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Long-term outcomes of very low birth weight infants with spontaneous intestinal perforation: A retrospective case-matched cohort study☆

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ABSTRACT

Background: Spontaneous intestinal perforation (SIP) is an intestinal complication that occurs in very ill preterms. We investigated whether SIP survivors have worse neurodevelopmental and gastrointestinal outcomes and a poorer quality of life than controls.

Methods: A retrospective case-matched cohort study was performed involving infants treated for SIP in a NICU between August 1994 and April 2014. Controls and SIP patients were matched to gestational age, gender, and birth period. Medical records were reviewed. Telephone surveys were conducted to evaluate the medical condition, quality of life (PedsQL™ 4.0), neuropsychiatric and gastrointestinal outcome. McNemar's and Wilcoxon tests were performed, and generalized linear models were computed.

Results: Forty-nine SIP patients were included. The percentages of children with multiple disabilities (40% vs. 17%, OR = 3.3) and requiring physiotherapy (86% vs. 60%, OR = 4.77) were higher in the SIP group than in the control group. Intraventricular hemorrhage (IVH) led to a worse neurodevelopmental outcome regardless of SIP (OR = 8.79 for disability), and female gender was a protective factor against disability (OR = 0.06). Reported quality of life and gastrointestinal comorbidities did not differ between the two groups.

Conclusion: SIP survivors tend to be at risk of multiple disabilities. IVH and female gender influence the neurodevelopmental outcome regardless of SIP.

Levels of evidence: Level III: case-control study.

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Spontaneous intestinal perforation (SIP) is a life-threatening condition that affects 2%–3% of very low birth weight infants (VLBWIs, birth weight < 1500 g). This complication is defined as a (mostly) single spontaneous perforation at the antimesenteric border of the bowel, most often at the terminal ileum [1]. Although the exact etiology of this condition is unknown, several possible risk factors have been identified such as male gender, severe chorioamnionitis, and the use of indomethacin and steroids [2–4]. Neonates affected by SIP typically present with abdominal distension and discoloration, and systemic involvement can also be observed [3,5]. Diagnosis is confirmed by detection of pneumoperitoneum on abdominal radiography [3,5]. SIP must be differentiated from necrotizing enterocolitis (NEC). Patient history and radiological/histological characteristics can help in this regard [3,5–8]. Therapeutic options include

laparotomy and primary peritoneal drainage [6,9]. Mortality is high (20%–40%). Rates of neonatal morbidity, such as a longer hospital stay, requirement for mechanical ventilation, and delay of enteral nutrition, are high among survivors [4,7,8,10]. In addition, the prevalence of neurodevelopmental impairment among VLBWIs is high [11].

Over the past decades, it has become clear that inflammatory disease, in addition to hypoxic-ischemic insults, is an important cause of perinatal brain damage [12,13]. Thus, patients with SIP can be expected to have neurological consequences. However, there are scarce data regarding the long-term neurological and gastrointestinal outcomes and quality of life of SIP patients [7,8,10,14]. To the best of our knowledge, only two groups have analyzed the neurodevelopmental outcome of SIP patients. They reported that the prevalence of neurodevelopmental impairment ranges from 26% to 62.8% [4,15]. We were unable to find any studies investigating the gastro-intestinal outcome of SIP patients.

We conducted the first case-matched cohort study comparing the long-term developmental and gastrointestinal outcomes and quality of life of preterm infants with SIP and preterm matched controls without SIP. We investigated the hypothesis that SIP patients have worse

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developmental and gastrointestinal outcomes and a poorer quality of life than matched preterm controls.

1. Methods

1.1. Patients and study design

This retrospective case-control cohort study was approved by the local ethical committee of the University Hospitals Leuven (Belgium). Patients with SIP who were treated at the tertiary neonatal intensive care unit (NICU) of the University Hospitals Leuven between August 1, 1994, and March 31, 2014, were included. The clinical files of preterm infants born at ≤ 32 weeks of gestation were reviewed [16]. SIP was diagnosed based on clinical, radiological, and histological findings (when available). Patients with suspected NEC, mechanical gastrointestinal obstruction, and congenital malformations were excluded from the study. Controls were matched for gender and gestational age (equal, plus or minus 1 week) and were born as close as possible to the birth date of their matched patients. In multiple pregnancies where one infant developed SIP, a sibling of the same gender was used as the control when possible. Exclusion criteria for controls were neonatal death, NEC requiring surgery, and associated congenital malformations. Each SIP patient was matched with one control patient. To compare illness severity during the neonatal period, the neonatal characteristics (e.g., CRIB II score [17], bronchopulmonary dysplasia, and retinopathy of prematurity requiring treatment) of patients and controls were recorded [16].

