Original Article

Mortality Prediction Score for Hirschsprung’s Disease-Associated Enterocolitis: A Novel Mortality Prediction Model

Syed Asif Shah Harooni, G R Prasad¹, Gayatri Reddy Danda², Mahera Naureen²

Associate Professor in General Surgery, ¹Professor & HOD Surgery, ²Junior Resident in General Surgery, DCMS, Hyderabad, Telangana, India

Submitted: 06-Dec-2021.
Revised: 18-Jan-2022.
Accepted: 12-Feb-2022.
Published: 09-Sep-2022.

ABSTRACT

Introduction: Enterocolitis associated with Hirschsprung’s disease is a fatal and serious complication. Number of scoring systems are in vogue to grade the severity of Hirschsprung’s disease associated with enterocolitis (HDAEC), but none of these scoring systems help predict mortality. Hence, we attempt to develop a mortality prediction model (MPM) for HDAEC.

Materials and Methods: A retrospective analysis of all cases of HDAEC encountered was analyzed. We also used the parameters of Elhalaby et al. for data collection. A total number of 71 cases were analyzed with regard to mortality in relation to each parameter. Sensitivity and specificity were calculated by statistician, and based on these values, a scoring model was proposed. All those with predicted mortality were given score 2 and those who did not were given score 1.

Results: A total score of more than 16 predicted mortality, a score of <10 predicted survival, and a score between 11 and 15 predicted survival with morbidity.

Conclusion: A MPM for HDAEC is being proposed.

Keywords: Hirschsprung’s disease, Hirschsprung’s disease associated with enterocolitis, mortality prediction model for Hirschsprung's disease associated with enterocolitis

INTRODUCTION

Hirschsprung-associated enterocolitis (HAEC) is a severe, serious, and often fatal complication of Hirschsprung’s disease. The incidence varies from 6% to 25%; a study conducted by Yulianda et al. showed incidence of 61/707 (8.6%).[1,2] A number of scoring systems for the diagnosis of HAEC are described,[3,4] but prediction of mortality has not been stressed in the literature. Mortality in enterocolitis varied from incidence of 18%,[5] 6%–30%[6] to 1%–10%.[7] Hence, we attempt to analyze the cases of HAEC and to develop a mortality prediction model (MPM).

Aims and objectives

The primary aim is to develop an MPM using statistical tools.

The secondary aim is to find out more reliable parameters among existing parameters used for the diagnosis of enterocolitis.

MATERIALS AND METHODS

HAEC in the present study is defined using the same criteria of Elhalaby et al.[5] and as per the score divided into mild, moderate, and severe.

The study comprises cases of Hirschsprung’s disease from 1984 to 2020; all the case records of HAEC were retrieved and analyzed. There were a total of 811 cases, of which reports of 700 cases were retrieved. Among those 700 cases only 91 cases were of enterocolitis, of which only 71 cases satisfied the criteria of elhalaby et al. All these 71 cases were divided into two groups, Group A- alive, n= 47 and Group B- dead, n=24 [Cohort Chart].

ADDRESS FOR CORRESPONDENCE: Dr. Syed Asif Shah Harooni, H.No: 22-4-177, Aliah Kotla, Hyderabad - 500 023, Telangana, India. E-mail: asifshahms@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Harooni SA, Prasad GR, Danda GR, Naureen M. Mortality prediction score for Hirschsprung's disease-associated enterocolitis: A novel mortality prediction model. J Indian Assoc Pediatr Surg 2022;27:594-9.
Cohort chart
The present study considered parameters adopted by Elhalaby et al.4 for analysis [Tables 1 and 2]. We added C-reactive protein (CRP) and procalcitonin as additional markers of sepsis. The parameters included (1) gender, (2) staged/single procedure, (3) fever, (4) blood in stools, (5) abdominal distension, (6) foul smelling, (7) sudden deterioration, (8) distended bowel loops on abdominal radiograph, (9) cutoff sign, (10) subdiaphragmatic air on X-ray, (11) total leukocyte count, (12) platelet count, (13) positive blood culture, (14) length of ganglionic segment, (15) down’s syndrome, (16) previous history of HDAEC, (17) procalcitonin, and (18) CRP. The parameter study was analyzed by third-party statistician who is not a part of the group.

