Mortality rate of infants with gastroschisis and healthcare-associated infections admitted in the neonatal and paediatric intensive care units in a tertiary hospital in Tshwane district, South Africa

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Background. Gastroschisis is associated with significant morbidity and mortality in neonates. Healthcare-associated infections (HAIs) worsen outcomes, with a high mortality, and timely management is crucial for survival. In South Africa, data regarding mortality and HAI management in neonates with gastroschisis are limited.

Objectives. To evaluate the incidence of mortality and factors associated with mortality in neonates with gastroschisis admitted in the intensive care unit (ICU) and treated for HAI.

Methods. A retrospective study was conducted from July 2017 to October 2023. Eligible infants were identified using intensive care admission registers and the neonatal database. Patient demographics, treatment modalities, and outcomes, including mortality, were analysed. The Score for Neonatal Acute Physiology II (SNAP-II) severity was calculated retrospectively.

Results. A total of 66 neonates with gastroschisis and HAI that were admitted in the intensive care units were included in this study. Three neonates were managed for HAI twice, resulting in 69 HAI episodes. The incidence of culture-positive HAI was 77.9%, with a mortality of 84.8% per included neonate. Approximately half of the positive bacterial cultures with sensitivity testing were resistant to at least three classes of antimicrobial drugs. A SNAP-II score ≥30 was associated with higher mortality (p=0.038). Inotropic support was required in 76.8% of cases, correlating with higher mortality (p<0.001).

Conclusion. HAI remains a major cause of mortality in neonates with gastroschisis. Higher SNAP-II scores and inotropic support were associated with poor outcome. The high incidence of multidrug-resistant pathogens highlights the need for tailored antimicrobial strategies. Further research is needed to improve survival rates in this high-risk populations.

Keywords. gastroschisis; neonate; healthcare-associated infection; outcome; mortality.

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Healthcare-associated infections (HAIs) are a significant concern in infants with gastroschisis. In low- and middle-income countries (LMICs), sepsis causes >90% of deaths in these infants.[1] Septic markers, including C-reactive protein (CRP) and full blood count, aid diagnosis[2] but have limitations, especially in neonates with gastroschisis,[2] and blood culture remains the diagnostic gold standard.[3] Knowledge of common pathogens and antimicrobial susceptibility is crucial for selecting antimicrobials.[4,5]

The Score for Neonatal Acute Physiology-II (SNAP-II) assesses illness severity and predicts outcomes, although it is rarely used beyond the first 24 hours. It includes six parameters: lowest mean blood pressure (BP); lowest temperature; PaO_2/FiO_2 (PF) ratio; lowest pH; presence of multiple seizures; and urine output. SNAP-II helps predict mortality, morbidity and treatment effectiveness in critically ill neonates.[6-8] In the context of gastroschisis, it has been used to predict mortality, hospital stay, ventilation duration, total parenteral nutrition (TPN) duration and severe cholestasis.[6]

Many infants with gastroschisis are admitted to the Steve Biko Academic Hospital (SBAH) neonatal intensive care unit (NICU) and paediatric intensive care unit (PICU) for HAI managemen. However, their overall outcome is unclear. In LMIC, public sector intensive care unit (ICU) beds are limited, with high demand, so infants with gastroschisis are not routinely admitted to ICU, necessitating clinical vigilance to identify HAI early to avoid ICU admission. This study aims to determine the mortality rates in ICU-admitted infants with gastroschisis and HAI and identify variables associated with poor outcomes.

Methods

This retrospective study included infants with gastroschisis admitted in the NICU and PICU and who were treated for HAIs from 1 July 2017 to 31 October 2023. The ICU registers and neonatal database were used to identify eligible infants. Records were retrieved to identify infants with HAI during ICU admission. HAI diagnosis was verified retrospectively using CRP (>10 mg/L (NHLS reference range)) and/or positive cultures (diagnostic gold standard) after 72 hours of life. CRP values were not adjusted for gastroschisis as done in other studies. Blood and sterile central-line-tip cultures were analysed; data on paired blood cultures for central line-associated bloodstream infection (CLABSI), and other HAI, such as catheter-related urinary tract infections or ventilator-associated pneumonias, were not collected. It is unknown whether central catheters were removed at diagnosis.

