ORIGINAL ARTICLE

Comparing the Time of Passage of the First Meconium (PoFM) in Neonates With and Without Hirschsprung's Disease (HD)

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Objective: To compare the age at "passage of the first meconium" (PoFM) in neonates with and without Hirschsprung's disease (HD) and determine the optimal cut-off age for predicting HD.

Materials and Methods: A retrospective investigation was conducted on selected neonates at Siriraj Hospital, including those with HD, between January 2000 and December 2022.

Results: The study included 800 neonates, including 38 with HD and 762 non-HD. At 24 hours, 3.0% of non-HD and 10.5% of HD had delayed PoFM, a statistically significant difference (p=0.035). Despite the common perception that the risk of HD increases if neonates did not pass their first meconium within the first 24 hours, 89.5% of HD patients pass their first meconium in less than a day. The median ages of PoFM were 10.5 hours for HD and 8.0 hours for non-HD, respectively, with no statistically significant difference between the groups (p=0.289). A receiver operating characteristic (ROC) curve and area under the ROC (AUC) were used to determine the optimal cut-off value of PoFM age (hour) for predicting HD. The AUC for PoFM age, in hour, was 0.551, and the optimal cut-off value could not be determined. Prenatal $MgSO_4$ or steroid therapy did not affect the age of PoFM (p=0.966 and 0.452, respectively).

Conclusion: Eighty-nine-point-five percent of HD patients passed their first meconium within 24 hours. The PoFM was similar for both HD and non-HD groups.

Keywords: Hirschsprung; Diagnosis; Meconium; Stool; Preterm; Neonate; Newborn

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Hirschsprung's disease (HD) is characterized by a deficiency of ganglion cells in the rectum and distal colon, making it difficult for feces to pass through these pathologic spots. Approximately 95% of full-term neonates pass their first meconium within the first 24 hours[1] and 99% do so within 48 hours[2,3]. HD is often suspected in patients with delayed "passage of the first meconium" (PoFM). The likelihood of HD increases if the neonate does not pass meconium within the first 24 hour[1] and even higher if PoFM was postponed beyond 48 hours[4].

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HD is often suspected in cases of delayed PoFM. However, related literature shows that only 10%[1] to 40%[5] of neonates with HD pass their first meconium within 24 hours. This indicates that delayed PoFM is present in some percentages of HD patients. Nevertheless, no research has directly compared the age of PoFM in neonates with and without HD.

The effects of prematurity[2,3,6], birth weight less than 2,500 g[7], the use of magnesium sulfate ($MgSO_4$) in preeclampsia/eclampsia[8-11], and the use of steroids in early labor[6,9] will be gathered and investigated in relation to the age of PoFM. These conditions are known to cause delayed PoFM.

The main objective of the present study was to compare the age at PoFM between neonates with and without HD. If a statistically significant difference is found, the optimal cut-off age at PoFM to predict HD will be determined. The secondary goal was to compare HD and non-HD cases to examine potential causes of delayed PoFM, such as prematurity, low birth weight, $MgSO_4$ administration, and steroid treatment.

Materials and Methods

A retrospective analysis was conducted on neonates treated or born at Siriraj Hospital, Faculty of Medicine, Mahidol University, Thailand, between January 2000 and December 2022, with permission from the Siriraj Institutional Review Board (COA. no. Si 469/2023).

The age at PoFM was defined as the neonate's age when meconium was first passed without rectal stimulation, whether it was inserting a thermometer, a per rectal examination, or inserting a rectal tube.

The researcher was aware of the issue prior to the study because they needed to access each HD patient's medical records to determine the age at which they first passed meconium. It was unknown at the time of medical recording whether the patient would receive an HD diagnosis, and such recording of the number of hours that feces occurred might not be broken down into hourly details. Thus, it was necessary to determine the sample size first.

Sample size calculation

The effect size was deemed large since the percentage of neonates with HD who reached PoFM within 24 hours ranged from 10%[1] to 40%[5], while the percentage of neonates without HD who reached PoFM within 24 hours ranged from 95% to 95%. The researcher determined the effect size of the comparison of the mean age of PoFM equal to 0.35. To obtain a sufficient sample size to find statistical significance for an effect size of 0.35 or more, when the significance level (α) was set to 0.05 percent, the power of the test was 80 (β=0.2), and the ratio of neonates with HD to neonates without HD was 1 to 10.

