

21. RISK FACTORS INFLUENCING ENTEROCOLITIS DEVELOPMENT IN PEDIATRIC PATIENTS WITH HIRSCHSPRUNG'S DISEASE

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ORIGINAL RESEARCH

RISK FACTORS INFLUENCING ENTEROCOLITIS DEVELOPMENT IN PEDIATRIC PATIENTS WITH HIRSCHSPRUNG'S DISEASE

Faktor Risiko Terjadinya Enterokolitis pada Pasien Pediatri dengan Penyakit Hirschsprung di RSUD Dr. Soetomo

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ABSTRACT

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Background: Hirschsprung-associated enterocolitis (HAEC) is one of the worst and most common complications of Hirschsprung's disease (HD). The mortality rate of HD patients with enterocolitis is still considered to be higher compared to that of those without enterocolitis. **Purpose:** This study aimed to identify and evaluate potential risk factors for HAEC development. **Methods:** A cross-sectional study was conducted using secondary data from the medical records of HD patients treated from January 2015 to September 2018 at Regional Public Hospital (RSUD) Dr. Soetomo, Surabaya. The inclusion criteria were HD patients who had or had not experienced enterocolitis. The analysis was done by comparing the presence of risk factors between groups of HD patients with and without preoperative and/or postoperative HAEC. The results were presented as the median value and frequency. To evaluate further, a prevalence ratio (PR) with a 95% confidence interval was performed. The Mann-Whitney U test was also performed with a significance level of $p < 0.05$ for one factor: length of aganglionic intestinal segments. **Results:** This study showed that 12 of the 40 HD patients studied (30%) had experienced enterocolitis. The risk of developing HAEC was associated with patients who had a history of previous enterocolitis (PR 6.60 [2.94 < PR < 14.80]). Regarding surgical details, patients who had had surgery only once (31.30% compared to 14.30%), surgery with one surgical method (29.40% compared to 20.00%), and a primary procedure had a higher incidence of HAEC (29.40% compared to 27.30%). **Conclusion:** HD patients with a history of previous enterocolitis were found to have a higher risk of developing HAEC.

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ABSTRAK

Pendahuluan: Hirschsprung-associated Enterocolitis (HAEC) merupakan salah satu komplikasi tersering dan terparah dari Penyakit Hirschsprung (PH). Tingkat mortalitas pasien PH yang disertai enterokolitis masih dianggap lebih tinggi dibandingkan dengan yang tidak mengalami enterokolitis. **Tujuan:** Penelitian ini bertujuan untuk mengidentifikasi dan mengevaluasi faktor risiko potensial pemicu terjadinya HAEC. **Metode:** Sebuah studi cross-sectional dilakukan menggunakan data sekunder dari rekam medik pasien PH yang dirawat pada Januari 2015 hingga September 2018 di RSUD Dr. Soetomo. Kriteria inklusi penelitian ini adalah pasien PH yang mengalami atau tidak mengalami enterokolitis. Analisis dilakukan dengan membandingkan adanya faktor risiko antara kelompok pasien PH dengan dan tanpa HAEC, baik praoperasi maupun pascaoperasi. Hasil penelitian ini disajikan dalam nilai median [IQR] dan frekuensi (%). Untuk evaluasi lebih lanjut, analisis Prevalence Ratio (PR) dengan Confidence Interval (CI) 95% dilakukan. Uji Mann-Whitney U juga dilakukan dengan nilai signifikansi $p < 0,05$ untuk satu faktor, panjang segmen usus yang aganglionik. **Hasil:** 12 dari 40 pasien PH yang diteliti (30%) mengalami enterokolitis. Risiko terjadinya HAEC secara signifikan terkait dengan pasien yang memiliki riwayat enterokolitis sebelumnya (PR 6,60 [2,94 < PR < 14,80]). Rincian bedah, dalam hal ini, pasien yang menjalani operasi hanya sekali, pasien yang menggunakan satu metode bedah dalam satu operasi, dan pasien yang menjalani operasi prosedur primer akan lebih cenderung untuk mengalami HAEC (berturut-turut, 31,30% dibandingkan dengan 14,30%, 29,4% dibandingkan dengan 20,00%, dan 29,4% dibandingkan dengan 27,30%). **Kesimpulan:** Pasien PH dengan riwayat enterokolitis sebelumnya memiliki risiko lebih tinggi untuk mengalami HAEC.