Coagulase-negative staphylococci (CoNS) were deemed significant if cultured as the sole organism in an acutely ill infant requiring ICU admission. Other likely contaminants (*Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp., *Propionibacterium* spp. and diphtheroids) were excluded. Culture results, inflammatory markers, and white cell counts were obtained from the National Health Laboratory System (NHLS); differential counts were mostly unavailable as they are not routinely requested in the paediatric surgical ward. SNAP-II scores were calculated retrospectively. For all infants without urinary catheters (*n*=4), urinary output was considered normal (≥1 mL/kg/h) if there were ≥8 wet nappies in 24 hours. Infants without HAI and infants where care was redirected towards palliation were excluded. ICU and overall mortality rates were estimated using data from the paediatric surgical and neonatal ward registers, and the neonatal database. Owing to incomplete paediatric surgical ward registers, these outcomes were only calculated for the last 12 months (1 November 2022 to 31 October 2023) of the study period.

Continuous data were reported as mean values with standard deviation (SD) or medians with interquartile ranges (IQRs), depending on data distribution. The two-sample *t*-test and Mann-Whitney *U*-test were used to assess significance ($p<0.05$). Discrete data were reported as percentages and analysed using Fisher's exact test. Pearson Chi-squared test identified variables associated with mortality. Odds ratio (OR) with 95% confidence intervals (CI) were determined using logistic regression.

Ethics approval was obtained from the University of Pretoria Faculty of Health Sciences Research Ethics Committee (ref. no. 565/2022), as well as institutional approval from the National Health Research Database (ref. no. GP_202210_030).

Results

Study participants and episodes of healthcare-associated infections

Fig. 1 shows 96 ICU care episodes for infants with gastroschisis during the study. After excluding 27 episodes, 69 episodes of infants with gastroschisis and HAI remained and were referred to as HAI episodes. Ten infants were in NICU before acquiring an HAI, while 59 were admitted to ICU for additional support. Some infants had multiple ICU admissions for HAI; thus, there were 69 HAI episodes involving 66 infants, with 3 requiring two separate admissions.

Infants with gastroschisis over a 12-month period

During the last 12 months of the study, 25 infants with gastroschisis were admitted to the hospital. A total of 17 infants were initially admitted to the paediatric surgical ward, with 9 (52.9%) later transferred to ICU for HAI management, and 4 others were transferred for non-HAI-related escalation of care. The remaining 8 infants were admitted directly to the neonatal ward. Overall, 84.0% (*n*=21/25) of the infants with gastroschisis were diagnosed with an HAI during admission.

Characteristics of included infants

Table 1 summarises the characteristics of the infants (*n*=66), including survivors (*n*=10) and non-survivors (*n*=56). Most infants were of low birthweight (LBW) (*n*=52; 78.8%) and premature (*n*=40; 63.5%). Two-thirds were born vaginally (*n*=43; 66.2%). The mean (SD) day of life of admission to SBAH was day 2 (1). The majority were admitted to the paediatric surgical ward (*n*=43; 65.2%). Indications for admission to NICU include birthweight <1 500 g and the need for invasive ventilation. Complex gastroschisis was associated with the following anomalies: fistula; atresia; perforation; malrotation; necrotic bowel; and absent caecum. Antenatal sonar was performed in 18.2% (*n*=12) of mothers, with four infants being diagnosed antenatally. Only seven (10.8%) infants underwent primary surgical repair and four (6.1%) underwent silo-bag reduction followed by surgical closure due to the presence of complications; i.e. intestinal fistula (*n*=1); small-bowel atresia (*n*=2); not documented *n*=1). The majority of infants (*n*=64; 97.0%) had a central venous catheter (CVC), with the most common type being a tunnelled CVC (Broviac (Becton Dickinson, USA)) (*n*=51; 79.7%). Enteral feeds were initiated in 19 of 62 infants (30.6%; missing data, *n*=4) during the admission, with 8 being initiated prior to HAI diagnosis. The mean (SD) day of initiation of enteral feeds was day 22 (9).