Therefore, the required sample sizes for this study were 71 neonates with HD and 707 neonates without HD, for a total of 778 children. Finding hourly meconium-passing data in HD that could be diagnosed over time proved to be quite challenging, the researcher discovered. There were 422 HD patients during the present study time. Therefore, according to the researcher's pre-study estimation, it would be feasible to gather data on the specifics of the defecation hours of HD patients born at Siriraj Hospital over a 22-year period, which should be more than 71 cases. This should be contrasted with the defecation hours of neonates without HD in 707 normal subjects who were randomized during the same time period.

The following demographic information gathered the date of birth, age of PoFM in hours, gender, gestational age in weeks, birth weight in grams, prenatal $MgSO_4$, and antenatal steroid use. HD was diagnosed based on a study of pathological data.

The exclusion criteria were neonates without information regarding the age of PoFM, neonates admitted to the intensive care unit or high-risk nursery ward, neonates with gastrointestinal dysfunction other than HD, neonates who underwent any surgery for the gastrointestinal system other than HD, and patients with severe respiratory and cardiac disorders requiring treatment with drugs that affect defecation.

Data was collected and analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Qualitative data were expressed as numbers and percentages, whereas quantitative data were expressed as the median and range (min, max). For qualitative data, factors causing delayed PoFM between HD and non-HD were compared using the Fisher's exact test or the chi-square test. The unpaired t-test or the Mann-Whitney U test was used to compare the mean or median, respectively, between HD and non-HD for quantitative data such as age, birth weight, and PoFM age.

To determine the optimal cut-off value of PoFM age for predicting HD, a receiver operating characteristic (ROC) curve and area under the ROC (AUC) analysis were conducted. An AUC of 0.5 indicates that the cut-off value of PoFM could not be used to diagnose HD. An AUC of 0.7 to 0.8 was considered acceptable, an AUC of 0.8 to 0.9 was deemed excellent, and an AUC greater than 0.9 was deemed outstanding[12]. Statistical significance was indicated by a p-value of less than 0.05.

Results

The researchers planned to find the age of PoFM in at least 71 HD patients out of the 422 patients with HD that were diagnosed between January 2000 and December 2022, but in reality, the researchers discovered that only 38 cases could be searched. To assess the age at PoFM of neonates with and without HD, these 38 HD cases were compared to 762 neonates without HD delivered within the same period at Siriraj Hospital.

Table 1 presents the demographic information for the 38 HDs and the 762 non-HDs. Compared to non-HD, HD had more term neonates at 37 weeks or more ($p<0.001$) and more normal weight at 2,500 g or more ($p<0.001$). Therefore, prenatal steroids used in pregnant women with premature labor were used less frequently in the HD group compared to the non-HD

Table 1. Comparison of HD and non-HD demographic data

Variables	HD (n=38) n (%)	Non-HD (n=762) n (%)	p-value
Sex			0.806
Male	18 (47.4)	387 (50.8)	
Female	20 (52.6)	375 (49.2)	
Gestational age			<0.001
Preterm (<37 weeks)	4 (10.5)	554 (72.7)	
Term (≥37 weeks)	34 (89.5)	208 (27.4)	
Birth weight			<0.001
Low birth weight (<2,500 g)	6 (15.8)	398 (52.2)	
Normal (≥2,500 g)	32 (84.2)	364 (47.8)	
Antenatal $MgSO_4$			0.304
No	36 (94.7)	667 (87.5)	
Yes	2 (5.3)	95 (12.5)	
Antenatal steroids			<0.001
None	36 (94.7)	165 (21.7)	
Incomplete	1 (2.6)	422 (55.4)	
Complete	1 (2.6)	175 (23.0)	

HD=Hirschsprung's disease

group (p<0.001).

Table 2 presents the number of neonates with PoFM at 24, 36, and 48 hours of age, along with a comparison of HD and non-HD neonates. The percentage of neonates with delayed PoFM at 24 hours was 10.5% for HD and 3.0% for non-HD, with the difference being statistically significant (p=0.035). At 36 hours, the percentages of delayed PoFM were 5.3% for HD and 0.3% for non-HD, also showing a statistically significant difference (p=0.012).

Despite the common belief that HD is more likely when a neonate does not defecate within the first 24 hours, most HD patients (89.5%) passed their first meconium within this timeframe. Therefore, it was not possible to conclude directly that HD neonates had a later PoFM than non-HD neonates. Consequently, this investigation compared the ages of PoFM in HD and non-HD cases. Notably, no neonate, including those with HD, had a delayed PoFM of more than 48 hours.