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INTRODUCTION

Hirschsprung's disease (HD) is a congenital disease associated with the developmental failure of the enteric nervous system in some parts of the intestines, especially the large intestines (colon), that causes functional obstruction of the gastrointestinal tract. As a congenital disease, it has a quite high incidence and occurs in one out of every 5,000 live births, especially in males; the male:female ratio is 4:1 (Ralls, Coran, Teitelbaum, Destro, & Lima, 2017). The most common and severe complication of HD is Hirschsprung-associated enterocolitis (HAEC). Even though the mortality rate of HAEC has begun to decline, it is still considered as the main cause of mortality and

morbidity in HD since mortality happens in about 50% of patients (Moore, 2016). As is known, HAEC may occur either preoperatively or postoperatively in HD with an incidence rate of 6%–26% and 5%–42%, respectively (Demehri, Halaweish, Coran, & Teitelbaum, 2017). Additionally, HD patients who have experienced HAEC are more susceptible to subsequent episodes of enterocolitis with a high incidence rate ranging from 5.20% to 41% (Li et al., 2016).

Almost every disease and its complications, including HAEC, have several risk factors that underlie their incidence. If those risk factors can manage to be controlled, the mortality and morbidity of any disease will be reduced, especially HAEC, which is a major cause of

mortality and morbidity in HD patients (Moore, 2016; Rossi et al., 2014). Therefore, knowing the risk factors for the development of HAEC is necessary to increase vigilance and reduce its incidence. In some literature works, late diagnosis of HD, gender, the length of aganglionic intestinal segments, trisomy 21, associated congenital anomalies, a history of previous enterocolitis, a history of family members with HD, and postoperative HD conditions have been mentioned to be risk factors for HAEC (Puri, 2019; Rossi et al., 2014). Other researchers have also found that patients with multi-stage pull-through (MSPT) or a secondary procedure for HD are more likely to be at risk of developing enterocolitis (Sulkowski et al., 2014). However, data about HAEC and its associated risk factors still remain limited, including in Indonesia, and not all of the previously mentioned risk factors had roles in developing enterocolitis simultaneously in each of those research works. Based on those research works, the aim of this study aimed to identify and evaluate potential risk factors for HAEC development.

METHODS

A cross-sectional study was conducted in Regional Public Hospital (RSUD) Dr. Soetomo, Surabaya, Indonesia, using inpatient HD pediatric patients' medical records between January 2015 and September 2018. The study's ethicality was approved by RSUD Dr. Soetomo' Ethics Committee with ethic number 0537/KEPK/VIII/2018. The inclusion criteria were all patients with HD who had or had not experienced enterocolitis. The exclusion criteria were all patients with HD who had not undergone therapeutic surgery for HD. The diagnostic criteria of HAEC were based on the complete data on diagnosing HAEC in the patients' medical records at the time of hospital admission, including abdominal distention, diarrhea, vomiting, fever, and/or lethargy (Demehri et al., 2017). The final total medical records to be evaluated were divided into two groups, patients with HAEC and without HAEC. Forty samples were collected with the total sampling method.

The patients' medical records were further analyzed, and some data were collected, including the possible risk factors (age at HD diagnosis [months], gender, length of the aganglionic intestinal segments, trisomy 21, associated congenital anomalies, history of previous enterocolitis, family history of HD, and surgical

details) (Puri, 2019; Rossi et al., 2014; Sulkowski et al., 2014), age at hospital admission (months), age at surgery (months), nutritional status, length of hospital stay (days), patient outcomes, preoperative bowel rest, examinations done on the patients, patients' clinical characteristics, and antibiotic treatment and/or prophylaxis given to the patients. The nutritional status was determined based on the weight-for-length or weight-for-height z-scores of the World Health Organization 2006 growth charts for ages 0–5 years old and the weight-for-height percentiles of the Center for Disease Control and Prevention 2000 growth charts for ages >5–18 years old (CDC, 2002; WHO, 2006). Surgical details were also collected about the number of surgeries performed, number of surgical methods used in a single surgery, and type of surgical methods used. The number of surgical methods used in a single surgery was said to be one if only laparoscopic-assisted transanal endorectal pull-through (LATEP) or transanal endorectal pull-through (TAEPT) was used (example) and if a combination surgery of sigmoidostomy and colostomy was used (example). The types of surgical methods were divided into two groups, primary procedure or single-stage pull-through (SSPT), which was defined as a direct definitive pull-through without previously making a stoma, and secondary procedure or MSPT, which was defined as a definitive pull-through on a patient with a previously made stoma (Sulkowski et al., 2014).