The method we adopted to develop MPM for HDAEC is by calculating the sensitivity and specificity of parameters by correlating with mortality. Chi-square was used for all parameters. Based on sensitivity, specificity, and P value, the parameters that correlated positively with mortality were given 2 points and parameters that did not correlate were given 1 point each. MPM scores were extrapolated to both groups and a trend was picked up using statistical formula that fell into the two groups. A survival group A and a dead group B. Survival group A is further subdivided into group A1 who survived without complications and group A2 who survived with complications.

RESULTS
The study showed incidence of 8.7%. Table 3 shows the parameters and their P values. Fever, blood in stools, sudden deterioration, and previous history of HAEC were the only 4 parameters that correlated positively with mortality. Thus a total score of 21, 2 points each for the above four parameters and 1 point each for remaining 13 parameters were given. The results clearly showed all those who died had a score of more than 16, all those who had score of <10 survived without complications, and those who had 11–15 score survived with morbidity.

DISCUSSION
Hirschsprung’s disease is a complex genetic disorder that occurs due to absence of ganglion cells in the Auerbach and Meissner plexus, which results in functional obstruction of colon. Hirschsprung-associated enterocolitis is the most dangerous and fatal complication of Hirschsprung’s disease in children.8,9 HAEC is associated with increasing mortality between 0% and 21%.2,5,10,11

HAEC has been diagnosed by criteria developed by Bill and Chapman,12 Pastor et al.,3 and Elhalaby et al.14

Exact mechanism although unclear, multiple theories like theory of obstruction,13,14 theory of bacterial stasis and overgrowth,14,15 chronic mucosal injury,14,17 theory of enteric nervous system affecting colonic hemostasis,14,17 defect in mucosal immune defence,15,16 theory of abnormal mucus from white goblet cells,14,17 theory of unacceptable gut microbiome,7,16–19 have been suggested. The occurrence of HDAEC both preoperative and postoperative is well established and David et al. suggested postoperative HDAEC as a type of inflammatory bowel disease.20 Zhao et al. carried on standard observation that definitive treatment does not prevent development of HDAEC.21 This confirms that background risk factors like colonic dysbiosis, impaired immune barrier state, and abnormal enteric nervous system played a key role.

Farokh R Demehri adopted Pastor et al. scoring system for the diagnosis of HDAEC.14 The diagnostic triad of abdominal distension with explosive watery diarrhea and fever sometimes leads to systemic sepsis and septic shock.2,10,22 Philip K. Frikman et al. used 4 as the cutoff mark to maximize sensitivity and specificity instead of 10.23 Gunadi et al. used 2 different cutoff values in HDAEC scoring system and found lower cutoff value increases the diagnostic accuracy of HDAEC.23,24

Reinaldo et al. using Pastor et al. scoring system graded HDAEC histologically into 5 grades. Ankush
Table 1: Parameters and their outcome