Table 3 compares the ages of PoFM between HD and non-HD patients concerning prematurity at less than 37 weeks and low birth weight at less than 2,500 g. The median ages of PoFM for HD and non-HD patients were 10.5 and 8.0 hours, respectively, with no statistically significant difference between them (p=0.289).

In the preterm group, the median ages of PoFM for HD and non-HD patients were 10.5 and 8.5 hours, respectively, with no statistically significant difference (p=0.141). The interpretation was limited by the dissimilar demographic data between HD and non-HD, indicating that the proportion of preterm neonates with HD was lower than that of non-HD (p<0.001). In the low birthweight group, at less than 2,500 g, the median ages of PoFM for HD and non-HD individuals were 10.5 and 8.0 hours, respectively, with no statistically significant difference (p=0.176). Additionally, interpretation was constrained by distinct demographic data, showing that HD had a higher percentage of normal weight at 2,500 g or more, compared to non-HD (p<0.001).

Figure 1 presents a study demonstrating an ROC curve and AUC analysis to determine the optimal cut-off value for the age of PoFM, in hours, to predict HD. The age of PoFM, in hour, had an AUC of 0.551 (95% CI 0.430 to 0.672), indicating an inability to distinguish between HD and non-HD based on these data[12]. As a result, it was not possible to calculate the optimal cut-off value from the curve coordinates.

The present study involved 38 patients with HD, of whom only two (5.3%) received prenatal magnesium and two received antenatal steroids. Consequently, it was not possible to draw any conclusions on the impact of these interventions

Table 2. Comparison of HD and non-HD infants, total number of neonates with PoFM at 24, 36, and 48 hours

	Total (n=800) n (%)	HD (n=38) n (%)	Non-HD (n=762) n (%)	p-value
PoFM ≤24 hours	773 (96.6)	34 (89.5)	739 (97.0)	0.035
PoFM >24 hours	27 (3.4)	4 (10.5)	23 (3.0)	
PoFM ≤36 hours	796 (99.5)	36 (94.7)	760 (99.7)	0.012
PoFM >36 hours	4 (0.5)	2 (5.3)	2 (0.3)	
PoFM ≤48 hours	800 (100)	38 (100)	762 (100)	NA
PoFM >48 hours	0 (0.0)	0 (0.0)	0 (0.0)	

HD=Hirschsprung's disease; PoFM=passage of the first meconium; NA=not applicable

Table 3. Compare the ages of PoFM patients from the HD and non-HD groups, considering low birth weight (<2,500 g) and prematurity (<37 weeks)

	HD (n=38) (hours) median (min, max)	Non-HD (n=762) (hours) median (min, max)	p-value
All (n=800)	10.5 (1, 48)	8.0 (0.5, 40)	0.289
Preterm	10.5 (10, 26)	8.5 (0.5, 40)	0.141
Term	10 (1, 48)	6.5 (0.5, 30)	0.199
Low BW (<2,500 g)	10.5 (1.5, 26)	8.0 (0.5, 40)	0.176
Normal BW (≥2,500 g)	10 (1, 48)	7.5 (0.5, 36)	0.481

HD=Hirschsprung's disease; BW=birth weight

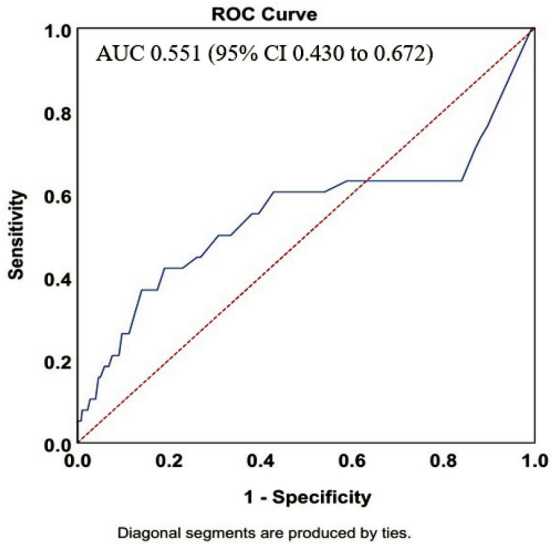

Figure 1. ROC curve and AUC for predicting Hirschsprung's disease based on the median age of PoFM (hours).

