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Original Article

Neonatal risk factors for functional gastrointestinal disorders in preterm infants in the first year of life

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ABSTRACT

Background. An assessment of functional gastrointestinal disorders (FGIDs) in premature infants in their first year of life and neonatal factors influencing the progression of FGIDs was conducted in this research.

Methods. Subjects selected for the retrospective study involved preterm infants being hospitalized in the neonatal department of Northern Jiangsu People's Hospital from September 2018 to September 2021. Data on neonatal risk factors such as gestational age, gender, birth weight, mode of delivery, feeding pattern, antibiotic administration and addition of probiotics, duration of hospitalization, maternal history of smoking, and mental health status, were all collected and analyzed. FGIDs were diagnosed according to Rome IV criteria.

Results. This study included 988 preterm infants, with 725 (73.4%) having at least one FGID, 449 (45.4%) with infant colic, 411 (41.6%) with infant regurgitation, 237 (24.0%) with infant dyschezia, 190 (19.2%) with functional constipation, and 34 (3.4%) with functional diarrhea throughout the first year of life. In total, 263 infants (26.6%) without FGID symptoms were included in the control group. Further, a higher prevalence of FGIDs was observed in preterm infants with infant colic as well as infant regurgitation in particular as being characterized by a low gestational age (<32 w), low birth weight (<1.5 kg), Cesarean section, formula feeding, neonatal antibiotics use, hospitalization longer than 7 days, and maternal history of smoking. It was found from association analyses that infants exclusively breastfed in their first month of life were at lower risk for regurgitation than those in the control group.

Conclusions. Unnecessary antibiotic use in the neonatal period, Cesarean delivery, passive smoking, lack of breastfeeding along with inappropriate probiotics usage are major risk factors for FGIDs, and their systematic control may be effective in reducing the susceptibility to and prevalence of FGIDs in preterm infants in the first year of life.

Key words: premature, infants, functional gastrointestinal disorders, risk factors.

Functional gastrointestinal disorders (FGIDs) are a group of diseases of the functional digestive tract which are age-related, chronic, or recurring, and are not addressed either by organic lesions or biochemical abnormalities.[1] FGIDs are redefined by the Rome IV criteria where FGIDs in infants include infant colic, infant regurgitation, infant dyschezia, functional constipation, functional diarrhea, rumination as well as cycling vomiting syndrome.[2]

According to multiple studies, around 50% of infants experience FGIDs (including regurgitation, infant colic, and constipation) during the first year of their lives following birth.[3,4] There is a higher rate of medical visits by infants and young children with FGIDs, and consequently, the quality of life is poorer for them[4,5], also causing unnecessary hardship for

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caregivers during early infancy.[2] In children, FGIDs not only affect their growth and development but also deteriorate their quality of life. Additionally, studies show that children with FGIDs are more prone to gastrointestinal illnesses and abdominal migraines as they age than children without FGIDs.[1] This affects the long-term health of children, as well as burdens the family with increasing additional healthcare costs.[6] Most FGIDs are usually treated with inadequate treatment modalities, which adds increased costs to healthcare systems in resource-constrained nations.[7] Possible influencing factors include genetic predispositions, psychological variables, aberrant intestinal motility, visceral hyperalgesia, gut inflammation, intestinal microbiota, early stressful experiences, and trauma, all have been suggested as determinants of FGID susceptibility.[2,8,9] FGIDs, however, remain largely unknown in terms of their pathophysiology. In recent years, the prevalence of FGIDs and disease risk factors have attracted the attention of pediatricians at home and abroad. The prevalence of FGIDs is higher in premature infants, and neonatal life events are crucial in programming later FGIDs in life.[10] Several authors speculate that infants are predisposed to FGIDs depending on the delivery mode, feeding practices, and early administration of antibiotics.[11,12] However, the most recent research subjects of FGIDs were term infants, and few studies have been conducted on premature infants. Therefore, the role of premature birth in FGIDs is less explored. A retrospective analysis concerning preterm infants is conducted in this study to look at the potential link between neonatal factors and the development of FGIDs within the first year of life.

Material and Methods

Study subjects and design

The study was retrospective and non-interventional. Therefore, it was not necessary to obtain informed consent from parents. The ethics committee of Northern Jiangsu People's Hospital approved this research (2022ky291). Preterm newborns at the hospital with gestational ages at birth ranging from 25 to 36 weeks were selected from the tertiary neonatal critical care unit between September 2018 and September 2021.

