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A prospective evaluation of the risk factors and utility of GutCheck^{NEC} scoring system to predict necrotizing enterocolitis in preterm newborns, in a tertiary care centre in North India

Abstract

Background: Necrotizing enterocolitis (NEC) is a serious gastrointestinal disease of neonate with high fatality. GutCheck^{NEC} scoring system can be used in predicting NEC and decrease NEC rate.

Aims: To assess risk factors and use scoring system GutCheck^{NEC} in predicting necrotising enterocolitis.

Methods: A prospective observational study with preterms, birth weight <1500grams was done. Risk factor assessment was done using GutCheck^{NEC} and serial scorings were done. Descriptive analyses of the various risk factors assessed were done.

Results: 51 babies included, with gestational age 24 to 35 weeks (Median (IQR) 30+2 (27+2, 31+6), birth weight 500 to 1500 grams (Median (IQR) – 1105 (893, 1300). 9 NEC cases, 6(11.5%) confirmed NEC and 2(22%) were surgical NEC. Absence of ANS, HsPDA and late onset sepsis were risk factors. The median (IQR) scoring at 72 hrs., 86 hrs., 7 days, 14days, 21days and 28 days were 34 (31, 38), 34 (30, 39), 34 (26, 43), 31 (23, 35), 35 (23, 38), 35 (30, 40). The median risk for developing NEC was high (33-36) on all days except day 14, when it was moderate (20-32). The sensitivity and specificity for a cut off >32 at 86hours was 85.7% and 48.5% (PPV – 26.1%, NPV – 94%) for medical NEC and 100% and 44.7% (PPV – 8.7%, NPV – 100%) respectively for surgical NEC.

Conclusion: Hence we conclude that GUTCHECK can help in early prediction of NEC and prevention of NEC.

Keywords: antenatal steroids, GUTCHECK, HsPDA, NEC, necrotising enterocolitis

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Introduction

Necrotizing enterocolitis (NEC) is a very grave disease of newborns, particularly preterm and very low birth weight babies.[1] The incidence of NEC is 7 and 13% in babies born between 22 to 28 weeks and is a principal cause of death in VLBW. The mortality rate is between 16 to 42%.[2] Fatalities is highest in those requiring surgical NEC and in extreme preterms.[2] They are also prone to severe long-term complications such as neurodevelopmental sequelae and short bowel syndrome. As the clinical features of NEC overlap with sepsis and other mimickers of NEC, commonly called NEC-like diseases, rendering it difficult for an early diagnosis and specific treatment. Even identifying NEC in its early stage is important to reduce the extent of intestinal damage and widespread sepsis. Researches are going on to develop markers and scores which can predict the development of NEC.[1,3]

An audit performed showed that our NICU had a high rate of NEC (12.1%) amongst VLBW babies, during the year 2019. Hence, we designed a prospective study to evaluate NEC frequency, to assess the various associated risk factors and we intended to prospectively study the utility of GutCheck^{NEC} score in predicting the development of NEC in our centre, with the aim to prevent NEC rate in future.

Methods

A prospective observational study was conducted, from July 2020 to June 2021,with VLBW newborns admitted to our NICU .Risk factors were assessed using a predefined proforma The various risk factors assessed included growth restriction, birthweight, gestational age, use of glucocorticoid, perinatal asphyxia, 5min APGAR<6,chest compression or epinephrine in delivery room, umbilical cord pH<7.1 from, not kept nil per oral while transfusion, use of antenatal steroids, standardised feeding guideline in unit, use of exclusive human milk feeding, probiotics , cold stress, cocaine use in pregnancy, placental abruption, centre's annual NEC rate among <1500gms use of histamine receptor lockers, hemodynamic resuscitation in first week of life, hypertensive diseases in mother, type of enteral feeding, congenital cyanotic heart disease in newborn, presence of hemodynamically significant patent ductus arteriosus(HsPDA), indomethacin or surgical treatment for PDA,

presence of multiple(>2) infections in first week of life before NEC, use of triple antibiotic therapy or initial antibiotic course more than 4 days, early or late onset sepsis and chorioamnionitis. GutCheck^{NEC} scoring were done on these newborns at 72hrs, 84hrs, 7days, 14 days and 28 days, on basis of gestational age, inborn-outborn status, NICU NEC rate, number of culture proven infection since day 3 of life, PRBC transfusion, presence of hypotension requiring inotrope use, metabolic acidosis, use of exclusive human milk feeding, use of probiotics.[4]

Babies were followed up for development of NEC till 28days of life or discharge or death. Subjects were divided into those at low risk, moderate risk, high risk or very high risk of developing NEC

according to the score. When any subject developed NEC, staging was done according to BELL staging and also into medical/surgical NEC. Data thus collected were entered in excel sheets and analysed using SPSS software. Descriptive analyses of the various risk factors assessed were done. Comparisons of risk factors were done between those who developed NEC and those who didn't develop NEC.

