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Quality of life of down syndrome children with gastrointestinal disorders using pediatric quality of life inventory™ (Pedsql™) assessment

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***Abstract*---**GI disorders affect the quality of children. Children with Down syndrome have a high prevalence of GI disorders. This study aims to determine the life quality of Down syndrome children with GI disorders. This is a cross-sectional study using the PedsQL GI Symptoms Scale questionnaire & the ROME IV Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorder for Children & Adolescents. Samples of Down syndrome children were collected in January-May 2022. The analysis was performed using IBM SPSS Statistics 25. The study samples include 101 Down syndrome children aged 2-18 years. Nonstructural GI disorders consist of those with GERD (8.9%), those with GERD & diarrhea (1%), those with GERD & constipation (1%), those with diarrhea 3%, and those with constipation 18.8%. Structural GI disorders consist of those with duodenal atresia, Hirschsprung's disease, duodenal stenosis with annular pancreas, and anal atresia (1%, 3%,1%, and 4%, respectively). Down syndrome children without GI disorders had a good quality of life, while 51.5% of Down syndrome children with nonstructural GI disorders have a poor quality of life. The quality of life is impaired on the sub-symptom scale of food and drink limits, swallowing trouble, heartburn and reflux, gas and bloating, constipation, blood in bowel movements.

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Introduction

Health-related quality of life is an indirect indicator of the severity of a disease, especially in the absence of reliable biological markers, as is the case with Functional Gastrointestinal Disorders (FGID). The concept of quality of life assessment is an assessment of the state of individuals in terms of their value system and culture influenced by chronic and frequent conditions such as mental retardation. It is relatively essential for children with physical dysfunction to enjoy daily activities at home and in the community (El-Hady et al., 2018). Down syndrome is a genetic disorder caused by abnormal cell division resulting in a full or partial copy of chromosome 21. The majority of down syndrome individuals have an extra copy of chromosome 21 due to an imbalance number of genes that causes an increase in the number of human chromosome 21 (Hsa21) genes which results in increased gene expansion (Antonarakis et al., 2005). Based on the results of the national basic health research (RISKESDAS) in 2018, the number of new cases of Down Syndrome outpatients in hospitals in Indonesia in 2017 amounted to 4130 cases (Wardah et al., 2019).

Studies reveal that Down Syndrome patients' quality of life is most negatively related to the burden of medical conditions (Haddad et al., 2018). Down syndrome has a variety of signs and symptoms such as intellectual and developmental or neurological features disabilities, congenital heart defects, Gastrointestinal (GI) abnormalities, facial features, and other congenital abnormalities (Roper et al., 2006). A 10-year retrospective study stated that Down Syndrome has a high prevalence of GI disorders, namely 612 out of 1,207 (50.7%) (Bermudez et al., 2019). The Pediatric Quality of Life Inventory*™* (PedsQL™) questionnaire was utilized to measure the quality of life of patients with acute and chronic diseases (Brown et al., 2004). PedsQL 4.0 with generic instruments has also been utilized to measure the quality of life of pediatric patients with functional GI disorders and organic disease GI disorders (Varni et al., 2015). The PedsQL™ measurement consists of generic and disease-specific modules. The generic measurement scale consists of 23 items designed according to the health dimensions recommended by WHO (Brown et al., 2004). No study has been conducted on the quality of life of the Down Syndrome population with GI disorders. For this reason, this study is conducted to determine the GI disorders and the quality of life of Down syndrome children with GI disorders.

Method

This study is a cross-sectional study utilizing a questionnaire to assess the GI disorders and the quality of life of Down syndrome children with GI disorders. The study was conducted from December 2021 to May 2022. The quality of life of children with GI disorders was measured using the Pediatric Quality of Life Inventory*™* Gastrointestinal Symptom Scale*™* Instrument, while the FGID was measured using the ROME IV Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorder for Children and Adolescents. The data was collected through an internet survey using questionnaires and online interviews with the

parents of the research subjects. The data collection was conducted from January to May 2022. The quality of life of the subjects was analyzed using the PedsQL™ 3.0 Gastrointestinal Symptom Scale questionnaire.

The population in this study were Down syndrome children aged 2 to 18 years and their parents/guardians/caregivers who were willing to take part in this study through online interviews. The independent variables in this study include GERD, constipation, diarrhea, duodenal atresia, duodenal stenosis, annular pancreas, Hirschsprung's disease, imperforate anus/anal atresia, age, parent's occupation, gender, and parent's income. The dependent variable in this study is the quality of life of the Down syndrome children. The analysis was performed using statistical measures (median and distribution table). This study aims to determine the distribution of data on the GI disorders and the quality of life of Down syndrome children with GI disorders. The data were analyzed by chi-square test and Wilcoxon Mann Whitney test using IBM SPSS Statistics 25.