1.2. Data collection

All available clinical neonatal, neurological, mental health, and gastrointestinal follow-up data were reviewed. VLBWIs were followed up closely by a multidisciplinary team at corrected ages of 7–11 and 18–22 months. Bayley Scales of Infant Development II (BSID II) were scored by trained psychologists and physiotherapists to evaluate cognitive and motor development [18]. Further clinical evaluations were conducted depending on the child's needs. Results of BSID II scoring and intelligence tests (IQ) were noted whenever they were performed.

To evaluate long-term well-being, a telephone survey was conducted between January 2015 and September 2017 by two (para)medically trained staff (see list 1, Appendix A). Parents were asked questions about the general medical condition (biometrics, medical history, and current medication use) of their child, the use of rehabilitation services (such as speech therapy, physiotherapy, psychotherapy, and home-based care) by their child, and the type of school education of their child. In Belgium, the regular educational system (composed of pre-school, primary school, and three types of secondary school) is distinguished from the specialized educational system. The latter is adapted to special needs children with the following disabilities: developmental delay, motor problems, hearing impairment, visual impairment, mental health problems, learning disturbances, or a combination thereof.

To evaluate neurodevelopmental impairment, functional disabilities were classified into the following four categories: severe, moderate, mild, and no disability. Diagnosis was performed by an experienced neuropsychiatrist based on the criteria used in the EPIPAGE studies [19]. Severe disability was defined as nonambulatory cerebral palsy (CP), severe bilateral hearing loss, severe visual loss that persisted even with visual correction ($<3/10$ bilaterally), or severe cognitive disability (IQ of less than 55). Moderate disability was classified as CP requiring the use of walking aids, moderate cognitive disability (IQ of 55–69), refractory epilepsy and severe learning disorders requiring an adapted educational system. Mild disability was classified as ambulatory CP, mild cognitive disability (IQ of 70–85), unilateral visual loss ($<3/10$ unilaterally), epilepsy controlled by medication, and mild conduct problems (compatible with the regular educational system). Children without disabilities were classified into the “no disability” category. Children with disabilities in more than one functional field

(e.g., motor problems and visual impairment) were classified as having multiple disabilities. When parents reported mental health problems, medical files were reviewed in order to obtain a confirmed diagnosis. Mental health disorders were classified into 4 categories: attention problems, internalizing and externalizing problems, conduct disorders and autism spectrum disorders. For the analysis of mental health issues, we only included patients with confirmed diagnosis of mental health disorder.

Weight, height, and weight for height were converted into standard deviations using the most recent Flemish reference growth charts [20]. Use of the following six types of medication was recorded: laxatives, antidiarrheal drugs, anticonvulsants, growth hormones, asthma drugs, and muscle relaxants. Use of laxatives and antidiarrheal drugs was indicative of impaired bowel function, use of anticonvulsants was indicative of severe brain damage, and use of psychotropic drugs was indicative of mental health problems. Growth hormones can be prescribed to preterm infants who are small for their gestational age and whose growth does not catch up.

Gastrointestinal problems were screened by conducting a short survey based on the PedsQL™ Gastrointestinal Symptoms Scales [21,22]. A validated Dutch translation of these scales is unavailable.

Quality of life was quantified using the validated PedsQL™ Quality of Life Inventory, version 4.0, in Dutch [23,24]. Parents were questioned about their child.

1.3. Data analysis

Data of SIP patients and matched controls were statistically compared using SPSS software (SPSS Statistics for Windows, Version 25.0; SPSS Inc., Chicago). Categorical data were analyzed using McNemar's test, and noncategorical data were analyzed using the paired Wilcoxon test. Given the matched nature of this study, only SIP patients and their matched controls for whom data were collected were included in statistical analyses. $p < 0.05$ was considered significant.