Data processing and statistical analyses were performed using prevalence ratios (PRs) and 95% confidence intervals (CIs). An associated factor was considered to be a risk factor if the PR value was >1 with a 95% CI range that did not include value 1. The data were presented in median values for continuous variables and frequency or percentage values for qualitative variables. One factor, the length of aganglionic intestinal segments, was compared as a univariate variable between patients with HAEC and without HAEC using the Mann–Whitney U test with a significance level of $p < 0.05$.

RESULTS

A total of 40 patients' medical records were further analyzed, consisting of 12 patients with HAEC (30.00%) and 28 without HAEC (70.00%). There were some missing data (shown as not available) due to incomplete written information recorded in the patients' medical records.

The basic characteristics of the patients are shown in Table 1. The time of enterocolitis presentation of seven patients with HAEC (58.30%) was preoperative, and that of the other five (41.70%) was postoperative. More than half of the patients were male ($n = 27$; 67.50%). No difference was found in patients with HAEC and without HAEC between the median age at hospital admission (1.77 months [0.37; 19.30] and 0.54 months [0.07; 115.37], respectively) and at surgery (1.86 months [0.43; 19.53] and 1.00 months [0.10; 115.57], respectively), meaning that those patients were corrected surgically as soon as they were diagnosed with HD. Our findings also showed a very late-diagnosed patient with HD; this patient was nine years old. The median age of the patients with HAEC and without HAEC at surgery was 1.86 months (0.43; 19.53) and 1.00 months (0.10; 115.57), respectively. The median length of hospital stay of the patients with HAEC and without HAEC was 17.5 days [4; 51] and 18.5 days [2; 38], respectively. Trisomy 21 was found in two patients, who were both diagnosed with congenital heart disease; one of them also had gastrointestinal malformation. An anatomical pathology examination was only done in six (15.00%) patients because, in RSUD Dr. Soetomo, it is used for establishing the diagnosis of HD and not for establishing the diagnosis of HAEC.

Among the 11 patients with HD with associated congenital anomalies, eight patients had congenital cardiac or heart disease consisting of atrial septal defect, ventricular septal defect, patent ductus arteriosus, aortic bicuspid, aortic stenosis, and tricuspid regurgitation. Two patients had central nervous system (CNS) abnormalities consisting of microcephaly, global developmental delay, cerebral palsy, and periventricular leukomalacia. Three patients had urogenital tract (UGT) abnormalities consisting of anal atresia, rectovesical fistula, and single kidney. One patient had a gastrointestinal tract (GIT) abnormality consisting of rectal or anal stenosis. Moreover, three patients had overlapping anomalies between congenital heart disease and either CNS, UGT, or GIT.

The clinical characteristics and the use of antibiotics of the patients with HD are shown in Table 2 and Table 3. Most of the patients' clinical presentation ($n = 34$) was abdominal distention. Diarrhea was found significantly more frequently in patients with HAEC (75.00% compared to 19.40%). Ampicillin ($n = 27$) and gentamicin ($n = 24$) were the two most common antibiotics used as prophylaxis, while metronidazole was the most

common antibiotic used for treating HAEC ($n = 11$).

On the univariate analyses of the risk factors (see Table 1), the risk of developing HAEC was only associated with a history of having previous enterocolitis or HAEC (PR 6.60 [2.94 < PR < 14.80]). No associations as risk factors were found between the other factors and the incidence of HAEC, including the length of aganglionic intestinal segments ($p = 0.75$ in the Mann–Whitney U test comparing the three groups). The number of surgeries performed, number of surgical methods used in a single surgery, and type of surgical methods used were also analyzed as potential risk factors for HAEC (see Table 4). The surgical factors were not risk factors in the development of HAEC. However patients who had had surgery only once (31.30% compared to 14.30%), surgery with one surgical method (29.40% compared to 20.00%), and a primary procedure had a higher incidence of HAEC (29.40% compared to 27.30%).