Table 4. Age comparison of PoFM between newborns receiving antenatal magnesium and prenatal steroids

	Age of PoFM (hours) median (min, max)	p-value
Antenatal $MgSO_4$		0.966
No (n=703)	8 (0.5, 48)	
Yes (n=97)	8 (0.5, 26)	
Antenatal steroids		0.452
None (n=201)	8.5 (1, 48)	
Incomplete doses (n=423)	7.5 (0.5, 40)	
Complete doses (n=176)	8.5 (5, 37)	

PoFM=passage of the first meconium

on delayed PoFM in HD patients. Thus, the age distribution of PoFM across the entire group of 800 patients was compared for those receiving prenatal magnesium and antenatal steroids. The results are presented in Table 4. The age of PoFM was unaffected by the administration of prenatal $MgSO_4$ (p=0.966) or antenatal steroids (p=0.452).

Discussion

According to reports, 95%[1] and 99%[2,3] of neonates born at full term pass their first meconium within the first 24 and 48 hours, respectively. The present study's findings, consistent with these earlier publications[1-3] showed that 97.0% and 99.7% of non-HD neonates passed their first meconium within the first 24 and 36 hours, respectively. Additionally, it is widely recognized that delayed PoFM is often the first sign that prompts a neonatologist to suspect HD. The present study findings corroborated the anecdotal statement that HD is more likely when an infant does not pass meconium within the first 24 hours[1] and 48 hours[4]. In the present study, the percentages of delayed PoFM at 24 hours were 10.5% for HD and 3.0% for non-HD, a statistically significant difference (p=0.035). Similarly, the percentages of delayed PoFM for 36 hours were 5.3% for HD and 0.3% for non-HD, also statistically significant (p=0.012). It was not feasible to draw the conclusion that HD should be linked to delayed PoFM because the vast majority of HD participants in the present study (89.5%) passed their first meconium in less than a day.

The previous studies[1,5] have surprisingly reported that between 10%[1] and 40%[5] of patients with HD passed their first meconium after 24 hours of life. No published work has examined the number of hours it takes for a neonate with HD to pass meconium. Diagnosing HD at birth may be challenging, but it often becomes apparent later, when these babies show symptoms of severe abdominal distention, constipation, and Hirschsprung's enterocolitis. In the present series, of the 422 children diagnosed with HD over the 22-year study period, only 38 had sufficient information available to establish their PoFM ages.

As far as the authors were aware, no studies have directly compared the age of PoFM in neonates with and without HD. In the present study, the median ages of PoFM for HD and non-HD were 10.5 and 8.0 hours, respectively, with no statistically significant difference (p=0.289). The optimal cut-off age of PoFM, in hour, to predict HD was determined using a ROC curve and AUC, which showed an AUC of 0.551 (95% CI 0.430 to 0.672). This data indicates an inability to distinguish between HD and non-HD[12].

Within 24 hours, the majority of HD patients (89.5%) passed their first meconium. Therefore, it was not possible to directly infer that HD had a later PoFM than non-HD. There are reasons why certain HD patients might not be able to pass meconium within the first 24 hours of life. Additional research is needed to determine the factors that cause some HD patients to delay passing meconium. The failure to pass feces within 24 hours of birth was used as the diagnostic cut-off point for HD, even though most HD patients passed meconium on the first day.

In addition, the present research examined other potential causes of delayed initial meconium passage, including low birth weight, preterm birth, and the use of steroids and/or $MgSO_4$.

Delayed meconium passage was also observed in premature neonates[2,3,6], however, it primarily

affected preterm neonates aged 31 to 34 weeks[6]. Premature neonates make up about 7% of HD patients[13]. In the present research, 10.5% of HD patients were premature. Due to intrinsic gastrointestinal tract immaturity, premature neonates may experience intestinal dysmotility, resulting in symptoms such as delayed meconium transit that resemble HD[14]. No comparative study has been conducted to determine whether premature neonates with HD have a longer meconium transit delay than premature neonates without HD. Table 3 shows that the median ages of PoFM for HD and non-HD in the preterm group were 10.5 and 8.5 hours, respectively. The difference between them was not statistically significant (p=0.141), but interpretation was limited because the demographic data indicated that HD had a higher percentage of term births, at 37 weeks or more, than non-HD (p<0.001).

