


Predicting mortality in neonates with gastroschisis in a Southeastern state of Brazil

Virginia Maria Muniz^{1,2} , Antônio Lima Netto² , Katia Souza Carvalho³ , Claudia Saleme do Valle⁴ , Cleodice Alves Martins⁵ , Luciane Bresciani Salaroli^{1,5*} , Eliana Zandonade¹ 

SUMMARY

OBJECTIVE: This study aimed to verify risk factors associated with gastroschisis mortality in three neonatal intensive care units located in the state of Espírito Santo, Brazil.

METHODS: A retrospective cohort study of neonates with gastroschisis was performed between 2000 and 2018. Prenatal, perinatal, and postsurgical variables of survival or nonsurvival groups were compared using chi-square statistical test, t-test, Mann-Whitney U test, and logistic regression. Tests with $p < 0.05$ were considered statistically determined.

RESULTS: A total of 142 newborns were investigated. Mean maternal age, gestational age, and birth weight were lower in the group of nonsurvival ($p < 0.05$). Poor clinical conditions during admission, complex gastroschisis, closure with silo placement, the use of blood products, surgical complications, and short bowel syndrome were more frequent in the nonsurvival group ($p < 0.05$). Complex gastroschisis [adjusted odds ratio (OR) 3.74, 95% confidence interval (95%CI) 1.274–11.019] and short bowel syndrome (adjusted OR 7.55, 95%CI 2.177–26.225) increased the risk of death. Higher birth weight inversely reduced the risk for mortality (adjusted OR 0.99, 95%CI 0.997–1.000).

CONCLUSION: Complex gastroschisis and short bowel syndrome increased the risk of death, with greater birth weight being inversely correlated with the risk of mortality. The findings of this research can contribute to the formulation of protocols to improve the quality and safety of care in order to reduce neonatal mortality associated with gastroschisis.

KEYWORDS: Infant, newborn. Gastroschisis. Infant mortality. Congenital abnormalities. Risk factors.

INTRODUCTION

The advances in neonatal intensive care, improvement of parenteral nutrition solutions, and evolution of pediatric surgical strategies have contributed to reduce the mortality of gastroschisis rates to less than 10% in high-income countries (HICs). However, postsurgical complications and length of stay remain high. In these countries, efforts to improve outcomes in gastroschisis are centered on reducing morbidity and the burden on hospitals and healthcare systems¹. Contrariwise, in low-middle income countries (LMICs), morbidity and mortality rates related to this congenital anomaly are still unacceptably high, conceivably due to limited financial resources and the fragility of the healthcare systems^{2,3}. Among the risk factors associated with mortality in newborns with gastroschisis are low birth weight⁴, prematurity^{4,5}, complex gastroschisis (CG)⁵, sepsis^{4,6}, no antenatal diagnosis, outborn babies, and poor clinical conditions at admission⁷.

Assuredly, the proper identification of risk factors for gastroschisis mortality may have a pivotal role in the definition of strategies by public health authorities and hospital managers to improve the survival rates of neonates with this birth defect. The aim of this study was to identify risk factors associated with gastroschisis mortality in three neonatal intensive care units located in the Metropolitan Region of Great Vitória of Espírito Santo (GVMR-ES), Brazil. We present the following article in accordance with the STROBE reporting checklist⁸.

METHODS

Study population

A retrospective cohort study was conducted with all newborns admitted to three neonatal intensive care units (NICU) at

¹Universidade Federal do Espírito Santo, Postgraduate Program in Collective Health – Vitória (ES), Brazil.

²Hospital Estadual Infantil Nossa Senhora da Glória – Vitória (ES), Brazil.

³Hospital Estadual Infantil e Maternidade Alzir Bernardino Alves – Vila Velha (ES), Brazil.

⁴Hospital Estadual Dr. Jayme Santos Neves – Serra (ES), Brazil.

⁵Universidade Federal do Espírito Santo, Postgraduate Program in Nutrition and Health – Vitória (ES), Brazil.

*Corresponding author: lucianebresciani@gmail.com

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GVMR-ES between January 2000 and December 2018, with the diagnosis of isolated gastroschisis, confirmed by a pediatric surgeon. The data collection period varied according to the availability of medical records from each hospital: NICU A from January 1, 2000, to December 31, 2018; NICU B from February 23, 2013, to December 31, 2018; and NICU C from November 11, 2010, to December 31, 2018. Exclusion criteria were genetic syndromes or other major congenital malformations and newborns who were transferred to other hospitals.