Premature newborns with severe acute infection or neonatal problems such as inherited metabolic disorders, congenital deformities, and death during hospitalization were excluded.

Data collection

Data on neonatal risk factors such as gestational age, gender, birth weight, mode of delivery, feeding pattern, antibiotic administration and addition of probiotics, duration of hospitalization, maternal history of smoking, and mental health status, were all collected from hospital records and telephone follow-up records. FGIDs were diagnosed as per the Rome IV criteria.[1]

Diagnostic criteria for infant colic:

For clinical purposes, must include all of the following:

1. An infant who is <5 months of age when the symptoms start and stop;
2. Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers;
3. No evidence of infant failure to thrive, fever, or illness.

Diagnostic criteria for infant regurgitation

Must include both of the following in otherwise healthy infants 3 weeks to 12 months of age:

1. Regurgitation 2 or more times per day for 3 or more weeks;
2. No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing.

Diagnostic criteria for infant dyschezia

Must include in an infant <9 months of age:

1. At least 10 minutes of straining and crying before successful or unsuccessful passage of soft stools;
2. No other health problems.

Diagnostic criteria for functional constipation

Must include 1 month of at least 2 of the following in infants up to 4 years of age:

1. 2 or fewer defecations per week;
2. History of excessive stool retention;
3. History of painful or hard bowel movements;
4. History of large-diameter stool;
5. Presence of a large fecal mass in the rectum.

In toilet-trained children, the following additional criteria may be used:

6. At least 1 episode/week of incontinence after the acquisition of toileting skills;
7. History of large-diameter stool that may obstruct the toilet.

Diagnostic criteria for functional diarrhea

Must include all of the following:

1. Daily painless, recurrent passage of 4 or more large, unformed stools;
2. Symptoms last more than 4 weeks;
3. Onset between 6 and 60 months of age;
4. No failure to thrive if caloric intake is adequate.

Statistical methods

Data were analyzed statistically with the aid of SPSS Statistics (21.0). Continuous variables were presented as the mean ± standard deviation (SD) and analyzed using the Student's t-test. Categorical variables were described as proportions and were analyzed using the chi-square test or Fisher exact probability method. The risk factors were identified by performing univariate as well as multivariate logistic regression analyses. For each risk factor, odds ratio (OR) estimates, 95% confidence intervals, and p-values from the Wald chi-square test were all determined, where $p < 0.05$ indicated a statistical significance level. Multiple logistic regression has been applied if the p-value of any of the factors was less than 0.05.

Results

A total of 988 preterm infants have been involved in this study, and their data for the first year of their lives were evaluated and analyzed. Among a total of 988 subjects, in at least 725 (73.4%), a single FGID was documented within the first year of life. There are 484 (49.0%) cases with a single kind of FGID, 210 (21.3%) with two kinds, 31 (3.1%) with three kinds, and no case with four or more FGIDs. Among the 988 participants, there were 449 (45.4%) and 411 (41.6%) cases of infant colic and regurgitation, respectively, making them frequently occurring disorders. Of the 988 participants, 237 (24.0%) claimed dyschezia, 190 (19.2%) claimed functional constipation, and 34 (3.4%) claimed functional diarrhea. There were no cases of infant rumination syndrome as well as recurrent vomiting syndrome.

The demographic characteristics of subjects are shown in Table I. Of the 988 infants who completed the study, 725 with FGIDs were allotted to the case group and 263 without symptoms associated with FGIDs were allotted to the control group. As expected, all 988 preterm-born infants displayed considerable differences (variations) in gestational age, birth weight, the incidence of cesarean delivery, rate of breastfeeding, antibiotic usage, probiotics intake, and maternal history of smoking, anxiety, and hospital stay (Table I). There were no considerable variations in gender between the case group and the control group.

It was observed that the prevalence of FGIDs among preterm newborns varied considerably

Table I. Baseline demographic characteristics of the enrolled population.