The ethical feasibility of this study will be submitted to the Health Research Ethics Committee (Komite Etik Penelitian Kesehatan or KEPK) of Dr. Soetomo General Hospital, Surabaya. The research was started after obtaining permission and approval from the Health Research Ethics Committee of Dr. Soetomo General Hospital number KEPK/0301/KEPK/XI/2021. The subject data are well maintained by applying an anonymous study design by not mentioning the names of the subjects. The data generated from the result of this study are utilized for research purposes.

Results and Discussion

The subjects of this study were 101 Down syndrome children with an average age of 6.6 years and the highest age range was 2-4 years amounted to 38.6%. A total of 53 subjects (52.5%) have undergone the Karyotyping test, while 48 (47.5%) of them have not undergone the test. All subjects were clinically diagnosed by a pediatrician according to the characteristics of Down's Syndrome. The majority of the subjects were male, totaling 59.4%. The literature states that Down syndrome children are more common in male than female, with a ratio of 1:1,059. It is considered to be caused by the failure of chromosomal segregation during spermatogenesis (Kovaleva et al., 2001; Shin et al., 2009). Of the 101 total participants, 42 subjects (41.6%) had GI disorders, while 59 subjects (58.4%) did not have GI disorders. Patients with trisomy 21 have many structural and functional abnormalities related to the GI tract (Holmes et al., 2014). Bermudez's study stated that GI abnormalities occurred in 612/1,207 (50.7%) Down syndrome patients (Bermudez et al., 2019). In this study, 82.2% of the Down syndrome children had a good quality of life and 17.8% had a poor quality of life. The concept of quality of life assessment is an assessment of the state of individuals in terms of their value system and culture influenced by chronic and frequent conditions such as mental retardation. It is relatively essential for children with physical dysfunction to enjoy daily activities at home and in the community (El-Hady et al., 2018).

This study utilizes a standardized questionnaire, namely ROME IV Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorder for Children and

Adolescents, to classify the subjects with GI disorders without structural disorders, hereinafter referred to as non-structural, while the structural disorders in the subjects were grouped based on a history of GI structural disorders that had been diagnosed by a pediatrician or pediatric surgeon, including subjects who had surgical intervention or not. Table 1 presents the distribution data of Down syndrome children with GI disorders in this study.

Table 1
GI Disorders in Down Syndrome Children

Gastrointestinal Disorders (n = 42)	n (%)
Nonstructural disorders[a]	33 (78.5)
Structural disorders[b]	9 (21.5)

[a] subject with one of the GI disorders: GERD, diarrhea, or constipation; [b] Subjects with one of the GI disorders: duodenal atresia, duodenal stenosis, Hirschsprung's disease, annular pancreas, anal atresia.

GI disorders in Down syndrome children correlates to embryonic and genetic formation, as well as environmental factors that play a role in the formation of Down syndrome genotypes (Malt et al., 2013; Maris et al., 2012). Congenital and acquired neurologic dysfunction of the esophagus and colon is common in Down syndrome patients and are associated with a higher incidence of gastroesophageal reflux disease and intestinal constipation (Smith et al., 2014). Bermudez's study stated that GI abnormalities occurred in 612/1,207 (50.7%) Down syndrome patients. Structural GI disorders are found in 32/612 (5%) cases, GERD is found in 14% of cases, and constipation is found in 49% of cases (Bermudez et al., 2019). Malt's study (2013) revealed that structural GI disorders in Down syndrome patients are found in 4-10% of cases (Malt et al., 2013).

The under-four-year group is dominated by children who do not experience GI disorders, totaling 46.2%, while the most impaired groups are the under-four-year and the four-to-eight-year groups with nonstructural GI disorders, totaling 38.4% and 37.1%, respectively. The diagnosis of structural disorders is conducted in the prenatal period and immediately after birth because symptoms appear early in life, thereby corrections are made during this period (Bermudez et al., 2019). Subject age had no statistical correlation with GI disorders with a p-value of 0.290 (Table 2).