| Parameter                                                                 | Alive, n (%) | Dead, n (%) |
|---------------------------------------------------------------------------|--------------|-------------|
| **Age at diagnosis**                                                      |              |             |
| Age                                                                       |              |             |
| 1 month                                                                   | 10 (14)      | 5 (7)       |
| 1 month-1 year                                                            | 18 (25)      | 13 (18)     |
| 1-3 years                                                                 | 13 (18)      | 6 (8)       |
| 3-5 years                                                                 | 2 (3)        | 0           |
| 5-10 years                                                                | 2 (3)        | 0           |
| >10 years                                                                 | 2 (3)        | 0           |
| **Gender and mortality**                                                  |              |             |
| Male                                                                      | 36 (51)      | 15 (21)     |
| Female                                                                    | 11 (15)      | 9 (13)      |
| **Staged versus single staged surgery and mortality**                     |              |             |
| Single                                                                    | 35/47 (49)   | 17/24 (24)  |
| Staged                                                                    | 12/47 (17)   | 7/24 (10)   |
| **Fever and mortality**                                                   |              |             |
| Present                                                                   | 14/47 (20)   | 12/24 (17)  |
| Nil                                                                       | 33/47 (46)   | 12/24 (17)  |
| **Blood in stools and mortality**                                         |              |             |
| Blood in stools                                                           | 4/47 (6)     | 16/24 (23)  |
| No blood                                                                  | 43/47 (61)   | 8/24 (11)   |
| **Abdominal distension and mortality**                                    |              |             |
| Mild to moderate                                                          | 14/47 (20)   | 10/24 (14)  |
| Massive                                                                   | 33/47 (46)   | 14/24 (20)  |
| **Foul smelling stool and mortality**                                     |              |             |
| Foul smelling stool                                                       | 32/47 (45)   | 22/24 (31)  |
| Nonfoul-smelling stool                                                    | 15/47 (21)   | 2/24 (3)    |
| **Sudden detoriation and mortality**                                      |              |             |
| Sudden                                                                    | 10/47 (14)   | 16/24 (23)  |
| Gradual                                                                   | 37/47 (52)   | 8/24 (11)   |
| **Dilatation of bowel loops in abdominal radiograph**                     |              |             |
| Outcome                                                                   | 47/47 (66)   | 24/24 (34)  |
| **Cut off sign**                                                          |              |             |
| Present                                                                   | 40/47 (56)   | 18/24 (25)  |
| Absent                                                                    | 7/47 (10)    | 6/24 (8)    |
| **Sub diaphragmatic air on abdominal radiograph**                         |              |             |
| Present                                                                   | 1/47 (1)     | 3/24 (4)    |
| Absent                                                                    | 46/47 (64)   | 21/24 (30)  |
| **Total leukocyte count**                                                 |              |             |
| <2500                                                                     | 2/47 (3)     | 5/24 (7)    |
| >18,000                                                                   | 45/47 (63)   | 19/24 (27)  |
| **Platelet counts**                                                       |              |             |
| Normal                                                                    | 40/47 (56)   | 16/24 (23)  |
| <90,000                                                                   | 7/47 (10)    | 8/24 (11)   |
| **Blood culture and mortality**                                           |              |             |
| Positive                                                                  | 2/47 (3)     | 8/24 (11)   |
| Negative                                                                  | 45/47 (63)   | 16/24 (23)  |
| **Length of segment and mortality**                                       |              |             |
| Long                                                                      | 7/47 (10)    | 6/24 (8)    |
| Short                                                                     | 32/47 (45)   | 17/24 (24)  |
| **Total colonic aganglionosis**                                           |              |             |
| 6/47 (8)                                                                  | 1/24 (1)     |
| **C reactive protein and mortality**                                      |              |             |
| Raised                                                                    | 17/47 (24)   | 14/24 (20)  |
| Normal                                                                    | 30/47 (42)   | 10/24 (14)  |

Contd...
Gosain et al. tried to grade severity of HDAEC into possible HDAEC, definite HDAEC, and severe HDAEC [Table 4]. In each group, they have taken some clinical criteria, some physical findings, and some radiological findings, but real scoring system is not there for predicting mortality in HDAEC. The present study also used the same criteria for scoring HAEC and did not correlate histology.

Pastor et al. used 20 criteria for developing a scoring system for the diagnosis of HAEC giving cutoffs <4 or <10. Cutoff of <4 had a positive correlation of histopathology with severity of HDAEC. Pastor group developed these parameters by Delphi method. The same parameters have been used to develop scoring system, adding CRP and procalcitonin as markers of sepsis. The authors gave a value to each parameter based on their correlation with mortality. Sensitivity and specificity of these parameters were also calculated. The parameters that correlated with mortality were given a value of 2 each and the rest of the non-correlating parameters a value of 1 each. Only four parameters, fever, blood in stools, sudden deterioration, and previous history of HDAEC, had sensitivity and specificity of more than 0.8. Statistician developed a scoring system using total points of 21. These points were extrapolated for both survival and nonsurvival groups. The score of more than 16 predicted mortality with hundred percent sensitivity and specificity. Those with <10 survived without morbidity. The children with score between 11 and 15 survived with morbidity. Thus, the authors feel this mortality prediction module using the parameters will help predict and take proactive measures to reduce mortality.