Subsequently, multivariate analyses were performed, meaning to control for potential confounding by the matching variables [25]. We identified 5 potential risk factors for outcome namely the matching criteria (gender, gestational age, birth weight), SIP and IVH. Models were computed for the main outcome parameters (BSID II, disability and multiple disabilities, regular educational system, PedsQL™ and gastrointestinal questionnaire) and for the outcome parameters that were significantly different in the univariate analysis. On the one hand, generalized linear models (GLMs) with a gamma distribution and the log-link function were used to estimate the predictors of health-related quality of life (PedsQL™), BSID II and growth parameters [26]. On the other, binary logistic model was used to estimate the predictors of all binomial data (e.g., disability, physiotherapy). Intraventricular hemorrhage (IVH) (grade 3 and 4), intestinal perforation and gender were set as fixed factors in the models, while birthweight and gestational age were set as covariates. The main effects and an intercept were modeled, and odds ratios and their 95% Wald confidence limits were calculated for all factors and covariates. Akaike's information criterion (AIC) was calculated to assess the multivariate model quality.

2. Results

2.1. Study subjects (Fig. 1)

Between August 1, 1994, and March 31, 2014, 3131 neonates born at ≤ 32 weeks of gestation were admitted. Sixty-four (2.04%) patients were diagnosed with SIP. Two patients were excluded owing to associated congenital malformations requiring surgery. Thirteen (21.0%) patients died during the neonatal period. No patients with SIP died after discharge. Forty-nine SIP patients were finally included in the study, and these patients were matched with 49 controls according to the aforementioned criteria.

Fig. 1. Study design. ¹Due to multiple congenital malformations.

The parents of 42 (86%) SIP patients completed the telephone questionnaire; the parents of five patients refused to participate, and two patients were lost to follow-up (Fig. 1). The parents of 47 (96%) controls completed the telephone survey; the parents of two controls refused to participate. Median age at evaluation was 13 years in both groups (range, 3–20 years). Data of 42 (85.7%) SIP patients and matched controls were analyzed (Fig. 1). The characteristics of the SIP patients and their matched controls are described in Table 1.

For Bayley neurodevelopmental indices, 33 (67%) pairs were evaluated at 7–11 months (median age: 9 months) and 20 (40.8%) pairs were reevaluated at 18–22 months (median age: 19 months). In both groups, 24 (48.9%) children underwent IQ testing when 4–10 years old. Among these, data of only 14 pairs of SIP patients and matched controls could be analyzed.

2.2. Neurodevelopmental outcome (Tables 2, 3)

Results from the univariate analysis are summarized in Table 2 (unless multivariate analysis was stated). Table 3 summarizes the Odds Ratios obtained from the multivariate analyses of the data.

Table 1

Demographic and clinical characteristics of SIP patients and controls.

Variable	SIP patients N = 42	Controls N = 42
Male gender, n (%)	33 (78.5)	33 (78.5)
Birth weight (g) ^a	929.0 ± 97.9	975.2 ± 86.9
Gestational age (weeks.days) ^a	26.6 ± 4.6	26.9 ± 3.9
Ventilation (days) ^{a c}	26.4 ± 6.9	9.7 ± 4.2
Days to full enteral nutrition ^{a *}	54.8 ± 7.7	38.4 ± 7.9
Length of stay (days) ^{a *}	114.3 ± 12.1	76.4 ± 10.2
Bronchopulmonary dysplasia (%) ^b	21 ± 6.2 (50)	17 ± 6.2 (40.5)
Retinopathy requiring treatment (%) ^b	12 ± 5.7 (28.6)	7 ± 4.8 (16.7)
CRIB II score ^a	10.3 ± 1.3	10.4 ± 1.1

Significant data marked in bold.

^a Mean ± SD.

^b n ± SD.

^c Ventilation was defined as an infant being on conventional or high-frequency ventilation.

* Significance level: $p < 0.05$.

During their stay at the NICU, 13 (31%) SIP patients developed an IVH of grade 3 or higher. The prevalence of hydrocephalus at discharge was higher in the SIP group than in the control group (21.4% vs. 7.1%; OR = 8.139; $p = 0.01$; GLM). Hydrocephalus appeared to be related to severe IVH in this SIP group (OR = 65.195; $p < 0.0001$; GLM). Eight SIP patients required a ventriculoperitoneal shunt (19.0%). Periventricular leukomalacia was diagnosed based on transfontanellar ultrasonography in both SIP patients and controls (11.9% vs. 14.2%; NS).

The BSID II PDI score was worse in the SIP group than in the control group at a corrected median age of 19 months (OR = 0.847; $p = 0.04$; GLM). The prevalence of CP was similar in the SIP and control groups (16.7% vs 14.3%).