Table 2
Correlation Analysis between Research Subject Characteristics and GI Disorders

Frequency Variable	No GI disorders[a] n = 59	Nonstructural GI disorders[a] n = 33	Structural GI disorders[a] n = 9	P-value
Subject Age (year)				0.290
<4	18 (46.2)	15 (38.4)	6 (15.4)	
4-8	16 (59.2)	10 (37.1)	1 (3.7)	
8-12	16 (72.7)	6 (27.3)	0 (0)	
12-18	9 (69.2)	2 (15.4)	2 (15.4)	

Sex				0.373
Male	34 (57.6)	21 (63.6)	5 (71.4)	
Female	25 (60.9)	12 (29.3)	4 (9.8)	
Father's Occupation				0.164
Civil Servant	10 (47.6)	8 (38.1)	3 (14.2)	
Private Employee	43 (64.1)	21 (31.4)	3 (4.5)	
Member of Indonesian National Armed Forces	1 (100)	0 (0)	0 (0)	
Self-employed	4 (44.5)	3 (33.3)	2 (22.2)	
Unemployed	1 (33.3)	1 (33.3)	1 (33.3)	
Father's Income				0.184
> IDR3 million	34 (58.6)	21 (36.2)	3 (5.2)	
IDR1-2 million	3 (42.8)	2 (28.6)	2 (28.6)	
IDR2-3 million	21 (63.6)	9 (27.3)	3 (9.1)	
No income	1 (33.3)	1 (33.3)	1 (33.3)	
Mother's Occupation				
Civil Servant	6 (46.2)	4 (30.8)	3 (23)	0.061
Private Employee	19 (82.6)	3 (13)	1 (4.4)	
Self-employed	4 (66.7)	2 (33.3)	0 (0)	
Unemployed	30 (50.8)	24 (40.7)	5 (8.5)	
Mother's Income				
> IDR3 million	14 (70)	5 (25)	1 (5)	0.238
IDR1-2 million	4 (80)	0 (0)	1 (20)	
IDR2-3 million	11 (64.8)	4 (23.5)	2 (11.7)	
No income	30 (51.7)	24 (41.4)	4 (6.9)	
Karyotyping[b]				0.302
Has been performed	29 (54.7)	17 (32)	7 (13.2)	
Has not been performed	30 (62.5)	16 (33.3)	2 (4.2)	

Table 3 presents the frequency distribution of Gastrointestinal disorders in Down syndrome children. This study describes non-structural GI disorders in Down syndrome children with GERD as many as 9 (8.9%). The literature states that the prevalence of GERD in Down syndrome patients is 87 (7.2%) with classic symptoms, including vomiting, regurgitation, and retrosternal burning or discomfort after eating, as well as lung symptoms, including aspiration pneumonia, chronic cough, and difficulty controlling asthma (Bermudez, 2019). Careful evaluation of these cases is very crucial due to the high frequency of complications in 43% of cases (Malt et al., 2013; Maris et al., 2012). This study found GERD disorders accompanied by diarrhea in only one subject (1%), and GERD disorders accompanied by constipation in only one subject (1%). A total of 3 subjects experienced diarrhea (3%). Das et al. (2015) stated that Down syndrome children in developing countries always experience malnutrition (Das et al., 2015; Valenzuela et al., 2011). In this study, 19 (18.8%) Down syndrome

children were found to have constipation. The prevalence reported in the literature varies from 19% to 56% (Wallace, 2007). Down syndrome is associated with a higher incidence of gastroesophageal reflux disease and constipation (Smith et al., 2014). Constipation in Down syndrome patients is caused by hypotonia, but in severe cases, Hirchsprung's disease should be excluded, as well as hypothyroidism and celiac disease (Malt et al., 2013; Maris et al., 2012).

This study found two subjects (2%) with a history of Hirschsprung and one subject (1%) with a history of Hirschsprung with diarrhea. Hirschsprung's disease is an inherited disorder characterized by the absence of ganglion cells in the Meissner plexus in the submucosa and the Auerbach plexus in the muscularis in the terminal rectum that extends proximally in varying distances (Martucciello, 2008). The quality of life of Hirschsprung patients depends on the degree of fecal continence. There is only a limited number of literature discussing the quality of life of Hirschsprung patients.

Table 3
Frequency Distribution of Gastrointestinal Disorders in Down Syndrome Children

Variables	Frequency[a] n =101
Nonstructural Disorders	
GERD	9 (8.9)
GERD + Diarrhea	1 (1)
GERD + Constipation	1 (1)
Diarrhea	3 (3)
Constipation	19 (18.8)
Structural disorders[b]	
Duodenal atresia	1 (1)
Duodenal stenosis + annular pancreas[c]	1 (1)
Hirschsprung's disease	3 (3)
Anal Atresia	4 (4)
No GI Disorders	59 (58.3)

[a]: n(%); [b]: structural disorders from the subject's past medical history.