Early Identification of high-risk patients, early diagnosis, grading, and scoring the risk severity was found to be the primary component of treatment of HDAEC. Treatment of HDAEC primarily revolved around saline lavage and intensive organ support. Proximal Colostomy and re-

| Table 1: Contd... | Alive, n (%) | Dead, n (%) |
|-------------------|-------------|-------------|
| Procalcitonin and mortality |             |             |
| Raised            | 28/47 (39)  | 15/24 (21)  |
| Normal            | 19/47 (27)  | 9/24 (13)   |
| Downs syndrome and mortality |             |             |
| Downs associated  | 3/47 (4)    | 3/24 (4)    |
| Previous history of HDAEC |             |             |
| Present           | 4/47 (6)    | 13/24 (18)  |
| Nil               | 43/47 (61)  | 11/24 (15)  |

HDAEC: Hirschsprung’s disease associated with enterocolitis

| Table 2: Elhalaby Hirschprung-associated enterocolitis score | Score |
|-------------------------------------------------------------|-------|
| History                                                     | Score |
| Diarrhoea with explosive stool                              | 2     |
| Diarrhoea with foul smelling stool                          | 2     |
| Diarrhoea with bloody stool                                 | 1     |
| Previous history of enterocolitis                           | 1     |
| Physical examination                                        | Score |
| Explosive discharge of gas and stool on rectal examination | 2     |
| Distended abdomen                                           | 2     |
| Decreased peripheral perfusion                              | 1     |
| Lethargy                                                    | 1     |
| Fever                                                       | 1     |
| Radiology                                                   | Score |
| Multiple air fluid levels                                   | 1     |
| Dilated loops of bowel                                      | 1     |
| Saw tooth appearance with irregular mucosal lining           | 1     |
| Cut off sign in recto-sigmoid with absence of distal air    | 1     |
| Pneumatosis                                                 | 1     |
| Laboratory                                                  | Score |
| Leukocytosis                                                | 1     |
| Shift to left                                               | 1     |

HDAEC: Hirschsprung’s disease associated with enterocolitis

| Table 3: Parameters and their P values | Parameters                      | P     | Interpretation |
|---------------------------------------|---------------------------------|-------|----------------|
| Gender and mortality                  | >0.5                            | Not significant |
| Staged versus single staged and mortality | >0.5                        | Not significant |
| Fever and mortality                   | <0.5                            | Significant   |
| Blood in stools and mortality         | <0.5                            | Significant   |
| Abdominal distension and mortality    | >0.5                            | Not significant |
| Sudden deterioration and mortality    | <0.5                            | Significant   |
| Cut off sign                         | >0.5                            | Not significant |
| Sub diaphragmatic air on radiograph   | >0.5                            | Not significant |
| Total leucocyte count                 | >0.5                            | Not significant |
| Platelet count                       | >0.5                            | Not significant |
| Positive blood culture                | >0.5                            | Not significant |
| Length of segment                    | >0.5                            | Not significant |
| C - reactive protein                  | >0.5                            | Not significant |
| Procalcitonin                        | >0.5                            | Not significant |
| Previous history of HDAEC            | <0.5                            | Significant   |
| Dilatation of bowel loops            | >0.5                            | Not Significant |
| Downs syndrome                      | >0.5                            | Not significant |
do pull through procedures have also been suggested. Use of probiotics based on gene sequencing of fecal microbiome was suggested by Georg Singer. Nita Mariana and others showed interleukin (IL)-23 mRNA expression correlated with the development of HDAEC in children with Hirschsprung’s disease. Thus, IL-23 mRNA expression might help predict and treat at risk babies proactively.