Mortality, ICU admission, management (ventilation and inotropic support) and length of stay

In the last 12-month period, overall mortality rate for infants with gastroschisis was 72.0% (*n*=18/25) and mortality secondary to HAI was 52.0% (*n*=13/25). However, over the entire study period, the mortality rate per included infant in ICU with HAI was 84.8% (*n*=56/66) and per HAI episode was 81.2% (*n*=56/69). Of the HAI episodes, 95.7% (*n*=66/69) were admitted in NICU and 3 infants were admitted to PICU (presumably due to bed shortages). For the included HAI episodes, the mean (SD) age at death was 19 days (15). The median (IQR) day of life of admission to ICU was 8 (3 - 16) days. Similarly, the median (IQR) day of life that HAI was diagnosed was 8 (5 - 17.5) days. All infants required invasive ventilation with a median (IQR) length of 5 (3 - 16) days. The median (IQR) length of ICU stay was 7 (3 - 11) days; 6 (3 - 11) days for non-survivors and 10 (7 - 12) days for survivors, which were significantly different ($p=0.027$). Three-quarters (*n*=53; 76.8%) of episodes required inotropic/vasopressor support, with a significant difference between surviving and non-surviving episodes (15.4% (*n*=2) v. 91.1% (*n*=51), respectively ($p<0.001$)).

Healthcare-associated infections with positive cultures and resistance patterns

Three-quarters of HAI episodes had at least one positive culture (*n*=53; 77.9%) and two infants had no culture performed. Twelve, 3 and 1 infant had a second, third and fourth positive culture of a different organism during a single ICU admission, with a total of 69 positive cultures overall. Six cultures grew more than one organism (total organisms cultured, *n*=76). Sixty-six were blood and 3 were central-line tip cultures (CRPs of all 3 infants >100 mg/L). Some positive cultures of different organisms were identified during the same HAI episode, while others indicated the onset of a new HAI. Most pathogens were bacterial (*n*=60/76; 78.9%), led by *Acinetobacter baumanii* (*n*=19; 25.0%), all of which were carbapenem-resistant, followed by *Klebsiella pneumoniae* (*n*=11; 14.5%), with 7 cultures exhibiting carbapenem resistance. *Candida parapsilosis* was the third most common isolate (*n*=8; 10.5%) followed by *Candida albicans* and *Escherichia coli* (*n*=5 each; 6.6%). The most recent positive culture was carbapenem-resistant *Acinetobacter* (CRA) in 15 episodes and carbapenem-resistant *Enterobacterales* (CRE) in 5 episodes, neither having a significant survival difference ($p=0.415$ and $p=1.000$, respectively). Of 62 bacterial organisms with resistance data, 28 (45.2%) were resistant to ≥3 antimicrobial classes.

Antimicrobial choice and duration

The median (IQR) duration of antimicrobials was 5.5 (3 - 9) days and 7 (4 -14) days for the first and second HAI episode, respectively. Meropenem plus linezolid was the most common regimen in first episodes (53%; *n*=35) followed by meropenem monotherapy

(22.7%; *n*=15) and piperacillin-tazobactam plus amikacin (12.1%; *n*=8). For second episodes, 46.2% (*n*=6) were already receiving antimicrobials and were not changed, while 23.1% (*n*=3) were initiated on meropenem plus linezolid. Micafungin was added in 21.7% (*n*=15/69) and 40% (*n*=6/15) of first and second episodes, respectively. Amphotericin B was rarely used (*n*=2).