Many preterm infants receive rehabilitation therapy later in life, and this was the case for both SIP patients and controls. The percentage of children who received physiotherapy was significantly higher in the SIP group than in the control group (85.7% vs 59.5%; OR = 4.8; $p = 0.01$; GLM). The main reasons for starting physiotherapy were developmental delay (38.1%) and hypertonias (23.8%).

The percentage of disabled children was higher in the SIP group compared to the control group (59.5% vs. 40.5%; OR = 2.04; NS; GLM). Seventeen SIP patients had multiple disabilities, in comparison with only seven controls (40.5% vs. 16.7%; OR = 3.3; $p = 0.04$; GLM). Fig. 2 shows determinants of (multiple) disability calculated by multivariate analysis. The percentage of children who attended special needs schools was almost 2-fold higher in the SIP group than in the control group, although this difference was not significant (45.2% vs. 25.2%; OR = 1.77; $p = 0.29$; GLM). Multifactorial testing revealed that this difference was because the number of patients with IVH was higher in the SIP group than in the control group (OR = 8.73; $p = 0.009$; GLM). Female gender was a protective factor against disability (OR = 0.06; $p = 0.001$; GLM), multiple disabilities (OR = 0.196; $p = 0.04$; GLM), and the requirement for special needs education (OR = 0.172; $p = 0.03$; GLM) in our cohort, regardless of intestinal perforation or IVH. Appendix B contains information about the quality of multivariate model fitting.

Parents of 15 SIP survivors and 8 controls reported mental health problems. Review of the available medical files provided accurate diagnoses in 15 SIP patients and 7 controls (35.7% vs. 16.7%; OR = 2.68; $p =$

Table 2
Comparative analysis of SIP patients and controls.

Variable	SIP patients Number (%)	Controls Number (%)	P-value	Odds ratio
Neurologic outcome				
Normal brain ultrasound at admission	26 (61.9%)	25 (59.5%)	1	1.11
Intraventricular hemorrhage (grade ≥ 3)	13 (31.0%)	6 (14.3%)	0.09	2.69
Normal brain ultrasound at discharge ^a	16 (38.1%)	28 (66.7%)	0.06	0.353
Hydrocephalus at discharge^a	11 (21.4%)	3 (7.1%)	0.01	8.139
Periventricular white matter disease	5 (11.9%)	6 (14.2%)	1	0.81
BSID II				
MDI at 7–9 months	74.8	77.4	0.64	
PDI at 7–9 months	94.3	92.5	0.72	