Variables	Case group (n=725)	Control group (n=263)	Test	*P* value
Gestational age, w, mean±SD	31.7±1.3	34.8±0.6	-50.9	<0.001
Male, n (%)	418 (57.7)	139 (52.9)	1.81	0.178
Birth weight, kg, mean±SD	1.6±0.1	2.1±0.2	-38.80	<0.001
Cesarean delivery, n (%)	487 (67.1)	106 (40.3)	58.06	<0.001
Exclusive breastfeeding, n (%)	218 (30.1)	127 (48.3)	28.19	<0.001
Exclusive formula feeding, n (%)	396 (54.6)	85 (32.3)	38.42	<0.001
Antibiotic use, n (%)	479 (66.1)	95 (36.1)	71.10	<0.001
Probiotics use, n (%)	256 (35.3)	145 (55.1)	31.45	<0.001
Maternal anxiety, n (%)	351 (48.4)	63 (24.0)	47.43	<0.001
Maternal smoking, n (%)	327 (45.1)	59 (22.4)	41.67	<0.001
Hospital stay, d, mean±SD	29.4±21.3	6.2±3.5	28.29	<0.001
≤7 d, n (%)	173 (23.9)	153 (58.2)	102.78	
>7 d, n (%)	552 (76.1)	110 (41.8)	102.78	

SD: standard deviation

in terms of gestational age (χ^2 = 21.83; p <0.001), especially in the case of infant colic (χ^2 = 28.10; p <0.001) and infant regurgitation (χ^2 = 33.13; p <0.001) (Table II).

In addition, there were also found differences in infants according to the different weight at birth in at least one FGID (χ^2 = 16.00; p = 0.003), infant colic (χ^2 = 27.18; p <0.001), and infant regurgitation (χ^2 = 18.11; p <0.001) (Table III). There was no significant difference in the others.

There are several neonatal risk factors associated with FGIDs, as shown in Table IV. Univariate analysis revealed that FGIDs were significantly associated with gestational age, birth weight, cesarean delivery, breastfeeding, exclusive formula feeding, use of neonatal antibiotics and probiotics, maternal anxiety, maternal smoking, and hospitalization longer than 7 days (Table IV). The risk from infantile colic ([<28 weeks: OR = 5.28, 95% CI = 1.10-12.4, p = 0.003], [28-32 weeks: OR = 4.16, 95% CI = 1.05-11.5, p = 0.008])

Table II. Proportion (%) of infants born preterm with FIGDs, according to gestational age at birth.

Gestational age (weeks)	Infant colic n (%)	Infant regurgitation n (%)	Infant dyschezia n (%)	Functional constipation n (%)	Functional diarrhea n (%)	At least 1 FGID n (%)
< 28	9	8	5	4	1	12
(n=14)	(64.3)	(57.1)	(35.7)	(28.6)	(7.1)	(85.7)
28 - 32	113	127	79	58	6	206
(n=244)	(46.3)	(52.0)	(32.4)	(23.8)	(2.5)	(84.4)
32 - 34	98	140	74	59	13	238
(n=300)	(32.7)	(46.7)	(24.7)	(19.7)	(4.3)	(71.0)
34 - 36	122	136	79	69	14	269
(n=430)	(28.4)	(31.6)	(18.4)	(16.0)	(3.3)	(68.8)
χ^2 value	28.10	33.13	5.85	6.87	2.05	21.83
P value	<0.001	<0.001	0.119	0.076	0.562	<0.001

FGID: functional gastrointestinal disorder

Table III. Proportion of infants reporting FGIDs, according to type of disorder and birth weight group.

Birth weight (kg)	Infant colic n (%)	Infant regurgitation n (%)	Infant dyschezia n (%)	Functional constipation n (%)	Functional diarrhea n (%)	At least 1 FIGD n (%)
<1	8	7	3	3	1	10
(n=12)	(66.7)	(58.3)	(25.0)	(25.0)	(8.3)	(83.3)
1 – 1.5	89	85	35	30	9	119
(n=148)	(60.1)	(57.4)	(23.6)	(20.3)	(5.4)	(80.4)
1.5 – 2.5	282	280	151	130	21	472
(n=631)	(44.7)	(44.4)	(23.9)	(20.6)	(3.3)	(74.8)
2.5 – 3	60	53	36	21	3	96
(n=152)	(39.5)	(34.9)	(23.7)	(13.8)	(2.0)	(63.2)
>3	10	16	12	6	1	28
(n=45)	(22.2)	(35.6)	(26.7)	(13.3)	(2.2)	(62.2)
χ^2 value	27.18	18.11	0.20	5.00	5.00	16.00
P value	<0.001	0.001	0.995	0.287	0.287	0.003