DISCUSSION

Hirschsprung-associated enterocolitis remains the most common complication of HD because it has a quite high mortality and morbidity rate. Knowing the characteristics of patients and the potential risk factors of HAEC development is very important to reduce the incidence of HAEC. We assessed all the possible risk factors of HAEC as well as the possibility of the number of surgeries performed, number of surgical methods used in a single surgery, and type of surgical methods used as risk factors of HAEC (Rossi et al., 2014; Sulkowski et al., 2014).

The age at HD diagnosis was associated with the incidence of HAEC (Puri, 2019). The younger a patient's age at HD diagnosis, the less likely the patient would be to have HAEC, especially if the patient had been diagnosed at less than one week of age. In this study, the most common age range found was 0–3 months of age. To further analyze this factor, the age at HD diagnosis was divided into neonatal age (<1 month) and post-neonatal age (>1 month). Our results showed that the age at HD diagnosis was not concluded as a risk factor in the development of HAEC due to its Prevalence Ratio (PR) being less than one with a 95% CI including value 1. Three other studies—carried out after the two older literature works previously mentioned—stated the same results that the age at HD diagnosis was no longer a risk factor for HAEC either preoperatively or postoperatively

(Chung, Yu, Wong, & Tam, 2019; Huang, Li, Zhang, & Zhang, 2018; Le-Nguyen, Righini-Grunder, Piché, Faure, & Aspirot, 2019).

Enterocolitis in HD is found significantly more frequently in long-segment HD (L-HSCR) compared to short-segment HD (S-HSCR). The longer the aganglionic intestinal segments, the more likely enterocolitis will happen (Parahita, Makhmudi, & Gunadi, 2018). In contrast, our findings did not show an association of the three types of HD with the incidence of HAEC. This study result supported three other studies, which suggested that the length of aganglionic intestinal segments is not a potential risk factor for enterocolitis in HD (Cheng et al., 2017; Le-Nguyen, Righini-Grunder, Piché, Faure, & Aspirot, 2019; Sellers et al., 2018). Although there were two other literature works stating that enterocolitis incidence is more likely to happen in L-HSCR, it was still not significantly different than the enterocolitis incidence in S-HSCR (Puri, 2019).

Previous studies have frequently stated that HD with trisomy 21 has a strong possibility of developing into enterocolitis. This is caused by a disturbance in cytotoxic T-lymphocyte function and is also accompanied by humoral immune system disorder and interferon production deficiency. Patients with HD with associated congenital anomalies also have a tendency to be twice as likely to experience enterocolitis compared to patients with HD without associated congenital anomalies (Le-Nguyen, Righini-Grunder, Piché, Faure, & Aspirot, 2019). However, our univariate analysis on trisomy 21 and associated congenital anomalies showed no possibilities of them being risk factors in the development of HAEC (PR > 1 with 95% CI including value 1). The limited number of HD patients found with trisomy 21 might have been the cause of this finding, but we were unable to investigate further. The same result was shown by three studies that failed to report trisomy 21 as a risk factor because of the small number of HD patients with trisomy 21 (Chung, Yu, Wong, & Tam, 2019; Kwendakwema et al., 2016; Le-Nguyen, Righini-Grunder, Piché, Faure, & Aspirot, 2019).

Moreover, this limited number is known to have an impact on the result analysis of associated congenital anomalies because there is evidence of coexistence between trisomy 21 and associated congenital anomalies. This coexistence might be

able to blur the possibility of associated congenital anomalies being single potential risk factors (Stoll, Dott, Alembik, & Roth, 2015).

Several previous studies have stated that a history of previous enterocolitis in patients with HD is not a risk factor for developing HAEC (Chung, Yu, Wong, & Tam, 2019; Le-Nguyen, Righini-Grunder, Piché, Faure, & Aspirot, 2019). However, Frykman et al (2018) and (Huang, Li, Zhang, & Zhang, 2018) stated the opposite of the former studies, i.e., that a history of previous enterocolitis has a role as a risk factor. Our results supported those two studies and demonstrated an association between a history of previous enterocolitis and the HAEC incidence in the patients with HD. In addition, this study also showed that patients with a history of previous enterocolitis are six times more vulnerable to developing HAEC. The significant reduction of fecal short-chain fatty acids (SCFAs) and altered SCFA profile found in HAEC patients with a history of previous enterocolitis may explain this finding. Those changes may lead to alteration of the gut microbiota diversity, further causing the patients to be more susceptible to experiencing other episodes of enterocolitis later in life (Demehri et al., 2016; Prato et al., 2019).