Patients were treated by healthcare teams from each study site. NICU A is located in a pediatric hospital and only admits outborn babies. NICU B is attached to a maternity hospital and only admits inborn babies. NICU C is also attached to a maternity hospital; however, it admits both inborn and outborn babies.

Patients were divided into two groups: survival and non-survival. To determine the possible association of probable causes of mortality after birth, the study included data from prenatal, perinatal, and postsurgical care until the outcome of discharge or death.

Study variables

Variables of prenatal and perinatal periods were maternal age, prenatal diagnosis by ultrasound, number of prenatal consultations, route of delivery, 1-min APGAR score and 5-min APGAR score⁹ bulletin 1 and 2, gestational age by somatic Capurro method, birth weight, gender, birthplace (inborn or outborn), time between birth and first repair surgery, and clinical conditions at admission indicated by clinical pediatrician's notes as poor conditions (dysthermia, hypoactivity, hydroelectrolytic or metabolic disorders, and infection) or good conditions, since none of the three services have used a standardized neonatal death prediction score. Variables of postoperative care were the type of gastroschisis according to the surgeon's report by complex (atresias, strictures, volvulus, necrosis, and large gastroschisis) or simple¹⁰, time on mechanical ventilation (MV), total parenteral nutrition time (TPN), use of vasoactive substances, use of antimicrobials, type of venous access (peripherally inserted central catheter [PICC], central intravenous access catheter by puncture or dissection, and peripheral intravenous access), use of blood products, clinical neonatal sepsis diagnosed by attending physician or confirmed by blood culture, surgical complications (surgical reinterventions, compartment syndrome, and necrotizing enterocolitis [NEC] after closure), short bowel syndrome (SBS) defined as the need for TPN greater than 60 days after intestinal resection or intestinal length less than 25% of expected for age¹¹, and length of stay (LOS). Furthermore, only variables with complete data in the medical record were included in this study.

Statistical analysis

The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22.0 for Windows. Data were presented with absolute and relative frequencies for categorical variables. The chi-square test was used for categorical variables. For quantitative variables, normality tests were performed. In the case of normality, Student's t-test was performed, and results were presented with means and standard deviations. In the case of non-normality, Mann-Whitney nonparametric test was utilized, and results were presented with median and interquartile range (IQR). The level of significance adopted was 5% ($p < 0.05$).

Some variables were included in the logistic regression model when the p-value is less than 0.20 in bivariate analysis. For logistic regression, the entry of variables in blocks by the Enter method was used. Crude odds ratios (OR) and adjusted OR (aOR) were calculated with 95% confidence intervals (95%CI). The level of significance adopted was 5% ($p < 0.05$).

Ethical and legal aspects of research

This project was approved by Research Ethics Committee – Opinion n° 2671249/CEP – CIAS/Unimed-Vitória (CAAE 87878918.1.0000.5061). Terms of adherence to this research by hospitals were obtained through the Secretary of State for Health – ES.

RESULTS

The data from 144 newborns with gastroschisis were assessed, and the data from 2 newborns were excluded since they were transferred to another NICU not a participant in the current study, after being operated on.

NICU admissions by birthplace were: NICU A–74 (100% outborn), NICU B–29 (100% inborn), and NICU C–39 (87% inborn/13% outborn). The total mortality rate was 33% (NICU A: 21/28%, NICU B: 10/35%, and NICU C: 17/43%, $p=0.266$). Sepsis was the most common cause of death (58%), followed by NEC (19%) and compartment syndrome (8%). Moreover, complications that led to SBS were multiple surgeries with bowel resection (13/42%), NEC (9/29%), dependency on parenteral nutrition over 60 days after surgery to repair intestinal stenosis or atresias (8/26%), and compartment syndrome (1/3%). The total rate of CG was 44% (63/142). The SBS rate in patients with CG was 74% (23/31, $p=0.000$).

Table 1 shows the bivariate analysis regarding the characteristics of the prenatal, perinatal, and postsurgical cares for neonates, according to groups of survival or nonsurvival.

