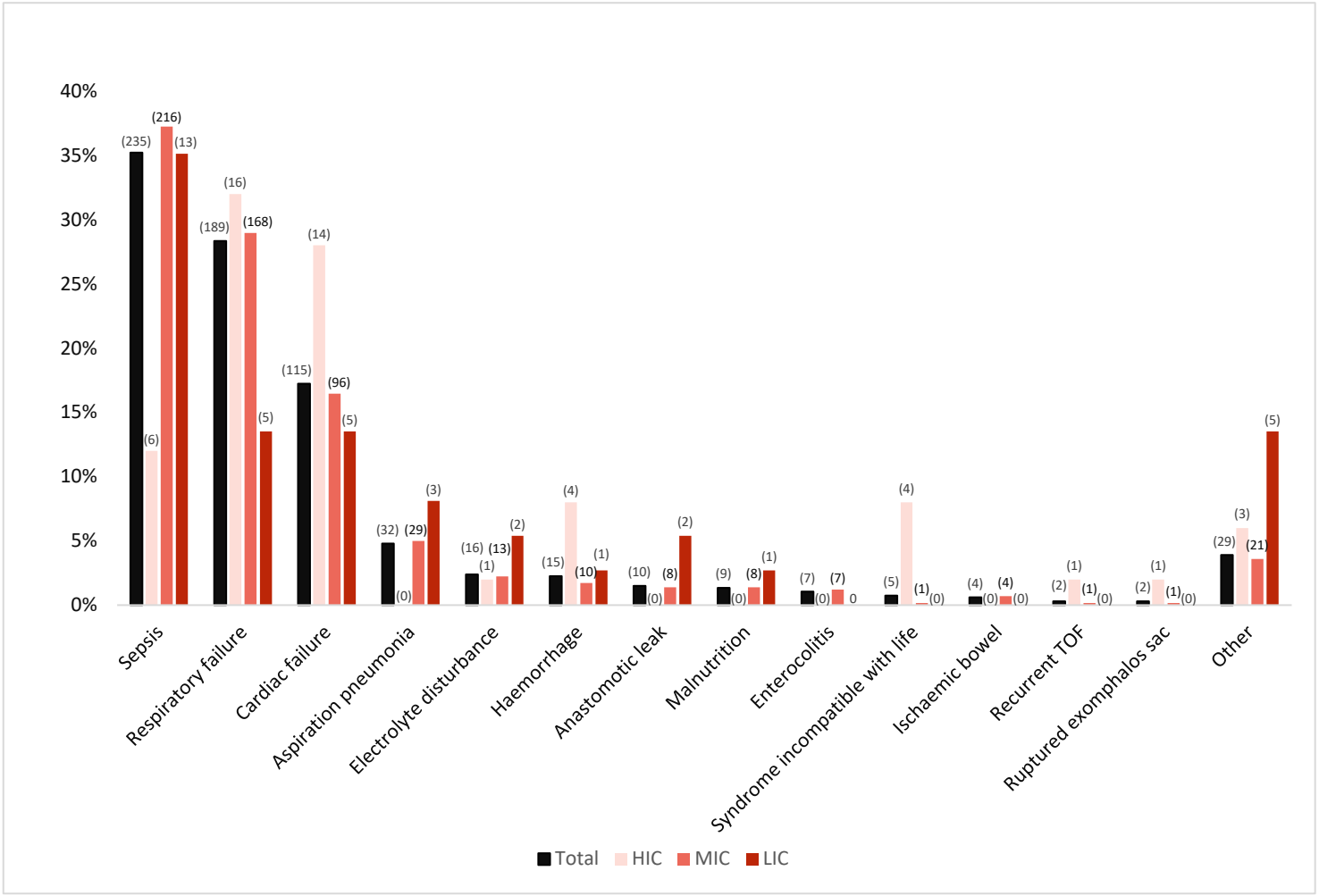
*Vs non-condition (i.e. study patients with oesophageal atresia vs study patients without oesophageal atresia). †Vs spontaneous vaginal delivery. ‡At presentation. §When required. ARM: Anorectal malformation. ASA: American Society of Anesthesiologists score at primary intervention. BT: Blood transfusion. CDH: Congenital diaphragmatic hernia. C-section: Caesarean section. GA: General anaesthetic. PICC: Peripherally inserted central catheter. PN: Parenteral nutrition. Non-paed surgeon: Non-paediatric surgeon. Further intervention: Need for unplanned re-intervention within 30 days of surgery. Additional anomaly includes additional study condition(s) if present. Figure shading demarcates the variables into the following groups, respectively: demographics, antenatal care and birth, distance from home to study hospital and clinical condition at presentation, intra-operative factors, perioperative factors, and secondary outcomes. Of the 2953 study patients from low- and middle-income countries, 2868 were included within this multivariable model (n=85 excluded due to missing data).

Figure 6: Multivariable analysis of factors affecting mortality in high-income countries



* Vs non-condition (i.e. study patients with oesophageal atresia vs study patients without oesophageal atresia). †Vs spontaneous vaginal delivery. ‡At presentation. ARM: Anorectal malformation. ASA: American Society of Anesthesiologists score at primary intervention. CDH: Congenital diaphragmatic hernia. C-section: Caesarean section. GA: General anaesthetic. PICC: Peripherally inserted central catheter. PN: Parenteral nutrition. Further intervention: Need for unplanned re-intervention within 30 days of surgery. Additional anomaly includes additional study condition(s) if present. Figure shading demarcates the variables into the following groups, respectively: demographics, antenatal care and birth, distance from home to study hospital and clinical condition at presentation, intra-operative factors, perioperative factors, and secondary outcomes. Of the 896 study patients from high-income countries, 857 were included within this multivariable model (n=39 excluded due to missing data).

Figure 7: Causes of death, % (no. of patients)



HIC: High-income countries. LIC: Low-income countries. MIC: Middle-income countries. TOF: Tracheo-oesophageal fistula.