In the study, 2 (2%) subjects had Gastrointestinal Structural Duodenal atresia. Duodenal atresia was the most frequent cause requiring surgical intervention as GI malformations occurred in 13/32 (40.6%) of cases (Bermudez et al., 2019). One subject (1%) in this study had an annular pancreatic malformation accompanied by duodenal stenosis. Previous literature stated that the annular pancreas was found in 1-5% of Down syndrome children, and it was found in 0.05% of non-Down syndrome children (Malt et al., 2013; Maris et al., 2012). From 101 Down syndrome subjects, this study found 4 subjects (4%) with structural GI disorders, constipation, and a history of anal atresia. Regarding constipation that occurs in anal atresia after surgical correction, the literature states that such constipation generally occurs in low-lying anal atresia. Inadequate treatment, type of colostomy, and postoperative anal or stoma structures and stenotic fistulas are key factors that contribute to postoperative constipation (Levitt, 2007).

The quality of life of the subjects in this study was measured using the PedsQL 3.0 gastrointestinal symptom scale parents report according to the age classification on the questionnaire. It was found that 83 subjects (82.2%) had a good quality of life and 18 subjects (17.8%) had poor quality of life (Table 4). Down syndrome children usually experience generalized muscle weakness, as well as slow postural reactions and response times, in addition to hyperflexible joints that interfere with their daily activities and result in a lower quality of life. Most studies emphasize primary motor and sensory disorders and fail to address functional outcomes (Martin, 2009; El-Hady et al., 2018).

Table 4
Analysis of Quality of Life of Down Syndrome Children with GI Disorders

Variables	Quality of Life of Down Syndrome Children		
	Good[b,d] n = 83	Poor[c,d] n = 18	P-value
GI Disorders			< 0.001*
No disorder	59 (100)	0 (0)	
Gastrointestinal			
Nonstructural disorders	16 (48.5)	17 (51.5)	
Structural Disorders	8 (89.9)	1 (11.1)	

[a]: analysis quality of life using the PedsQL GI Symptom scale parents report questionnaire; [b]: PedsQL score >/= 70%; [c]: PedsQL score <70%; [d]: n (%). Pearson Chi-Square test, Fisher Exact test as appropriate; *: a p-value of less than 0.05 means the variable is statistically significant.

A total of 59 subjects (100%) consisting of Down syndrome children with no GI disorders had a good quality of life. Meanwhile, 16 subjects (48.5%) consisting of Down syndrome children with nonstructural GI disorders had a good quality of life, and 17 of them (51.5%) had a poor quality of life Overall, 7 (100%) subjects with structural GI disorders had a good quality of life. The nonstructural GI disorder group was dominated by those experiencing poor quality of life. The literature states that symptoms related to health-related quality of life in children include bloating, vomiting, and headaches (Ranasinghe et al., 2018). A similar study conducted on adolescents with GI disorders in Sri Lanka reported an association between vomiting and bloating and health care (Devanarayana et al., 2014). There was a significant correlation between symptom severity (severity of abdominal pain, dyspepsia, and bowel symptoms, as well as the frequency of abdominal pain) and scores obtained for Health-related QoL (Devanarayana et al., 2014).

Table 5
The average value of the Symptom Scale on the PedsQL 3.0 GI Symptom Scale for Down Syndrome Children

Symptom scale[a]		No GI Disorders (n = 59)	Nonstructural GI Disorders (n = 33)	Structural GI Disorders (n = 9)
	Scores[b]	Median	Median	Median
Stomach Pain and Hurt	600	600	600	600
Stomach discomfort when eating	500	500	450	500
Food and drink limits	600	425	325	325
Trouble Swallowing	300	200	100	81.25
Heart Burn and reflux	400	400	400	400
Nausea and Vomiting	400	400	400	400
Gas and Bloating	700	650	550	631.25
Constipation	1,400	1,400	350	1,137.5
Blood in bowel movement	200	200	200	200
Diarrhea	700	700	700	575

The data are not normally distributed, so the median is used to describe the data; [a] ten symptom scale items on the PedsQL 3.0 GI symptom scale questionnaire; [b] maximum score for each symptom scale.