One-time surgery, surgery with one surgical method, and primary procedure were found more frequently in the HAEC group. Only one-time surgery was done to reduce the length of hospital stay, which in turn had an impact on reducing the hospitalization costs spent by the patients (Isa, Syahputra, & Hutagalung, 2019).

No influence was found between the surgery performed/surgical method and the incidence of HAEC. Furthermore, this study also showed no possibilities of the type of surgical method being a risk factor in the incidence of HAEC (all PRs were more than one with a 95% CI including value 1). Surgery may not a potential risk factor of HAEC. Even though no possible risk factors were found in this study, patients who had undergone one-time surgery, surgery with one surgical method, and a primary procedure had a higher tendency to experience enterocolitis. Regardless of these findings, enterocolitis in HD might still happen independently due to disruption of the gut mucosal immune system and dysbiosis of the gut microbiome following the surgery process, either in the aganglionic segments or in the normal segments (Neuvonen et al., 2018; Till, Castellani, Moissl-Eichinger, Gorkiewicz, & Singer, 2015).

Table 1
Hirschsprung's Disease Patients' Basic Characteristics and Potential Risk Factors for HAEC

Basic Characteristic	Incidence of HAEC				Total		PR (95% CI)
	Yes		No		n	%	
	n	%	n	%			
Age at HD diagnosis, N/A=4							
>1 month (post-neonatal)	5	38.50	8	61.50	13	100.00	0.68
<1 month (neonatal)	6	26.10	17	73.90	23	100.00	(0.26<PR<1.79)
Sex							
Female	4	30.80	9	69.20	13	100.00	0.96
Male	8	29.60	19	70.40	27	100.00	(0.35<PR<2.62)
Length of aganglionic intestinal segment, N/A=15							
TCA	1	25.00	3	75.00	4	100.00	–
L-HSCR	2	40.00	3	60.00	5	100.00	
S-HSCR	4	25.00	12	75.00	16	100.00	
Nutritional status, N/A=5							
Obesity	0	0.00	0	0.00	0	0.00	
Overweight	0	0.00	1	100.00	1	100.00	
Normal	6	23.10	20	76.90	26	100.00	–
Moderate wasting	3	50.00	3	50.00	6	100.00	
Severe wasting	1	50.00	1	50.00	2	100.00	
Trisomy 21							
Yes	1	50.00	1	50.00	2	100.00	1.73
No	11	28.90	27	71.10	38	100.00	(0.40<PR<7.53)
Associated congenital anomalies							
Yes	3	27.30	8	72.70	11	100.00	0.88
No	9	31.00	20	69.00	29	100.00	(0.29<PR<2.66)
History of previous enterocolitis							
Yes	7	100.00	0	0.00	7	100.00	6.60
No	5	15.20	28	84.80	33	100.00	(2.94<PR<14.80)
Family history of HD							
Yes	0	0.00	1	100.00	1	100.00	–
No	12	30.80	27	69.20	39	100.00	
Surgical procedures, N/A=1							
LATEP/TAEPT	4	23.50	13	76.50	17	100.00	
Soave procedure	2	100.00	0	0.00	2	100.00	
Duhamel procedure	0	0.00	1	100.00	1	100.00	–
Sigmoidostomy	4	36.40	7	63.60	11	100.00	
Ileostomy	0	0.00	6	100.00	6	100.00	
Colostomy	2	28.60	5	71.40	7	100.00	
Patients outcomes, N/A=1							
Died	2	28.60	5	71.40	7	100.00	–
Lived	10	31.30	22	68.80	32	100.00	
Preoperative bowel rest, N/A=1							
10	30.30	23	69.70	33	100.00	–	
Examination done to the patients							
Complete blood count	12	30.80	27	69.20	39	100.00	–
Radiology	10	38.50	16	61.50	26	100.00	–
Anatomical pathology	1	16.70	5	83.30	6	100.00	–
Total	12	30.00	28	70.00	40	100.00	

L-HSCR, Long Segment Hirschsprung's Disease; N/A, Not available; S-HSCR, Short Segment Hirschsprung's Disease; TCA, Total Colonic Aganglionosis; –, not analyzed