MDI at 18–20 months ^a	72.8	84.2	0.40	0.941
PDI at 18–20 months^a	91.4	89.8	0.04	0.847
Rehabilitation services				
Speech therapy	32 (76.2%)	29 (69.0%)	0.55	1.43
Physiotherapy^a	36 (85.7%)	25 (59.5%)	0.01	4.77
Developmental delay	16 (38.1%)	8 (19.0%)	0.06	2.62
Hypertonia	10 (23.8%)	11 (26.2%)	1	0.88
Psychotherapy	10 (23.8%)	12 (28.6%)	0.80	0.78
Home based care	19 (45.2%)	15 (35.7%)	0.45	1.49
Wearing glasses^a	22 (52.4%)	12 (28.6%)	0.02	3.084
Wearing hearing aids	3 (7.1%)	2 (4.8%)	1	1.54
Follow-up				
Tertiary referral center	18 (42.9%)	12 (28.6%)	0.18	1.88
Psychiatric	6 (14.3%)	2 (4.8%)	0.22	3.33
Regular educational system ^a	21 (54.8%)	31 (74.8%)	0.29	1.77
Medication use				
Psychotropic drugs	8 (19.0%)	4 (9.5%)	0.34	2.24
Anticonvulsant drugs	5 (11.9%)	1 (2.4%)	0.22	5.54
Asthma medication	3 (7.1%)	2 (4.8%)	1	1.54
Baclofen	2 (4.8%)	1 (2.4%)	1	2.05
Growth hormones	3 (7.1%)	2 (4.8%)	1	1.54
Cerebral palsy				
Cerebral visual impairment	7 (16.7%)	6 (14.3%)	1	1.2
Mental health disorder ^a	5 (11.9%)	2 (4.8%)	0.45	2.70
	15 (35.7%)	7 (16.7%)	0.09	2.68
	6 (14.3%)	3 (7.1%)	0.51	2.18
	4 (9.5%)	1 (2.4%)	0.25	4.32
	7 (16.7%)	3 (7.1%)	0.29	2.60
Disability				
Severe disability	8 (19.0%)	5 (11.9%)	0.55	1.74
Moderate disability	7 (16.7%)	7 (16.7%)	1	1
Mild disability	10 (24.8%)	5 (11.9%)	0.12	2.32
Multiple disabilities^a	17 (40.5%)	7 (16.7%)	0.04	3.317
Disability ^a	25 (59.5%)	17 (40.5%)	0.20	2.038
Biometrics				
Height (mean SD) ^a	−1.43	−1.08	0.60	0.780
Weight (mean SD) ^a	−1.26	−0.83	0.22	0.687
Weight for height (mean SD)	−0.4	−0.65	0.63	
Gastrointestinal outcome				
Admission for bowel (sub)obstruction	5 (11.9%)	0 (0%)	0.06	
Use of laxatives/antidiarrheal drugs	8 (19.0%)	3 (7.1%)	0.13	3.06
Dietary restrictions	12 (28.6%)	5 (11.9%)	0.09	2.96
PedsQL™ Gastrointestinal Symptoms Scales ^a	6.60	4.52	0.13	1.808
Incontinence	6 (14.3%)	4 (9.5%)	0.72	1.58
Abdominal pain	8 (19.0%)	5 (11.9%)	0.42	1.70
Obstipation	7 (16.7%)	14 (33.3%)	0.15	0.40
Fecal urgency	8 (19.0%)	2 (4.8%)	0.11	4.71
Nausea	8 (19.0%)	6 (14.3%)	0.83	1.41
Watery stools ^a	11 (26.2%)	2 (4.8%)	0.08	2.564
Quality of life				
PedsQL™: Quality of Life Inventory ^a	78.1	82.8	0.39	0.957
Physical health ^a	79.5	89.5	0.23	0.903
Emotional health	75.8	74.6	0.78	
Social health	75.0	80.5	0.29	
School functioning	80.4	82.0	0.74	