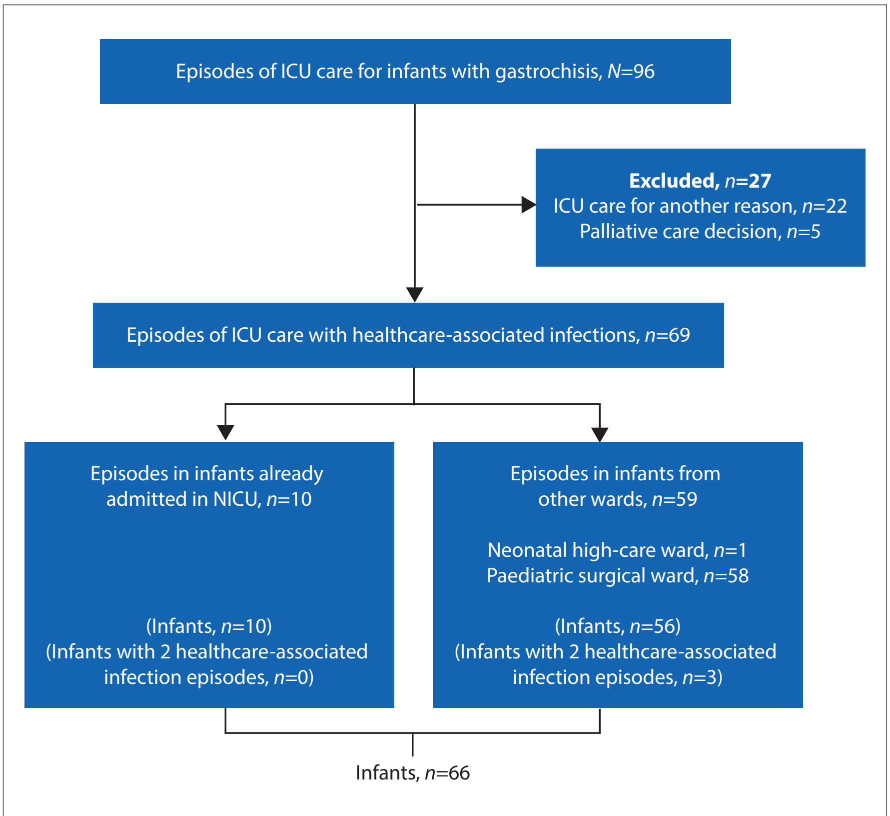

Fig. 1. ICU care episodes for infants with gastroschisis.

Infection markers

The mean (SD) CRP at diagnosis of first HAI episode was 125 (78) mg/L (*n*= 67; 2 samples rejected by NHLS). The highest mean (SD) CRP per HAI episode (*n*=68) exceeded 100 mg/L in both survivor and non-survivor episodes (105 (71) mg/L v. 148 (76) mg/L; *p*=0.068). The highest mean (SD) peak white cell count (WCC) per HAI episode was 21.3 $\times 10^9$/L (13.7) and the lowest was 8.5 $\times 10^9$/L (4.4). NHLS WCC normative values vary by age: 1 - 7 days: 9.0 - 30.0 $\times 10^9$/L; 8 - 28 days: 5.0 - 20.0 $\times 10^9$/L; >28 days: 5.0 - 19.5 $\times 10^9$/L

SNAP-II and association with mortality

SNAP-II scores were calculated retrospectively where information was available (*n*=66). For infants already admitted in ICU, scores were determined from the variables available at clinical deterioration when inflammatory markers and cultures were performed; and for those who were not already admitted to ICU, the score was calculated using variables recorded at the time around admission to ICU. The overall mean (SD) score was 28 (15), significantly higher in non-surviving episodes compared with surviving episodes (30 (15) v. 18 (12); *p*=0.017). A SNAP-II score of ≥30 was associated with an increased odds for mortality (OR 5.0; 95% CI 1.0 - 27.2; *p*=0.038) (Table 2).

Logistic regression

Logistic regression showed that the probability of death was 88% for a SNAP-II score ≥30 (sensitivity 53%, specificity 61%). However, the probability of death was 91% for a score ≥35 (sensitivity 45%, specificity 90%). Each 1-point increase in the SNAP-II score was associated with a 6.5% increase in mortality (*p*=0.024).

Associations with mortality

SNAP-II parameters (pH, BP, PF ratio and temperature), base deficit (BD) and lactate levels were analysed to determine an association with mortality but showed no significant associations. Additional variables

Table 1. Variables of all included infants, including anthropometry, place of birth, gender, HIV-exposure and type of gastroschisis (*N*=66), *n* (%)*

	All infants (*n*=66)	Survivors (*n*=10)	Non-survivors (*n*=56)	*p*-value
Mean (SD) birthweight (g)	2 118 (523)	2 308 (629)	2 084 (501)	0.215
Mean (SD) gestational age (weeks)	36 (2)	37 (2)	36 (2)	0.287
Outborn (including BBA)	57 (86.4)	9 (90.0)	48 (85.7)	1.000
Male	37 (56.1)	3 (30.0)	34 (60.7)	0.092
5-minute Apgar score ≥7†	62 (98.4)	9 (100)	53 (98.1)	1.000
HIV-exposed	14 (21.2)	2 (20.0)	12 (21.4)	1.000
SGA (birthweight <10th percentile)†	31 (49.2)	4 (44.4)	27 (50.0)	1.000
Admitted to paediatric surgical ward	43 (65.2)	6 (60.0)	37 (66.0)	0.730
Complex gastroschisis‡	14 (21.9)	2 (22.2)	12 (21.8)	1.000
Silo-bag reduction§	54 (83.1)	7 (77.8)	47 (83.9)	0.606

BBA = born before arrival; SD = standard deviation; SGA = small-for-gestational age.
*Unless otherwise specified.
†Missing information for 3 infants (all infants=63; survivors=9; non-survivors=54).
‡Missing information for 2 infants (all infants=64; survivors=9; non-survivors=55).
§Missing information for 1 infant (all infants=65; survivors=9; non-survivors=56).

analysed included place of birth, birthweight, gestational age, SGA, 5-minute Apgar score <7, admission ward, age at diagnosis of HAI, positive culture, type of gastroschisis, method of closure, and inotropic/vasopressor support (Table 2). Only inotropic/vasopressor support were significantly associated with mortality.