Table 2
Hirschsprung's Disease Patients' Clinical Characteristics

Clinical Characteristic	Incidence of HAEC				Total	
	Yes		No		n	%
	n	%	n	%		
Meconial delay, N/A=11	7	36.80	12	63.20	19	100.00
Diarrhea, N/A=1	6	75.00	2	25.00	8	100.00
Abdominal distention, N/A=4	10	29.40	24	70.60	34	100.00
Fever	9	39.10	14	60.90	23	100.00
Vomiting, N/A=1	10	37.00	17	63.00	27	100.00
Lethargy	10	31.30	22	68.80	32	100.00
Bleeding	3	42.90	4	57.10	7	100.00
Tachycardia	1	33.30	2	66.70	3	100.00
Total	12	30.00	28	70.00	40	100.00

N/A, Not available

Table 3
Distribution of Antibiotic Use for Treatment and/or Prophylaxis

Antibiotic Use	Incidence of HAEC				Total	
	Yes		No		n	%
	n	%	n	%		
Amikacin	1	33.30	2	66.70	3	100.00
Ampicillin	9	33.30	18	66.70	27	100.00
Cefazoline	1	25.00	3	75.00	4	100.00
Cefosulbactam	0	0.00	1	100.00	1	100.00
Cefotaxime	2	100.00	0	0.00	2	100.00
Ceftazidime	0	0.00	1	100.00	1	100.00
Ceftriaxone	2	33.30	4	66.70	6	100.00
Cefuroxime	1	25.00	3	75.00	4	100.00
Cloxacillin	1	100.00	0	0.00	1	100.00
Cotrimoxazole	0	0.00	1	100.00	1	100.00
Gentamicin	7	29.20	17	70.80	24	100.00
Meropenem	2	22.20	7	77.80	9	100.00
Metronidazole	11	45.80	13	54.20	24	100.00
Total	12	31.60	26	68.40	38	100.00

N/A, Not available

Table 4
Evaluation of Surgical Details as Potential Risk Factors for Hirschsprung-associated Enterocolitis

Surgical Details	Incidence of HAEC				Total		PR (95% CI)
	Yes*		No		n	%	
	n	%	n	%			
Number of surgery performed							
More than once (>1)	1	14.30	6	85.70	7	100.00	2.19
Only once (1)	10	31.30	22	68.80	32	100.00	(0.33<PR<14.42)
Number of surgical methods used in one surgery							
Two	1	20.00	4	80.00	5	100.00	1.47
One	10	29.40	24	70.60	34	100.00	(0.24<PR<9.16)
Type of surgical methods							
MSPT or Secondary procedures	6	27.30	16	72.70	22	100.00	1.08
SSPT or Primary procedures	5	29.40	12	70.60	17	100.00	(0.40<PR<2.94)
Total	11	28.20	28	71.80	39	100.00	

N/A; Not available; SSPT, Single-Stage Pull-Through

Overall, all of these risk factors were still influenced by many other factors, e.g., no patients experienced postoperative HAEC even though they had experienced preoperative HAEC and vice versa. This could have been caused by factors protecting the patients from enterocolitis: routine rectal washouts, good nutritional support, and administration of prophylactic antibiotics before and after the surgery (Gosain et al., 2017; Wang, Li, Xu, Wang, & Feng, 2014).

Research Limitation

Our study limitations are the small number of patients and lack of patients who had undergone surgery. This may have been due to the difference in the socioeconomic conditions among all of those patients having an impact on whether surgery was performed on them.

CONCLUSION

In summary, this study concludes that a history of previous enterocolitis is a risk factor of HAEC development. Patients who have undergone surgery only once, who have undergone surgery with one surgical method, and who have undergone a primary procedure are more likely to experience HAEC due to their higher incidence frequency.

CONFLICT OF INTEREST

The authors declare that no conflict of interest in this study.

AUTHOR CONTRIBUTION

All authors participate actively in this article and are responsible for the content of writing, including in preparation, draft writing, research design selection, analysis, and revision of the article. APW : Conceptualization, Methodology, Writing–Original draft preparation, Data curation, Investigation. AFA: Conceptualization, Supervision, Writing–Reviewing and editing, Validation, Visualization. IGBAH : Supervision, Writing – Reviewing and editing, Validation. IGMGRG : Supervision, Writing – Reviewing and editing

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