FGID: functional gastrointestinal disorder

and infant regurgitation ([<28 weeks: OR = 4.12, 95% CI = 1.63-11.3, p = 0.045], [28 - 32 weeks: OR = 3.28, 95% CI = 1.18-12.4, p = 0.049]) was considerably elevated for infants with low gestational age. Moreover, the risk of infantile colic ([<1 kg: OR = 6.84, 95% CI = 2.35-15.6, p = 0.004], [1-1.5kg: OR = 4.21, 95% CI = 1.58-13.2, p = 0.023]) and infant regurgitation ([<1 kg: OR = 2.57, 95% CI = 1.86-5.38, p = 0.012], [1-1.5kg: OR = 1.26, 95% CI = 1.01-6.39, p = 0.035]) was considerably high for infants with lower weight at birth. In addition, if the infant was delivered by cesarean, the risk of functional constipation was higher (OR = 1.99, 95% CI = 1.31-3.18, p = 0 .015). Furthermore, infants exclusively fed with formula following birth displayed a higher risk for infantile regurgitation (OR = 2.02, 95% CI = 1.32-1.38, p = 0.009). Infantile colic was significantly associated with the duration of antibiotic use in the neonatal period ([8-14 days: OR = 2.69, 95% CI = 1.29-4.37, p = 0.006], [> 14 days: OR = 3.24, 95% CI = 1.06-5.45, p <0.001]). The use of probiotics in the first month of life was considerably associated with infantile colic ([age of probiotics initiation ≤14 days, OR = 1.98, 95% CI = 1.06-2.78, p = 0.001], [Duration of probiotics use >14 days, OR = 1.37, 95% CI = 1.24-2.92, p = 0.032]) and functional constipation ([age of probiotics initiation ≤14 days, OR = 1.93, adjusted 95% CI = 1.37-1.29, adjusted p =0.002], [duration of probiotics use >14 days, OR = 1.88, adjusted 95% CI = 1.63-2.19, P = 0.009]). Maternal anxiety (OR = 3.23, 95% CI = 2.83-10.5, p = 0.023), maternal smoking (OR = 2.15, 95% CI = 1.38-3.34, p = 0.005), and hospitalization longer than 7 days (OR = 2.17, 95% CI = 1.32-2.48, p <0.001) were also considerably associated with infantile colic. Furthermore, there were no other significant associations found.

The results of the multivariate logistic regression analysis are shown in Table V. Infantile colic was substantially linked to a gestational age of 32 weeks or less and birth weight of 1.5 kg or less ([gestational age < 32weeks: adjusted OR = 4.08, adjusted 95% CI = 2.37-12.1, adjusted p = 0.013], [birth weight < 1.5kg: adjusted OR = 3.26, adjusted 95% CI =2.48-10.5, adjusted p = 0.026]) and infant regurgitation ([gestational age < 32 weeks: adjusted OR = 3.25, adjusted 95% CI = 2.19–6.84, adjusted p = 0.027], [birth weight < 1.5kg: adjusted OR = 2.78, adjusted 95% CI =1.48–5.25, adjusted p = 0.015]). Cesarean delivery (adjusted OR = 2.74, adjusted 95% CI = 1.28-11.3, adjusted p < 0.001) was considerably linked to functional constipation. Antibiotic use over 8 days (adjusted OR = 2.93, adjusted 95% CI = 1.28-5.39, adjusted p <0.001), maternal smoking (adjusted OR = 2.43, adjusted

Table IV. Neonatal risk factors against FGIDs.