Table 1. Bivariate analysis of sample characterization variables referring to prenatal, perinatal, and postsurgical care of patients with gastroschisis admitted to three neonatal care units at the Greater Vitória Metropolitan Region between 2000 and 2018, according to groups of survival or nonsurvival.

| Variables | Category | Survival N=94 | Nonsurvival N=48 | Total N=142 | P-value |
|--|------------------|------------------|---------------------|----------------|-----------------------|
| | | N (%) | N (%) | Total | |
| Admission hospital | NICU A | 53 (56.4) | 21 (43.8) | 74 (52.1) | 0.266 [†] |
| | NICU B | 19 (20.2) | 10 (20.8) | 29 (20.4) | |
| | NICU C | 22 (23.4) | 17 (35.4) | 39 (27.5) | |
| Maternal age (years) mean/SD | | 20 (±3.7) | 18.5 (±4.0) | 19.5 (±3.8) | 0.040 ^{†*} |
| Antenatal consultations | ≥6 | 45 (47.9) | 22 (45.8) | 67 (47.2) | 0.818 [†] |
| Antenatal diagnosis | Yes | 50 (53.2) | 32 (66.7) | 82 (57.7) | 0.124 [†] |
| Route of birth | Cesarean section | 57 (60.6) | 33 (68.7) | 90 (63.4) | 0.343 [†] |
| Gender | Male | 47 (50) | 31 (64.6) | 78 (54.9) | 0.099 [†] |
| Gestational age (weeks) mean±SD | | 37.2 (±1.8) | 35.8 (±2.4) | 36.7 (±2.1) | 0.001 ^{†***} |
| Birth weight (g) mean±SD | | 2.504 (±457) | 2.188 (±467) | 2.397 (±483) | 0.000 ^{†***} |
| Apgar 1 mean±SD | | 7.4 (±1.4) | 6.9 (±1.8) | 7.2 (±1.5) | 0.057 [†] |
| Apgar 2 mean±SD | | 8.5 (±0.9) | 8.5 (±1.1) | 8.5 (±0.9) | 0.833 [†] |
| Birth-surgery time (h) median (IQR) | | 3.0 (1–7) | 2 (1–7) | 3 (1–7) | 0.455 [§] |
| Birthplace | Inborn | 39 (41.5) | 24 (50) | 63 (44.4) | 0.334 [†] |
| Clinical conditions | Poor | 20 (21.3) | 21 (43.8) | 41 (28.8) | 0.005 ^{†***} |
| Gastroschisis | Complex | 28 (29.8) | 35 (72.9) | 63 (44.3) | 0.001 ^{†***} |
| Wall closure | Silo | 17 (18.1) | 23 (47.8) | 40 (28.1) | 0.001 ^{†***} |
| Venous access | PICC | 48 (51) | 19 (39.6) | 67 (47.2) | 0.378 [†] |
| Vasoactive substances | Yes | 60 (63.8) | 38 (79.2) | 98 (69) | 0.062 [†] |
| Antibiotics | ≥2 courses | 71 (75.5) | 36 (75) | 107 (75.4) | 0.945 [†] |
| Time on MV median (IQR) | | 6 (4–11) | 8 (3–15) | 6 (4–13) | 0.456 [§] |
| Time on TPN median (IQR) | | 22 (16–30) | 16 (0.5–35.5) | 21 (13–32) | 0.007 ^{§***} |
| Sepsis | Yes | 61 (64.9) | 37 (77.1) | 98 (69) | 0.137 [†] |
| Blood products | Yes | 66 (70.2) | 42 (87.5) | 108 (76.1) | 0.022 ^{†*} |
| Surgical complications | Yes | 18 (19.1) | 25 (52.1) | 43 (30.2) | 0.001 ^{†***} |
| Short bowel syndrome | Yes | 7 (7.4) | 24 (50) | 31 (21.8) | 0.001 ^{†***} |
| LOS median (IQR) | | 28.5 (19–44) | 24 (2–52) | 28 (18–44) | 0.002 ^{§***} |

[†]Chi-square test; [†]Student's t-test; [§]Mann-Whitney nonparametric test; *P-value <0.05; **P-value <0.01; SD: standard deviation; IQR: interquartile range; GS: gastroschisis; MV: mechanical ventilation, TPN: total parenteral nutrition; PICC: peripherally inserted central catheter; LOS: length of stay; poor clinical conditions: if the patient had one or more of following signs and symptoms: dysthermia, hypoactivity, hydroelectrolytic or metabolic disorders, and infection; good conditions: included cases that did not meet criteria for poor conditions; complex gastroschisis: according to surgeon's report by gastrointestinal tract or abdominal wall complications: atresias, strictures, volvulus, necrosis, and large gastroschisis.