This section discusses the description of the distribution of the value of each symptom and the average value of the subjects on the symptom based on the group of GI disorders. Symptoms Stomach Pain and Hurt, Heart Burn and reflux, Nausea and Vomiting, Blood in bowel movement in all groups had the same median value as the maximum score, meaning that all study subjects had no complaints about these symptoms (Table 5). It is different from the literature which stated that symptoms of heartburn and reflux occurred in 3.5% of the population, and this disorder will interfere with the quality of life of individuals (Choi et al., 2011).

The group with GI disorders had complaints of stomach discomfort when eating. Meanwhile, food and drink symptoms and limited symptoms of trouble swallowing occurred in all groups. GERD remains one of the most common causes of esophageal symptoms in Down syndrome (Zarate, et al., 2001). Down syndrome children often experience low suction power and swallowing disorders (Ravel, et al., 2020). Eating disorders in Down syndrome patients are not due to delays in relevant skill development but because of abnormal development and the fact that eating is a less enjoyable activity for them. Chewing and aspiration disorders are

common during breastfeeding, which delays the introduction of solid foods. Reflux of food through the nose is common in some individuals in early life, which seems to correlate to the shape of the palate that prevents full contact with the back of the tongue (Faulks et al., 2008; Ravel et al., 2020).

Table 6
Analysis of differences in the mean value of the Symptom Scale on PedsQL 3.0 GI Symptom Scale in Down Syndrome Children

Symptom Scale		No GI Disorders (n = 59)	No GI Disorders (n = 42)	P-value
	Scores[a]	Median[b]	Median[b]	
Stomach Pain and Hurt	600	600	600	0.31
Stomach discomfort when eating	500	500	500	0.055
Food and drink limits	600	425	300	0.002*
Trouble Swallowing	300	200	87.5	0.001*
Heart Burn and reflux	400	400	400	0.001*
Nausea and Vomiting	400	400	400	0.121
Gas and Bloating	700	650	587,5	0.001*
Constipation	1,400	1,400	725	<0.000*
Blood in bowel movement	200	200	200	<0.000*
Diarrhea	700	700	700	0.218

[a] maximum score for each symptom scale; [b] The data were not normally distributed, therefore the median was used, the Wilcoxon Mann Whitney test. * p-value below 0.05 means the variable is statistically significant.

The symptoms of gas and bloating occurred in all the group who have complaints. The literature states that complaints of bloating occur in 4% of patients with GI disorders. This disorder will interfere with the quality of life of individuals (Choi et al., 2011). The symptom of constipation was complained by most of the subjects, especially those with nonstructural GI disorders. The literature states that constipation occurs in 2.6% of patients with GI disorders. This disorder will interfere with the quality of life of individuals (Choi et al., 2011). Regarding the symptom of diarrhea in Down syndrome patients with structural GI disorders, on average, the subjects of this study stated that they had experienced diarrheal disorders/symptoms. It is in line with the literature, stating that one of the most common complications associated with Hirschsprung's disease is Hirschsprung-associated Enterocolitis (HAEC), which is defined as an inflammatory bowel disorder (Frykman et al., 2015).

Symptom scale on the PedsQL GI symptom scale questionnaire in Down syndrome children, the quality of life is impaired on the sub-symptom scale of food and drinks limits, swallowing trouble, heartburn and reflux, gas and bloating, constipation, and blood in bowel movement. There was a statistical difference between Down syndrome children with GI disorders and with no GI disorders with a p-value of 0.002 respectively; 0.001; 0.001; 0.001; <0.000; <0.000 (Table 6). The literature states that 19% of Down syndrome patients are treated for drinking disorders (Ravel et al., 2020). GERD was observed in 87 (7.2%) Down syndrome patients with GERD symptoms, including classic symptoms such as vomiting, regurgitation, retrosternal burning, or discomfort after eating, as well as pulmonary symptoms such as aspiration pneumonia, chronic cough, and difficulty controlling asthma (Bermudez, 2019). In this study, Down syndrome children on average had constipation disorders. It is in accordance with the literature, stating that constipation in Down syndrome is usually caused by hypotonia, but in severe cases (Malt et al., 2013; Maris et al., 2012).

Conclusion

The distribution of Down syndrome children with GI disorders is 41.6% and is dominated by GI disorders constipation. In addition, 51.5% Down syndrome children with GI disorders had a poor quality of life. Based on the Symptom Scale on the PedsQL 3.0 GI Symptom Scale, the poor quality of life is due to complaints of food and drink limits, swallowing trouble, heartburn and reflux, gas and bloating, constipation, and blood in bowel movement.

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