Newer concepts are emerging in the pathogenesis of HDAEC. Farokh R. Demehri et al. discussed the role of gut bacteria produced short chain fatty acids in etiopathogenesis. They also suggested the protective role of butyrate, a colonocyte-friendly fatty acid. The study postulated that altered short chain fatty acids lead to disequilibrium of short chain fatty acid producing microbiota making Hirschsprung diseased children more prone for HDAEC. Ankush Gosain showed in animal model work that multiple genes like GDNF, EDNRB, EDN3, and SOX10 are contributing to Hirschsprung’s disease. GALT (gut-associated lymphoid tissue defects) was cited as one of the causes of HDAEC. Nucleotide oligomerization domain 2 is a pattern recognition receptor which is implicated in Crohn’s disease were not found in children with HDAEC.

This study also has its strengths and limitations. This is first attempt to develop a MPM so that a reference is available to be used and validated by other authors. Weakness includes smaller number and single center study, needs validation by larger centers and numbers.

**Conclusion**

The authors presents a novel prediction system of mortality, which predicts with hundred percent high index of sensitivity and specificity. This mortality prediction module is the first of such an attempt to predict mortality in cases of HDAEC.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Witarto AP, Athiyyah AF, Adria Hariastawa IG, Ranuh R. Risk factors influencing enterocolitis development in pediatric patients with Hirschsprung’s disease. Jurnal Berkala Epidemiologi 2020;8:218.
2. Yulianda D, Sati AI, Makhmudi A, Gunadi. Risk factors of preoperative Hirschsprung-associated enterocolitis. BMC Proc 2019;13:18.
3. Pastor AC, Osman F, Teitelbaum DH, Caty MG, Langer JC. Development of a standardized definition for Hirschsprung’s-associated enterocolitis: A Delphi analysis. J Pediatr Surg 2009;44:251-6.
4. Elhalaby EA, Coran AG, Blane CE, Hirschl RB, Teitelbaum DH. Enterocolitis associated with Hirschsprung’s disease: A clinical-radiological characterization based on 168 patients. J Pediatr Surg 1995;30:76-83.
5. Aliev MM, Terebaev BA, Abzalova SR. A comparative study of the surgical procedures to treat Hirschsprung disease in children. Eur J Mol Clin Med 2020;7:3142-6.
6. Mariana N, Islam AA, Hatta M, Lampus HF. IL 23 mRNA expression in Hirschsprung-associated enterocolitis. J Med Sci 2020;20:76-83.
7. Gosain A. Established and emerging concepts in Hirschsprung-associated enterocolitis. Pediatr Surg Int 2016;32:313-20.
8. Sellers M, Udaondo C, Moreno B, Martínez-Alés G, Diez J, Martínez L, et al. Hirschsprung-associated enterocolitis: Observational study in a paediatric emergency care unit. An Pediatr (Engl Ed) 2018;88:329-34.
9. Iskandarani F, Hammoud C, Srour S, Pelizzo G, Nakib G, Calcetarra V, et al. Isolated ileal perforation in infancy: A lethal initial presentation of Hirschsprung’s disease. Pediatr Rep 2017;9:7084.

| Grade | Description | Clinical history | Physical examination | Radiographic findings |
|-------|-------------|------------------|----------------------|----------------------|
| Grade 1 | Possible HDAEC | Anorexia, Diarrhea | Mild abdominal distension | Normal |
| Grade 2 | Definite HDAEC | History of past episode of HDAEC, Explosive diarrhea, Fever, Lethargy | Fever, Tachycardia, Abdominal distension, Abdominal tenderness, Explosive gas/stool on DRE, Decreased peripheral perfusion | Ileus gas pattern, Air/fluid levels, Dilated loops of bowel, Recto-sigmoid cut-off, Pneumatosis |
| Grade 3 | Severe HDAEC | Obstruction, Obtunded | Hypotension, Altered mentation, Marked abdominal distension, Peritonitis, | Pneumoperitoneum |

HDAEC: Hirschsprung’s disease associated with enterocolitis, DRE: Digital rectal examination
10. Gunadi, Ningtyas HH, Simanjaya S, Febrianti M, Ryantono F, Makhmudi A. Comparison of pre-operative Hirschsprung-associated enterocolitis using classical criteria and Delphi method: A diagnostic study. Ann Med Surg (Lond) 2020;51:37-40.