Mean maternal age, gestational age at birth, and birth weight were lower in the nonsurviving group ($p < 0.05$). Percentages of newborns with poor clinical conditions at the time of admission, CG, staged closure of abdominal wall with the placement of silo, shorter time of TPN, use of blood products, and surgical complications were higher in the group of nonsurvival ($p < 0.05$). Among postsurgical complications, reinterventions were the most frequent ones (survival 13.8%/nonsurvival 22.9%). SBS was more frequent in neonates who died ($p < 0.05$). There were no statistical differences between the two groups, regarding NICU (A, B, and C) admission, number of prenatal consultations, diagnosis of gastroschisis during pregnancy, route of birth, gender, Apgar 1 and 2, birthplace, birth-surgery time, type of venous access, use of vasoactive drugs, use of antibiotics, time on MV, and sepsis. Table 2 shows the results of logistic regression. CG (aOR 3.74, 95%CI 1.274–11.019) and SBS (aOR 7.55, 95%CI 2.177–26.225) increased the risk of death. An increase in birth weight reduced the risk for mortality (aOR 0.99, 95%CI 0.997–1.000).

DISCUSSION

Very few studies on gastroschisis have been carried out in LMICs, where the mortality rates of this birth defect are the highest. Possibly, these unfavorable figures are related to the paucity of protocols for improving the quality of care to patients with gastroschisis in those countries¹². Implementation of such protocols has been shown to improve outcomes and reduce deaths in gastroschisis cohorts from LMICs¹³.

There were no statistically significant differences among mortality rates in the three NICUs. A previous study evaluated the influence of birthplace on outcomes of this cohort and concluded that this finding may reflect the fact that, once admitted to tertiary referral centers, the outborn patients can benefit over time from high technology used in neonatal care, which would reduce the differences faced in prehospital period¹⁴.

The mortality rate of 33% of this cohort was higher than the ones reported in other studies performed in the southeastern region of Brazil, which found a variation between 4 and 29%¹⁵, and lower than those reported by studies carried out in the country's north and northeast regions, where mortality

Table 2. Logistic regression with some variables of prenatal, newborns, and postsurgical care of patients with gastroschisis admitted to three neonatal care units at the Greater Vitória Metropolitan Region – Espírito Santo between 2000 and 2018, according to groups of survival or nonsurvival, for prediction of mortality as a proposed theoretical model.

| Variable | Category | Crude OR (95%CI) | P-value | Adjusted odds ratio (aOR) [†] (95%CI) | P-value |
|-------------------------|-------------------|-----------------------------------|----------------|--|----------------|
| Maternal age (years) | | 0.901 (0.815–0.997) | 0.043* | 0.924 (0.811–1.054) | 0.240 |
| Antenatal diagnosis | Yes No | 1.760 (0.853–3.631) 1 | 0.126 | 1.197 (0.423–3.387) | 0.734 |
| Birth weight (g) | | 0.998 (0.998–0.999) | 0.001** | 0.998 (0.997–1.000) | 0.027** |
| Gestational age (weeks) | | 0.746 (0.624–0.891) | 0.001** | 1.023 (0.745–1.330) | 0.993 |
| Gastroschisis | Complex Simple | 6.346 (2.924–13.775) 1 | 0.001** | 3.747 (1.274–11.019) | 0.016* |
| Wall closure | Silo Primary | 4.341 (1.997–9.436) 1 | 0.001** | 2.656 (0.888–7.945) | 0.080 |
| Surgical complications | Yes No | 4.589 (2.136–9.859) 1 | 0.001** | 2.489 (0.822–7.536) | 0.107 |
| Vasoactive substances | Yes No | 2.153 (0.954–4.859) 1 | 0.065 | 0.990 (0.299–3.281) | 0.987 |
| Sepsis | Yes No | 1.820 (0.822–4.031) 1 | 0.140 | 0.421 (0.111–1.604) | 0.205 |
| Blood products | Yes No | 2.970 (1.134–7.778) 1 | 0.027** | 3.031 (0.578–15.875) | 0.189 |
| Short bowel syndrome | Yes No | 12.429 (4.780–32.315) 1 | 0.001** | 7.556 (2.177–26.225) | 0.001** |
| Clinical conditions | Poor Good | 2.878 (1.353–6.119) 1 | 0.006** | 2.052 (0.727–5.791) | 0.174 |