Risk factors		Infant Colic		Infant regurgitation		Infant dyschezia		Functional constipation		Functional diarrhoea	
		OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Gestational age (weeks)	<28	5.28 (1.10-12.4)	0.003**	4.12 (1.63-11.3)	0.045*	5.42 (0.92-12.8)	0.468	1.21 (0.32-2.58)	0.362	1.62 (0.91-3.21)	0.796
	28– 32	4.16 (1.05-11.5)	0.008**	3.28 (1.18-12.4)	0.049*	4.26 (0.53-12.3)	0.890	1.19 (0.58-4.97)	0.098	1.43 (0.38-5.46)	0.591
	32– 34	3.56 (0.03-8.23)	0.358	2.89 (0.54-10.7)	0.935	2.03 (0.14-13.6)	0.591	0.99 (0.48-3.74)	0.486	1.83 (0.91-4.62)	0.454
	34– 36	1.24 (0.14-7.84)	0.681	1.02 (0.93-11.8)	0.391	2.08 (0.32-3.51)	0.723	1.15 (0.56-6.23)	0.537	1.16 (0.23-3.28)	0.327
Birth weight (kg)	<1	6.84 (2.35-15.6)	0.004***	2.57 (1.86-5.38)	0.012*	2.83 (0.35-5.83)	0.325	0.99 (0.01-3.57)	0.456	1.58 (0.45-6.72)	0.097
	1 – 1.5	4.21 (1.58-13.2)	0.023*	1.26 (1.01-6.39)	0.035*	2.35 (0.98-4.76)	0.285	1.03 (0.22-3.87)	0.518	1.07 (0.67-6.85)	0.085
	1.5– 2.5	3.26 (0.96-10.8)	0.784	1.13 (0.78-5.67)	0.563	1.78 (0.96-5.98)	0.387	1.19 (0.75-4.93)	0.257	2.23 (0.32-5.75)	0.196
	2.5– 3.0	1.42 (0.89-3.25)	0.256	0.92 (0.46-1.28)	0.359	1.85 (0.21-6.76)	0.149	0.97 (0.35-3.98)	0.768	1.45 (0.91-8.92)	0.799
	>3.0	1.37 (0.85-9.96)	0.478	1.01 (0.35-3.67)	0.192	1.21 (0.45-3.28)	0.293	1.98 (0.92-6.83)	0.358	0.92 (0.03-6.78)	0.596
Mode of delivery	Vaginal	0.89 (0.15-3.65)	0.476	0.96 (0.25-4.28)	0.532	1.03 (0.68-3.86)	0.321	0.32 (0.11-1.71)	0.065	0.08 (0.01-1.28)	0.093
	C-section	2.58 (0.43-10.5)	0.214	1.87 (0.71-3.23)	0.958	1.34 (0.51-2.27)	0.119	1.99 (1.31-3.18)	0.015*	1.56 (0.28-2.95)	0.315
Exclusive breast-feeding		1.65 (0.59-4.01)	0.168	1.67 (1.35-2.28)	0.002**	0.98 (0.03-2.6)	0.437	5.35 (0.78-6.39)	0.309	5.83 (0.25-8.74)	0.538
Exclusive formula feeding		0.98 (0.42-1.78)	0.279	2.02 (1.32-3.38)	0.009**	1.83 (0.67-3.65)	0.735	0.03 (0.01-1.78)	0.537	0.28 (0.15-1.19)	0.546
Duration of antibiotic use(days)	≤7	1.18 (0.54-2.45)	0.345	1.67 (0.27-3.46)	0.231	1.87 (0.54-2.45)	0.549	2.38 (0.84-4.78)	0.768	1.56 (0.26-3.75)	0.467
	8-14	2.69 (0.29-4.37)	0.076**	2.32 (0.14-4.85)	0.675	1.62 (0.43-2.78)	0.337	1.95 (0.25-3.27)	0.573	1.56 (0.26-3.75)	0.498
	>14	3.24 (1.06-5.45)	<.0001***	2.35 (0.01-2.65)	0.062	1.20 (0.94-1.52)	0.144	1.12 (0.85-1.46)	0.426	2.14 (0.51-2.56)	0.749
Age of probiotics initiation (days)	≤14	1.98 (1.06-2.78)	0.001**	1.26 (0.67-2.75)	0.345	0.87 (0.04-1.13)	0.258	1.93 (1.37-2.29)	0.002**	1.01 (0.08-1.69)	0.679
	>14	0.84 (0.01-1.23)	0.067	0.79 (0.12-1.65)	0.289	0.87 (0.25-1.67)	0.323	1.35 (0.65-2.37)	0.856	0.65 (0.02-1.58)	0.007
Duration of probiotics use (days)	≤14	1.36 (0.21-2.89)	0.062	1.84 (0.98-2.63)	0.328	2.36 (0.67-4.56)	0.129	2.36 (0.93-5.47)	0.685	2.36 (0.19-3.68)	0.474
	>14	1.37 (1.24-2.92)	0.032*	2.98 (0.13-3.96)	0.078	1.85 (0.83-2.92)	0.126	1.88 (1.63-2.19)	0.009**	0.92 (0.08-1.67)	0.287
Maternal anxiety		3.23 (2.83-10.5)	0.023*	3.36 (0.52-10.7)	0.058	4.43 (0.54-6.57)	0.374	2.08 (0.62-2.59)	0.708	1.42 (0.65-5.71)	0.657
Maternal smoking		2.15 (1.38-3.34)	0.005**	1.81 (0.27-2.64)	0.176	1.54 (0.83-3.29)	0.096	0.99 (0.27-2.64)	0.384	1.62 (0.77-2.83)	0.753
Hospital stay (days)	≤7	1.29 (0.87-2.58)	0.346	1.15 (0.57-1.94)	0.287	1.49 (0.91-2.03)	0.985	1.15 (0.59-3.86)	0.06	1.15 (0.86-2.74)	0.212
	>7	2.17 (1.32-2.48)	<.0001***	2.13 (0.56-3.49)	0.563	1.85 (0.65-2.56)	0.574	0.97 (0.56-1.49)	0.308	1.36 (0.67-1.99)	0.657