Univariate comparative analysis of the outcome data in a matched case–control study with 42 preterm infants who developed a spontaneous intestinal perforation (SIP) and their matched controls. For calculation of the Bayley developmental indices (BSID), 33 and 20 pairs were analyzed at 7–11 and 18–22 months, respectively, for the motor index.

McNemar's and Wilcoxon tests were performed.

For significant factors ($p < 0.05$) a generalized linear model was designed to control for possible cofounders. P-values and Odds-ratios noted for “^a” were obtained by multifactorial testing. Significant data marked in bold.

PDI: psychomotor developmental index; MDI: motor developmental index.

* Significance level: $p < 0.05$.

0.09; GLM). Six SIP survivors and 3 controls suffered from attention problems, conduct disorders were diagnosed in 4 SIP patients and 1 control and autism spectrum disorders was noted in 7 patients from the SIP group and 3 controls. Two SIP patients presented a combined diagnosis

of attention problems and autism spectrum disorders. There were no children with internalizing and externalizing problems in our cohort.

Use of medications (laxatives, antidiarrheal drugs, psychotropic or anticonvulsant drugs, muscle relaxants, asthma drugs, and growth

Table 3

Multifactorial analysis: Odds ratios (95% confidence intervals).

Outcome parameters	Risk factors				
	SIP	Female gender	Birth weight	Gestational age	IVH
Normal brain ultrasound at discharge	0.353 (0.118–1.052)	0.812 (0.187–3.537)	0.997 (0.996–1.001)	1.200 (0.803–1.793)	^a
Hydrocephalus at discharge	8.139* (1.588–41.702)	0.840 (0.170–4.161)	0.998 (0.994–1.001)	0.943 (0.983–1.575)	65.195** (11.43–371.91)
Motor index (MDI) at 18–20 months	0.941 (0.818–1.083)	1.024 (0.863–1.214)	1.000 (1.000–1.001)	0.962 (0.911–1.015)	0.908 (0.763–1.081)
Mental index (PDI) at 18–20 months	0.847* (0.723–0.992)	1.041 (0.847–1.279)	1.000 (1.000–1.001)	0.989 (0.929–1.053)	0.948 (0.746–1.176)
Physiotherapy	4.777* (1.445–15.8)	0.671 (0.146–3.088)	0.998 (0.995–1.001)	1.456 (0.917–2.312)	^a
Wearing glasses	3.084* (1.161–8.193)	1.032 (0.293–3.635)	1.000 (0.998–1.002)	1.289 (0.882–1.883)	0.474 (0.134–1.685)
Regular education system	1.771 (0.603–5.202)	0.172* (0.035–0.841)	0.997 (0.995–1.000)	1.211 (0.803–1.825)	8.729* (2.104–36.72)
Mental health disorder	2.676 (0.862–8.312)	0.210 (0.036–1.225)	1.002 (0.999–1.005)	0.987 (0.652–1.494)	1.236 (0.318–4.796)
Disability	2.038 (0.695–5.977)	0.061** (0.011–0.337)	0.996 (0.993–0.999)	1.489 (0.995–2.322)	8.79* (1.722–44.86)
Multiple disabilities	3.317* (1.066–10.320)	0.196* (0.041–0.943)	0.997* (0.994–0.999)	1.168 (0.784–1.739)	5.967* (1.608–22.145)
Height (mean SD)	0.780 (0.384–1.584)	2.727* (1.109–6.705)	1.002* (1.000–1.004)	0.913 (0.715–1.212)	0.466 (0.192–1.129)
Weight (mean SD)	0.687 (0.376–1.258)	1.425 (0.652–3.116)	1.001 (1.000–1.003)	0.984 (0.784–1.236)	0.654 (0.304–1.408)
PedsQL™: Gastrointestinal Symptoms Scales	1.808 (0.839–3.899)	0.488 (0.182–1.313)	0.998* (0.996–1.000)	1.275 (0.954–1.703)	0.815 (0.312–2.125)
Watery stools	2.564 (0.940–7.720)	0.538 (0.135–2.149)	0.999 (0.997–1.002)	1.133 (0.786–1.632)	3.488* (1.071–11.362)
PedsQL™: Quality of Life Inventory	0.957 (0.865–1.058)	1.050 (0.923–1.195)	1.000 (1.000–1.000)	0.993 (0.956–1.031)	0.872* (0.769–0.990)
PedsQL™: Physical health score	0.903 (0.763–1.069)	1.043 (0.840–1.296)	1.000 (1.000–1.001)	0.986 (0.929–1.051)	0.815 (0.660–1.007)

Odds ratios with 95% Wald confidence limits of determinants of the statistically significant results obtained after matched analysis of the outcome data in a matched case–control study with 42 preterm infants who developed a spontaneous intestinal perforation (SIP) (see Table 2). A generalized linear model (GLM) was computed using the matching criteria (gender, birth weight and gestational age) and IVH as covariates. Model based on an unconditional multivariate binary logistic model ($p < 0.001$) in case of binomial distribution; for the scaled data, a gamma log model was designed.

Model effect significance levels marked in bold * $p < 0.01$; ** $p < 0.001$.

IVH: Intraventricular hemorrhage.

^a Data numerically unsuitable; confidence intervals tend towards infinity.

hormones) did not significantly differ between the two groups, although more SIP patients than controls used antiepileptic drugs.

2.3. Biometrics (Tables 2, 3)

The height and weight of SIP patients and controls were lower than those in the general population. Weight for height was also below average for age, but did not differ significantly between SIP patients and controls.

2.4. Gastrointestinal outcome (Tables 2, 3)

In total, 80% of SIP patients underwent a laparotomy, mostly with an ileostomy (90%). Continuity was restored at 1–8 months after perforation. Six (15%) SIP patients underwent neonatal revision of their stoma owing to infection or obstructive complications. Five (11.9%) SIP patients were readmitted owing to small bowel (sub)obstruction after 5–17 years.

Table 2 summarizes the responses of parents to the gastrointestinal screening questionnaire. There were no significant differences between the two groups.

2.5. Quality of life (Tables 2, 3)

Parents of SIP patients and controls rated the quality of life of their children similarly at the time of evaluation (OR = 0.957; $p = 0.39$; GLM). However, multifactorial analysis revealed that patients with IVH reported a lower quality of life (OR = 0.872; $p = 0.034$; GLM).