* $P < 0.05$; ** $P < 0.01$. OR: odds ratio; CI: confidence interval; aOR was obtained through logistic regression and adjusted by the input of block variables using the Enter method; poor clinical conditions: if the patient had one or more of the following signs and symptoms: dysthermia, hypoactivity, hydroelectrolytic or metabolic disorders, and infection; good clinical conditions (included cases that did not meet criteria for poor conditions); complex gastroschisis: according to surgeon's report by gastrointestinal tract or abdominal wall complications: atresias, strictures, volvulus, necrosis, and large gastroschisis.

rates were 51.2 and 51.6%, respectively^{4,7}. In comparison to other countries, the mortality rate in our study was close to the 39% rate reported in China⁷. Although sepsis was not a risk factor associated with mortality in this cohort, it was the main cause of death. Sepsis is a common cause of mortality in studies performed in LMICs^{4,7}.

CG increased the risk of death in our study. Another study also reported this association¹⁶. However, a large population study was carried out in an HIC, and CG was not a risk factor for death. This fact was attributed to the progress of neonatal surgical techniques and the manipulation of safer parenteral feeding solutions¹⁷.

In this cohort, SBS was a risk factor associated with mortality, and its main cause was multiple surgeries with bowel resection. A study carried out in northern Brazil reported SBS in 25% of patients with gastroschisis. Most of those patients were outborn who had severe intestinal injuries on admission due to conditions that included inadequate neonatal transport⁴.

A significant number of neonates with gastroschisis are low birth weight¹⁸. In this study, the higher the birth weight, the lower the risk of death from gastroschisis. In Brazil, a retrospective cohort conducted in the northern region showed that patients with birth weight less than 2,500 g had 2.4 times increased risk of death⁴.

Young maternal age is an important risk factor associated with gastroschisis, and its prevalence among adolescent mothers is more than 7 times higher than those aged 25 years or older¹⁹. In this present study, the mean age of mothers in the group of nonsurvival was statistically lower than that of survival.

The mean gestational age at birth was lower in the group of individuals with gastroschisis who died. This fact may be related to low birth weight, which was one of the risk factors associated with mortality in this study. Prematurity may complicate the postoperative period of patients with gastroschisis due to its comorbidities²⁰. Two studies performed in an HIC found different results. In the first one, prematurity was associated with worse outcomes in gastroschisis, including mortality. In the second one, although prematurity is associated with greater morbidity, it was not a risk factor associated with gastroschisis mortality²¹.

Patients with poor clinical conditions on admission to the NICU were more frequent in the nonsurvival group. A study also carried out in Brazil observed that poor clinical conditions on admission to NICU increased the risk of death, which was higher among outborn patients⁷. Another study carried out in LICs found an increased risk of mortality in patients with CG and hypovolemia at admission, due to poor neonatal transport conditions. Furthermore, the use of blood products was more

frequent in patients who died, and this fact may be related to coagulation disorders caused by sepsis³.

TPN time was shorter in the nonsurvivors group. This finding may be explained by the fact that these patients presented clinical instability, a condition in which the use of TPN is not allowed.

Some limitations must be considered in this study. Since it is a retrospective and hospital-based study, it is subjected to information and selection bias. Moreover, the study period was long and uneven among the studied NICU. However, there was completeness of data, and the accuracy of gastroschisis diagnosis is ensured, as it was performed by pediatric surgeons, in contrast to what was found in studies using population databases, which have flaws in filling in some variables and under-reporting. Finally, future studies with prospective designs are expected to be carried out to better understand the effects of assistance on gastroschisis morbidity and mortality. To that end, a group of Brazilian surgeons, called Paedurg Brazil, has been recently created to investigate the most prevalent congenital surgical anomalies in Brazil, including gastroschisis²².

CONCLUSION

In this gastroschisis cohort, the CG and short bowel syndrome increased the risk of death, with greater birth weight being inversely correlated with the risk of mortality. We hope that our findings could be used as a tool for professionals who routinely assist patients with gastroschisis in the elaboration of protocols for the improvement of quality of care to reduce mortality from birth defects preventable by surgical treatment, such as gastroschisis.

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AUTHORS' CONTRIBUTIONS

VMM: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ALN:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **KSC:** Conceptualization, Data curation, Formal Analysis, Funding

acquisition, Investigation, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CSV:** Formal Analysis, Software. **CAM:** Visualization, Writing – original draft, Writing – review & editing. **LBS:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Project

administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **EZ:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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