*: p<0.05, **: p<0.01, ***: p<0.001. CI: confidence interval, FGID: functional gastrointestinal disorder, OR: odds ratio.

Table V. Multivariate analysis for risk factors associated with FGIDs.

Risk factors	Infant colic		Infant regurgitation		Infant dyschezia		Functional constipation		Functional diarrhoea	
	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value
Gestational age <32 weeks	4.08 (2.37-12.1)	0.013*	3.25 (2.19-6.84)	0.027*	4.21 (0.27-11.5)	0.532	2.74 (0.87-4.82)	0.286	2.62 (0.93-5.27)	0.663
Birth weight <1.5 kg	3.26 (2.48-10.5)	0.026*	2.78 (1.48-5.25)	0.015*	2.56 (0.27-5.92)	0.227	3.25 (0.51-7.62)	0.354	1.88 (0.61-5.63)	0.089
Cesarean delivery	3.58 (0.39-9.05)	0.147	2.08 (0.85-3.99)	0.263	2.38 (0.01-4.72)	0.206	2.74 (1.28-11.3)	<.0001***	4.56 (0.98-8.53)	0.764
Exclusive breast-feeding	0.95 (0.72-5.71)	0.211	1.87 (1.36-2.92)	0.003**	1.56 (0.33-3.26)	0.387	2.35 (0.78-6.29)	0.563	2.74 (0.47-7.35)	0.495
Exclusive formula feeding	1.65 (0.23 -2.86)	0.386	1.84 (1.21-3.83)	0.011*	1.96 (0.67-3.45)	0.564	3.21 (0.86-5.83)	0.485	2.75 (0.32-4.34)	0.381
Duration of antibiotic use ≥ 8 days	2.93 (1.28-5.39)	<.0001***	3.26 (0.28-5.47)	0.547	1.94 (0.37-3.91)	0.229	1.89 (0.35-3.16)	0.672	2.56 (0.89-4.22)	0.502
Duration of probiotics use >14 days	1.85 (1.65-2.23)	0.005**	1.25 (0.84-2.28)	0.108	0.73 (0.23-1.28)	0.227	1.84 (1.46-2.47)	0.021*	0.68 (0.21-0.92)	0.183
Maternal smoking	2.43 (1.57-4.29)	0.004**	2.35 (0.37-3.58)	0.701	2.32 (0.56-5.25)	0.129	1.56 (0.32-4.56)	0.371	2.32 (0.54-3.75)	0.698
Hospital stay > 7 days	2.27 (1.36-5.62)	<.0001***	3.26 (0.73-5.47)	0.335	2.47 (0.53-4.28)	0.229	1.75 (0.47-3.82)	0.834	2.52 (0.43-4.94)	0.469

aOR: adjusted odds ratio, FGID: functional gastrointestinal disorder, *: p<0.05, **: p<0.01, ***: p<0.001

95% CI = 1.57-4.29, adjusted p = 0.004), and hospitalization longer than 7 days (adjusted OR = 2.27, adjusted 95% CI = 1.36-5.62, adjusted p <0.001) were considerably linked to infantile colic. There was a lower prevalence in infantile colic owing to probiotic use lasting more than 14 days (duration of probiotics use >14 days, adjusted OR = 1.85, adjusted 95% CI = 1.65-2.23, adjusted p = 0.005) and functional constipation (duration of probiotics use >14 days, OR = 1.84, adjusted 95% CI = 1.46-2.47, p = 0.02). Following birth, both exclusive breastfeeding (adjusted OR = 1.87, adjusted 95% CI = 1.36-2.92, adjusted p = 0.003) and formula feeding (adjusted OR = 1.84, adjusted 95% CI =1.21-3.83, adjusted p = 0.011) were considerably linked to infant regurgitation.