3. Discussion

This retrospective study demonstrates that preterm infants who survive SIP tend to have a slightly worse neurodevelopmental outcome than matched controls. This finding seems to be related to the higher prevalence of severe IVH in the SIP group. The gastrointestinal outcome and overall quality of life did not significantly differ between the two groups.

We hypothesize that, in addition to SIP, four factors associated with the severity of illness contribute to the difference in neurodevelopmental outcome between SIP patients and controls. First, a higher percentage of SIP patients than controls suffered cerebral complications such as IVH and hydrocephalus. Severe IVH was an important comorbidity in the SIP cohort. Although IVH usually occurs in the first hours and days of life prior to intestinal perforation [1,3,5,27], both conditions reflect the severity of neonatal illness. The described multifactorial model allowed us to distinguish the effects of various factors, such as SIP, IVH, and matching criteria including gestational age, birthweight, and gender, on outcome parameters such as (multiple) disability. Second, the level of inflammation is elevated in SIP patients and this can contribute to brain damage [28]. SIP is not directly correlated with a pronounced inflammatory state because most patients do not present with an elevated C-reactive protein level, but can present with marked leukocytosis [29]. However, SIP is only the start of the disease process for these patients. Surgical treatments and complications (e.g., peritonitis and septicemia) are very likely to induce delayed inflammatory reactions [30]. Third, major surgery in neonates causes developmental problems. Although the

Fig. 2. Odds ratios of multivariate model. Odds ratios with 95% Wald confidence limits of determinants of disability (a) and multiple disabilities (b) in a matched case–control study with 42 preterm infants who developed a spontaneous intestinal perforation (SIP), based on an unconditional multivariate binary logistic model ($p < 0.001$). Model effect significance levels: * $p < 0.01$; ** $p < 0.001$.

underlying mechanism is not fully understood, general anesthesia may play a role [27,31]. Finally, SIP patients suffered more complications, such as prolonged ventilation and delayed enteral feeding, than controls during their stay at the NICU, as previously reported [16].

In an American cohort of 280 SIP patients, 62.8% displayed neurodevelopmental impairment at 24 months of age [14]. This percentage is similar to that reported in the current study, although the population was younger (mean gestational age, 24.8 weeks) and had a lower mean birth weight (710 g) in the previous study than in the current study. The percentage of children with neurodevelopment impairment at a corrected age of 12 months was lower in a smaller study involving 18 SIP survivors (38% had a Mental Developmental Index of $<85\%$, and 46% had a Psychomotor Developmental Index of $<85\%$) [7]. More recently, 26% of 23 SIP patients were reported to have CP at 6 years of age [15], while 15% of children had CP in both the SIP and control groups in the current study. In our study, female gender was a protective factor against disability. This effect is well-known but not fully understood [11].

A significantly higher percentage of SIP patients than controls required physiotherapy. In most cases, physiotherapy was started to stimulate gross motor development before evaluation at 9 months. Bayley developmental motor indices did not significantly differ between the two groups, although the data are probably not representative because half the patients were not formally evaluated. Our multifactorial model revealed a link between SIP and the need for physiotherapy that was independent of IVH. Factors that may minimally contribute to this early motor delay include longer hospitalization, abdominal stoma, and surgery for bowel continuity restoration. The retrospective nature of the present study hinders further analysis.

Findings regarding education did not significantly differ between the SIP and control groups. However, the percentages of children requiring specialized education in both groups were higher than normal (45%–26% SIP–non-SIP vs 4.2% of Flemish children attend special needs

schools) [32]. This is most likely because of the extreme prematurity of the SIP patients and controls [19,33]. IVH appeared to be an important risk factor for the requirement for specialized education later in life, while female gender was a protective factor in our cohort. This is likely because of the concomitant occurrence of (multiple) disability requiring adapted supportive educational measures.

In the present study, the prevalence of mental health disorders was 2-fold higher in the SIP group compared to the control group, but the difference was not significant. Extremely low birth weight infants are known to be at risk for mental health problems, with an increasing incidence proportional to the cumulative number of neonatal complications [34,35]. We therefore suggest that a formal psychiatric evaluation of the children should be done in order to provide more accurate information on the mental health well-being of SIP patients.

Abdominal surgery is a risk factor for intestinal obstruction owing to the formation of adhesions. The prevalence of intestinal obstruction in the SIP group (11.9%) was slightly higher than that reported after neonatal laparotomy but was similar to that reported after surgery for NEC [36,37]. The current study revealed that development of SIP in the neonatal period had no long-term consequences on digestive well-being. Watery stools seemed to be a minor problem that did not affect daily life.