11. Moore SW. Hirschsprung disease: Current perspectives. Open Access Surg 2016;9:39-50.

12. Bill AH, Chapman ND. The enterocolitis of Hirschsprung’s disease: Its natural history and treatment. Ann J Surg 1962;103:70-4.

13. Svetanoff WJ, Dekonenko C, Oysuchkuwu O, Oyetunji TA, Aguayo P, Fraser JD, et al. Inpatient management of Hirschprung’s associated enterocolitis treatment: The benefits of standardized care. Pediatr Surg Int 2020;36:1413-21.

14. Demehri FR, Halaweish IF, Coran AG, Teitelbaum DH. Hirschsprung-associated enterocolitis: Pathogenesis, treatment and prevention. Pediatr Surg Int 2013;29:873-81.

15. Singer G, Kashofer K, Castellani C, Till H. Hirschsprung’s associated enterocolitis (HAEC) personalized treatment with probiotics based on gene sequencing analysis of the fecal microbiome. Case Rep Pediatr 2018;2018:3292309.

16. Gosain A, Brinkman AS. Hirschsprung’s associated enterocolitis. Curr Opin Pediatr 2015;27:364-9.

17. Jiao CL, Chen XY, Feng JX. Novel insights into the pathogenesis of Hirschprung’s associated enterocolitis. Chin Med J (Engl) 2016;129:1497-17.

18. Tang W, Su Y, Yuan C, Zhang Y, Zhou L, Peng L, et al. Prospective study reveals a microbiome signature that predicts the occurrence of post-operative enterocolitis in Hirschsprung disease (HSBC) patients. Gut Microbes 2020;11:842-54.

19. Demehri FR, Frykman PK, Cheng Z, Ruan C, Wester T, Nordenskjöld A, et al. Altered fecal short chain fatty acid composition in children with a history of Hirschsprung-associated enterocolitis. J Pediatr Surg 2016;51:81-6.

20. Levin DN, Marcon MA, Rintala RJ, Jacobson D, Langer JC. Inflammatory bowel disease manifesting after surgical treatment for Hirschsprung disease. J Pediatr Gastroenterol Nutr 2012;55:272-7.

21. Zhao L, Dhall D, Cheng Z, Wang HL, Doherty TM, Bresee C, et al. Murine model of Hirschsprung-associated enterocolitis II: Surgical correction of aganglionosis does not eliminate enterocolitis. J Pediatr Surg 2010;45:206-11.

22. Frykman PK, Patel DC, Kim S, Cheng Z, Wester T, Nordenskjöld A, et al. Inflammatory bowel disease serological immune markers anti-saccharomyces cerevisiae mannan antibodies and outer membrane porin C are potential biomarkers for Hirschsprung-associated enterocolitis. J Pediatr Gastroenterol Nutr 2019;69:176-81.

23. Frykman PK, Kim S, Wester T, Nordenskjöld A, Kawaguchi A, Hui TT, et al. Critical evaluation of the Hirschsprung-associated enterocolitis (HAEC) score: A multicenter study of 116 children with Hirschsprung disease. J Pediatr Surg 2018;53:708-17.

24. Gunadi, Sukarelawanto A V, Ritana A, Balela N, Putri WJ, Sirait DN, et al. Postoperative enterocolitis assessment using two different cut-off values in the HAEC score in Hirschsprung patients undergoing Duhamel and Soave pull-through. BMC Pediatr 2020;20:457.

25. Sunggiardi R, Mariana N, Nurmantu F, Ahmadwirawan, Habar TR, Sulmiati, et al. Histopathological changes and Hirschprung’s associated enterocolitis (HAEC) scores. J Med Sci 2020;52:226-34.

26. Gosain A, Frykman PK, Cowles RA, Horton J, Levitt M, Rothstein DH, et al. Guidelines for the diagnosis and management of Hirschsprung-associated enterocolitis. Pediatr Surg Int 2017;33:517-21.