Discussion

Based on the retrospective evaluation of the preterm infant cohort in their first year of life, a high prevalence (73.4%) of FGIDs were found, which is in line with Salvatore's[1] study (76%). However, a higher prevalence (73.4%) of FGIDs was found than those reported in African (50%), American (24%), and European (25%) populations that were also based on the Rome IV criteria.[5,7,13] There may be an explanation for this situation as a significant portion of the subjects in this study were preterm infants receiving antibiotic treatment within the first month of their lives. This lower incidence in America might be attributed to the small sample size (n = 58). The low prevalence in the European population may be attributed to the fact that the subject's parents were interviewed by a healthcare professional who might interpret the symptoms differently. There are no specific biomarkers or investigations for diagnosing FGIDs. Therefore, clinical criteria are used instead, while organic disease warning signs are excluded. The Rome III criteria and, more recently, the Rome IV criteria give a thorough categorization of distinct FGIDs at various ages. Nevertheless, the likelihood of diagnostic

heterogeneity or misclassification among various physicians, as well as an overevaluation of the incidence of FGIDs, cannot be ruled out.

Infants with FGIDs suffer from a wide variety of disorders.[2] Over 70% of preterm subjects had at least one FGID, and 24.4% had more than one, with infantile colic and regurgitation being the most prevalent to present concurrently. Gastrointestinal infection along with early life experiences like gastric suction, cow milk protein allergies, inflammation, trauma, and stress have all been linked to a higher risk of visceral hyperalgesia and gastrointestinal problems late in life.[2,11,14-20] It is important to consider these results carefully and to replicate them in other preterm populations before drawing a general conclusion, as genetic and environmental factors, parental and physician perceptions, feeding patterns, and pharmacological treatments are all thought to be determinants of infant FGID rates.

The effects of different neonatal factors such as the gestation age, gender, birth weight, delivery type, feed patterns, antibiotics therapy, and probiotics therapy during the first month of life, maternal anxiety, maternal smoking, and duration of hospitalization in developing FGIDs among infants were simultaneously assessed. Both univariate and multivariate statistical analyses were conducted for the purpose of limiting the cumulative effects of various risk factors as well as for identifying the major factors contributing to FGIDs.

According to Milidou[21], infantile colic rates increase with decreasing gestational age. Further, the odds of infantile colic were higher among small-for-gestational-age infants possessing birth weights below the 10th percentile. We also found that infants with a gestational age of lower than 32 weeks have an enhanced risk of infantile colic and infant regurgitation. As reported in Danish and Italian studies, infants with lower birth weights are at double risk (or even higher) for developing infantile colic.[22,23] In line with this, our results indicated that low birth weight (<1.5 kg) was linked to an elevated risk of infantile colic as well as regurgitation.

In recent years, preterm birth as well as neonatal antibiotics usage during the first month of life has been linked with an ever-growing occurrence of FGIDs.[11,24] Premature birth and being exposed to a variety of variables that have been linked to influencing gastrointestinal homeostasis, pain perception, and sensitivity, lead to a higher incidence of preterm infants than term infants.[11,24] Compared with term neonates, the intestinal microflora of preterm infants is more susceptible to dysbiosis or imbalance in gut microbial communities, which is closely related to functional gastrointestinal disorders.[25] In this study, infants delivered by cesarean section were more vulnerable to functional constipation, which was the same as that reported by other studies.[26] Vaginal delivery is linked to considerably lower incidence of functional constipation; this phenomenon may be related to the intestinal microbiota of infants.[26] Several studies have shown that the mode of delivery influences gut microbiota among infants.[27] It is vertically transmitted maternal microbes to infants that contribute significantly to the establishment of the core gut microbiota. Notably, the microbiota of infants delivered via the vagina mimics their mother's vaginal microbiota, whereas those of cesarean-birthed neonates resemble the mother's skin microbiota.[28,29] Another study by Hojsak et al.[25] suggested that the early pattern of infant gut microbial colonization was critical for the suitable development of the human gastrointestinal tract.