Discussion

The present study highlights the high ICU mortality in infants with gastroschisis and HAI in LMIC. Similar to other South African (SA) studies, most infants were of LBW and premature.[9-11] Age of admission (2 days) was on average 1 day later than that reported in other SA studies,[9,10] with few inborn infants (13.6%). Similar to the findings of Stevens *et al.*,[10] admission ward was not associated with mortality.

Mortality and interventions to improve survival of infants with gastroschisis

The overall 12-month mortality rate for infants with gastroschisis was high (72%) compared with <5% in HICs.[12,13] ICU mortality for infants with HAI was even higher at 84.8%. Contributing factors may include late presentation, healthcare system differences, and high HAI prevalence. While overall mortality aligns with other LMICs (30 - 100%),[12] it exceeds rates reported in other SA studies (16.0 - 65.0%).[9-11] No previous studies focus specifically on ICU mortality in gastroschisis with HAI – the main aim of this study. However, ICU admission suggests higher illness severity. Wright *et al.*[13] suggest simple postnatal interventions can improve survival in LMIC. Wesonga *et al.*[14] reduced mortality from 98% to 58% in Uganda using a low-cost protocol without TPN or ICU facilities. Modifiable factors were lack of antenatal diagnosis, basic neonatal care, staffing, delayed surgery, limited TPN and intravenous access.[14] Oyinloye *et al.*[15] (Nigeria) identified similar factors to be responsible for the high mortality of 77.8%. We propose that delivery in a tertiary-level hospital equipped to manage gastroschisis will improve outcome and survival. In this study, only 13.6% of infants were inborn and 6.1% had an antenatal diagnosis, highlighting the need for improved antenatal screening and *in utero* referral to appropriate centres. Delayed admission (up to 2 days post-delivery) likely contributed to high HAI and mortality rates, which could be mitigated by antenatal diagnosis and inborn delivery. Although our institution has adequate intravenous access, TPN and ICU facilities, staffing shortages may delay recognition of deterioration, reflected by high SNAP-II scores. Late presentation likely precluded primary surgical closure, potentially increasing HAI risk due to prolonged skin barrier disruption.

Diagnosis of healthcare-associated infections in infants with gastroschisis

Table 2. Variables analysed for an association with mortality in infants with gastroschisis and HAIs

Variable	OR	95% CI	*p*-value
SGA	0.6	0.2 - 2.3	0.486
Outborn	0.5	0.1 - 4.1	0.768
Surgical ward admission	1.8	0.5 - 6.3	0.343
Complex gastroschisis	1.5	0.3 - 7.9	0.631
Silo-bag closure	0.7	0.1 - 6.9	0.667
Culture-positive HAI	2.8	0.7 - 10.8	0.115
SNAP-II ≥30	5.0	1.0 - 27.2	0.038
Inotrope/vasopressor support	51.0	4.4 - 591.4	<0.001

HAI =healthcare-associated infection; OR = odds ratio; CI = confidence interval; SGA = small-for-gestational age; SNAP-II = Score for Neonatal Acute Physiology II.

Although CRP was elevated in survivors and non-survivors, it was not statistically different. Most studies don't report on a CRP cut-off that is significant for diagnosis of HAI in infants with gastroschisis, although Gom *et al.*[9] reports using a CRP of >40 mg/L to define sepsis in the absence of a positive culture. In most studies, including this study, clinical assessment was used to support the suspicion of HAI. However, of the 16 infants with negative cultures in this study, 15 had a CRP >40 mg/L at the time of HAI diagnosis (one infant had a CRP of 39 mg/L).