Babies weighing fewer than 2,500 g at birth were said to have a delayed meconium passage compared to those weighing more than or equal to 2,500 g[7]. In the present study, as shown in Table 3, the median ages of PoFM for HD and non-HD in the low-birth-weight group, at less than 2,500 g, were 10.5 and 8.0 hours, respectively. The difference was not statistically significant (p=0.176), but interpretation was also limited because our demographic data revealed that HD had a higher normal weight of 2,500 g or more than non-HD (p<0.001).

In cases of preeclampsia/eclampsia, $MgSO_4$ is used to suppress neuromuscular transmission. This can lead to colonic hypomotility, impairing an infant's peristaltic function, and delaying the first meconium passage. Studies have shown that the use of $MgSO_4$ for tocolysis delays meconium passage[9,10], while others have observed the opposite[8,11]. Steroids are used in early labor cases. While reports[9] showed no significant differences in meconium passing, research by Kumar & Dhanireddy[15] observed that infants whose mothers received steroid injections had significantly delayed PoFM.

Only two (5.3%) of the 38 HD patients in the current study received prenatal magnesium, and two (5.3%), received antenatal steroids. As a result, no inferences of the effect of these therapies on delayed PoFM in HD patients could be made. Thus, the age distribution of PoFM across the entire group of 800 patients was compared for those receiving prenatal magnesium and antenatal steroids. The present research found that both prenatal steroids (p=0.452) and prenatal $MgSO_4$ dosage (p=0.966) had no effect on the age of PoFM.

Limitation

Because 422 HD patients were the subject of the present retrospective investigation, the researchers only needed 71 HD patients whose PoFM age was known prior to the study, which was sufficient to compare with the population of at least 707 healthy neonates born at the same time. Despite doing a thorough retrospective record analyses, only 38 HD patients with known PoFM ages were found, which was a small number. However, no study on the age of POFM hourly has ever been published in any medical journals. Additionally, the control group under study and comparison was chosen at random from the same institution throughout the same time period. The population of the control patients born at Siriraj Hospital, Thailand's largest university hospital, could differ from that of the hospital as a whole. Complicated pregnancies sent from various institutions may occur, and the non-HD group giving birth at Siriraj Hospital frequently has a risk of preterm and/or low birth weight[16]. Because of these, studying them is extremely challenging. No comparable study has ever been conducted previously. Since it was difficult to determine the age of PoFM in HD patients, more studies with bigger cohorts are needed.

Most HD individuals in the present study did not have abnormally delayed meconium passage. Though they made up a small percentage of HD patients, children who had delayed passage of meconium for more than 24 hours were suspected of having HD.

Compared to non-HD patients, HD patients had higher proportions of term and normal weight in the present study. It was challenging to compare the median ages of PoFM between HD and non-HD with regard to prematurity and/or low birth weight and evaluate these effects because of the disparities in demographic data. Additionally, prenatal magnesium and antenatal steroids were administered to just a small percentage of the 38 HD patients in the current study. Therefore, it was unable to draw conclusions about how these treatments affected HD patients delayed PoFM.

Conclusion

The present study supported the assertion that in HD neonates, "delayed POFM for more than 24 hours would be the first sign a neonatal doctor would be suspicious of." In non-HD neonates, the 24-hour delayed PoFM was 3.0%, whereas in HD neonates, it was 10.5%, a difference that was statistically significant (p=0.035). However, the majority of HD

patients (89.5%) in the present study were able to pass their first meconium in less than a day. The median ages of PoFM for HD and non-HD in the present study sample did not differ statistically significantly (p=0.289).

All babies should have their PoFM age included in the nursery note after birth. The age of PoFM was not a reliable indicator of HD, and even if neonates did not have delayed PoFM, HD could not be ruled out.

What is already known about this topic?

HD is often suspected of neonates with delayed PoFM. The likelihood of HD increases if the baby did not pass meconium within the first 24 hours and is even higher if PoFM was postponed beyond 48 hours.

What does this study add?

These findings corroborated the anecdotal statement that HD is more likely when an infant does not pass meconium within the first 24 hours. However, the majority of HD patients (89.5%) in this study were able to pass their first meconium in less than a day. The median ages of PoFM for HD and non-HD in the study sample did not differ statistically significantly (p=0.289).

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Conflicts of interest

The authors declare no conflicts of interest.

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