It was further observed that infants being exclusively breastfed following birth have reduced risk of infant regurgitation, whereas it is enhanced for formula-fed infants. As part of its pathophysiology, regurgitation can be attributed to limited esophagus volume combined with the immaturity of the lower esophageal sphincter, overfeeding, and infant posture.[2] Parents tend to overfeed in the case of bottle feeding owing to being less likely to respond to the infant's satiety cues.[30] This

might illustrate why formula-fed neonates have a higher proclivity for regurgitation. There is evidence that breastfed infants have different feeding patterns that are associated with reduced reflux due to self-regulation of milk consumption, resulting in increased frequency and decreased volume of feedings.[31] Furthermore, breastfed babies have quick stomach emptying. As a result, a low esophageal pH value, which is more likely to trigger peristalsis, leads to a shorter period of reflux.[32]

Interestingly, it was also found that the prevalence of infantile colic is considerably elevated in the case of antibiotic use over 8 days in the neonatal period. This result was consistent with previous studies.[1,33] Antibiotics have been comprehensively utilized in premature infants, and current evidence also reflects the negative effects of antibiotics on gut microbiota's composition and functions thereof. Antibiotic-induced dysbiosis is an important factor in functional gastrointestinal disorders. Genetically susceptible newborns are at higher risk of allergy and inflammatory bowel disease after being given antibiotics in the early stages of life.[34-36] Infections as well as antibiotic usage during early life can cause immunological dysregulation, abnormal barrier functioning, microbiota change, and altered gut sensory activities, all of which can lead to FGIDs in susceptible individuals.[14,37]

It was also observed that early use of probiotics (less than 14 days after birth) as well as their usage for more than 14 days can reduce the incidence of infantile colic and functional constipation. The use of probiotics can improve the bacterial flora imbalance caused by long-term use of antibiotics, thus relieving infantile colic. Probiotic preparations significantly shorten gastrointestinal passage time, increase defecation frequency, and improve fecal traits, promoting defecation.[38]

This study also revealed that infantile colic was considerably associated with maternal smoking and hospitalization longer than 7 days. A plausible explanation could be that passive smoking is linked to increased plasma and intestinal motilin levels and higher-than-average levels of motilin are linked to elevated risks of infantile colic.[39] The mechanism underlying the length of hospitalization and the incidence of functional gastrointestinal disorders is unknown and requires additional investigation.

This study is of clinical significance since it includes the examination of a large cohort of preterm infants and many neonatal variables along with the utilization of Rome IV criteria for classifying FGIDs. It should be noted that this study has some of the following limitations: First, our study did not have a multi-center design. Second, we attained symptom data from parents, which may be inaccurate. Lastly, parents of infants who experience symptoms are more likely to respond.

Gastrointestinal symptoms are typically stressful to the newborn and parents, resulting in a cascade of events involving infant discomfort, crying, parental concern, diminished quality of life, recurrent healthcare professional visits, and rising healthcare expenditures.[6,40,41] Recognizing the exact incidence pattern of FGIDs is critical for developing a targeted program for parents' education as well as clinical follow-ups. Furthermore, identifying linked neonatal risk factors for FGIDs is a necessary measure for designing potential early-life therapies to reduce FGIDs later in life.[28,42]

Herein, it has been postulated that FGIDs may be prevented by reducing the unnecessary use of neonatal antibiotics, probiotics, and cesarean deliveries as well as by promoting breastfeeding for promoting intestinal homeostasis among at-risk neonates.

In conclusion, the incidence rate of FGIDs among premature infants was higher during the first year. Herein, the data have shown that infantile colic, as well as infant regurgitation, are among prevalent FGIDs, and some infants presented with a variety of FGIDs. It is worth

noting that low gestational age (<32 wks), low birth weight (<1.5 kg), neonatal antibiotic use, cesarean section, hospital stay, formula feeding, and maternal smoking are risk factors for FGIDs in preterm infants. In contrast, postnatal breastfeeding and probiotics supplementation are protective factors against infant FGIDs.

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Ethical approval

The protocol, information letter to the parents/caregivers and written informed consent form were approved by the ethics committee of Northern Jiangsu People's Hospital (2022ky291), Jiangsu, China. The survey was conducted in accordance with the guidelines of the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: HJ and GS; data collection: DB and KY; analysis and interpretation of results: DB, KY, TG and LH; draft manuscript preparation: DB, HJ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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