Incidence of healthcare-associated infections and associated mortality in infants with gastroschisis

The proportion of infants with gastroschisis diagnosed with HAI (84.0%) over the last 12-month period of this study is higher than that reported by Stevens *et al.*[10] in the same setting (55.0%). However, HAI-related mortality was similar (52.0% v. 57.6%).[10] Gom *et al.*[9] and Oyinloye *et al.*[15] reported sepsis in 68.5% and 100% of infants, with a sepsis-related mortality of 61.6% and 78.6%, respectively. In contrast, van Eck[11] and Wesonga *et al.*[14] reported much lower sepsis-related deaths (6.4% and 11.8%, respectively). The substantially higher mortality observed in this study underscores the need for improved infection prevention, early HAI diagnosis and timely antimicrobial therapy.

Organism identification and antimicrobial choice

Gom *et al.*[9] reported Gram-negative bacteria were predominant (52.4%), followed by fungi (26.2%) and Gram-positive bacteria (21.3%). Similarly, this study found Gram-negative bacteria in 60.5% of cases (*n/N*=46/76), including *Acinetobacter baumannii* (25.0%) and *Klebsiella pneumoniae* (14.5%), both often carbapenem-resistant. Antimicrobial resistance significantly increases mortality risk, as shown globally.[16] Since local resistance data for non-surgical infants are unavailable, it is unclear if resistance is unique to gastroschisis cases. Fungi were the second most common pathogens (21.1%; *n/N*=16/76), followed by Gram-positive bacteria (18.4%; *n/N*=14/76), consistent with Gom *et al.*[9] but differing from a Brazilian study where Gram-positive bacteria were most prevalent (51.1%).[5] Most infants appropriately received Gram-negative antimicrobial cover at diagnosis; however, over half also received Gram-positive cover, which may have been unnecessary given that fewer than 20% of the isolates were Gram-positive. This practice may reflect patterns seen in other settings, such as Brazil, where Gram-positive infections predominate. However, based on our findings, we recommend initiating only Gram-negative cover pending culture results.

Timing of death and associated factors

The present study reports a mean age at deaths of 19 days compared to 10 days reported by Gom *et al.*[9] This difference cannot be explained by lack of ICU facilities, however. We postulate that perhaps they had more deaths earlier secondary to bowel necrosis, which was responsible for 28.9% of the deaths in their study;[9] such cases were excluded from our analysis owing to palliative care. A study in the USA also found that delayed antibiotic treatment was an independent risk factor for death,[17] which may explain the earlier deaths seen in Gom *et al.*'s study,[9] as 61.1% of deaths were sepsis-related.[9]

SNAP-II as a predictor of mortality

Higher SNAP-II scores were associated with increased mortality, particularly scores ≥30 (OR 5.0; *p*=0.038). A score ≥35 predicted a 91% probability of mortality, with high specificity (90%), but low sensitivity (45%), meaning some low-score deaths may be missed. However, a score ≥35 is a strong indicator of poor outcome. This aligns with global studies on SNAP-II's predictive value.[6-8]

Variables associated with mortality

The present study also investigated mortality associations with SNAP-II components, BD and lactate. Similar to Stevens *et al.*,[10] no association was found with variables such as 5-minute Apgar and BD. However, Stevens *et al*.[10] noted that each 1 mmol/L decrease in bicarbonate increased mortality 1.37-fold. In our study, only inotropic/vasopressor support was associated with death (OR 51.0; p<0.001), likely reflecting illness severity rather than a direct cause. In contrast, Sundaram *et al*.[7] reported a significant association with mortality with mean BP, lowest pH and urine output. The reason for this discrepancy remains unclear.

Study limitations

This retrospective study had some incomplete records. SNAP-II scores were calculated retrospectively, possibly introducing minor inaccuracy. Unfortunately, fewer HAI episodes than expected were identified (n=120), which may impact the validity of the results due to lower statistical power and reduced generalisability .

Conclusion and recommendations

The present study underscores the high mortality associated with gastroschisis and HAI treated in ICU. Given the limited availability of ICU beds in the public sector, objective tools like the SNAP-II score may help guide decision-making around ICU admission, particularly for infants with a poor prognosis. While no individual parameter was significantly associated with outcome, a SNAP-II score of ≥35 was associated with a 91% probability of mortality among infants with gastroschisis admitted in ICU for HAI. We therefore propose that the SNAP-II score be considered prior to ICU admission; however, priority should be given to strengthening infection prevention and early recognition of clinical deterioration, potentially reducing the need for ICU admission. Although the present study aligns with previous research, prospective research to validate the predictive accuracy of the SNAP-II score in this context is needed.

Future research should focus on reducing infection and improving survival, drawing on successful gastroschisis protocols from other LMICs to identify and address local care gaps.

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