Overall quality of life, as reported by parents, did not significantly differ between the two groups, indicating that all of the aforementioned differences were of little significance to daily life. However, our multifactorial model revealed that patients who developed severe IVH during the neonatal period had a lower quality of life. This finding is consistent with the finding that the percentage of children with disability and multiple disabilities was higher among these patients. Our data are also consistent with a previous study concerning quality of life among children with posthemorrhagic hydrocephalus after preterm birth [38].

This study is the first to report valuable information about the long-term outcomes of SIP survivors and is the largest matched control cohort of such patients to date. The single center design of this study guarantees uniformity of treatment between the patient and matched control. The response rate was high (86% follow-up at 3–20 years; median, 13 years). In addition, this is the first study to investigate the gastrointestinal outcome and quality of life of SIP patients.

This study has a number of limitations. First, SIP patients were recruited over 20 years, during which treatment strategies changed. However, we limited the influence of this factor by matching SIP patients and controls in terms of the birth period. Although the response rate was high, the sample size was restricted by the decreasing frequency of SIP in our NICU. AIC of the multivariate analysis showed that model fitting was relatively good for the binary data, but also indicated that the models investigating PedsQL™ scores must be interpreted with caution. Second, the results are based on the responses of parents to a telephone questionnaire, and no medical evaluation was performed. Responders tended to be mothers. The interviewers noticed that the accuracy of the answers differed according to the education level of the parents; answers were recorded verbatim. However, the education level of mothers did not significantly differ between the two groups. The PedsQL™ Quality of Life Inventory has been validated for delivery by telephone [24]. Finally, owing to the retrospective nature of the study, some information was only available for half the patients. Consequently, BSID II scores must be interpreted with caution because data are lacking for more than half of the cohort at 18–22 months.

4. Conclusion

This retrospective case-matched cohort study compared the neurodevelopmental and gastrointestinal outcomes and quality of life of SIP patients and matched controls without SIP. As an important comorbidity in both groups, severe IVH led to a worse neurodevelopmental outcome requiring specialized education. Patients

with IVH also reported a lower quality of life. Female gender was a protective factor against disability. In our cohort, SIP survivors also tended to be at risk of multiple disabilities. Gastrointestinal comorbidities did not differ between the two groups. Overall quality of life, as reported by the parents, was similar in the two groups.

Declarations of interest: none.

Appendix A. English translation of a telephone survey completed by parents of SIP patients and controls

General questions:

What is the height and weight of your child?

Has your child been admitted to hospital after discharge from the NICU?

Has your child undergone surgery after discharge from the NICU?

Does your child take daily medication?

Is your child being followed by any doctor?

Did your child receive speech therapy/physiotherapy/psychotherapy/home based care?

Does your child wear glasses/hearing aids?

Is your child on a restricted diet?

What type of school does your child attend? Does he/she receive specialized guidance at school?

What is your highest education level (*mother of the patient*)?

Gastrointestinal screening form (maximum score: 52, minimum score: 0):

In the past months, to what extent has your child been affected by the following problems?

Problem	Never	Almost never	Sometimes	Often	Almost always
Feels pain or hurt in his/her stomach					
Has trouble swallowing					
Suffers from gastroesophageal reflux					
Feels the urge to vomit/does vomit					
Feels his/her stomach is full of gas					
Has hard bowel movements					
Has watery bowel movements					
Feels pain when he/she has a bowel movement					
Has to rush to the bathroom to have a bowel movement					
Is incontinent					
Cannot eat certain foods because they make him/her vomit					
Worries about stomach pain					
Worries about bowel movements					
Score	×0	×1	×2	×3	×4

Appendix B

Model quality of multifactorial analysis	
Parameter	AIC
Normal ultrasound at discharge	91
Hydrocephalus	53
MDI at 18 22 months	504
PDI at 18 22 months	444
Physiotherapy	88
Wearing glasses	116
Mental health disorders	97
Disabilities	102
Multiple disability	92

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Model quality of multifactorial analysis	
Parameter	AIC
Educational system	103
Length	311
Weight	295
Peds QL™ Gastrointestinal questionnaire	473
Watery stools	154
PedsQL™: Physical health score	1179
PedsQL™: Quality of Life Inventory	1260

AIC: Akaike's information criterion.

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