Statistical analysis:

Statistical analysis was performed using SPSS software version 26. The continuous variables are represented as mean with standard deviation or median with inter quartile range and compared between the groups using the non-parametric Mann-Whitney U. Categorical variables are summarized as proportion and comparison between the groups was done by Fisher's exact test. P value less than 0.05 was considered as significant. The sensitivity and specificity of cut-off values were also calculated.

Results

A total of 380 NICU admissions were made during the study period and of these 52 babies had a birth weight of less than 1500 grams (13.7%). Gestational age ranged from 23 to 35 weeks (Median (IQR) – 30+2 (27+2, 31+6) weeks), birth weight ranged from 500 to 1500 grams (Median (IQR) –1105 (893, 1300) grams). 55.8% (n=29) were inborn and the male: female ratio was 1.1:1. Multiple gestation constituted 34.6% (n=18) of all births. The duration of hospital stay ranged from less than 24 hours to 91 days (Median - 19 days; IQR -2- 34 days).

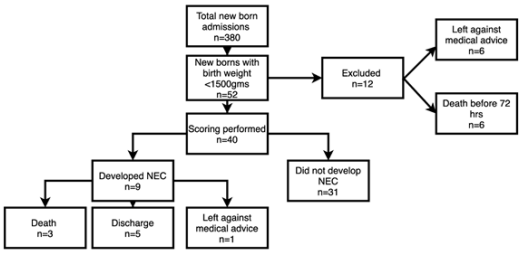

Figure 1 Study flowchart.

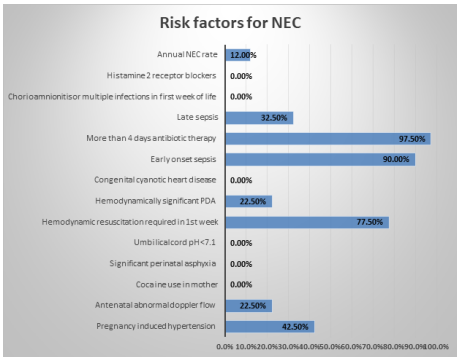

Figure 2 Risk factors for NEC in new born.

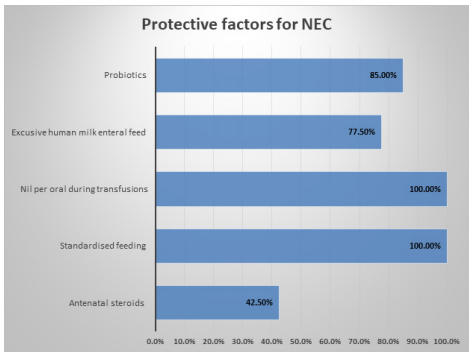

Figure 3 Protective factors for NEC.

Out of 52 NBs enrolled, GUTCHECK scoring could be performed in 40 (77%). The scoring was not performed in the rest because they either expired due to critical illness (n=6) or left against medical advice (n=6) from our institution within 72hrs of birth (Figure 1).

The median (IQR) GUTCHECK scoring at 72 hrs., 86 hrs., 7 days, 14days, 21days and 28 days were 34 (31, 38), 34 (30, 39), 34 (26, 43), 31 (23, 35), 35 (23, 38), 35 (30, 40). The median risk for developing NEC was high (33-36) on all days except day 14, when it was moderate (20-32) (Figure 4).NEC was diagnosed in 9/52 (17.3%) NBs admitted during the study period. Surgical NEC was detected in 2(22%) and the rest were medical NEC. The median age of development of NEC was 5 days (range (IQR) - 2-18 (4, 12) days). Of the NB who developed NEC, 3 expired, 1 left against medical advice and the rest survived to discharge.

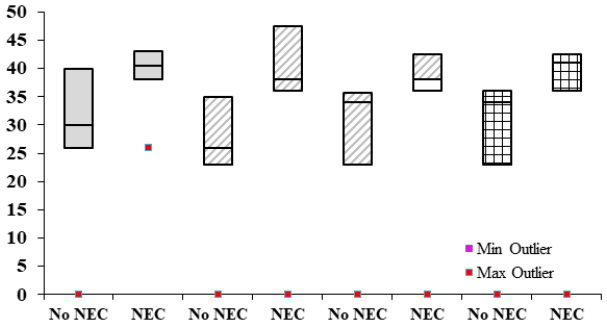

Figure 4 Box Whisker plots comparing Gut Score at various time intervals.

The risk factors for the development of NEC were assessed in these 40 babies (Figure 2). The mother had pregnancy induced hypertension (PIH) in 42.5% (n=17) of them. Abnormal Doppler flow was detected in antenatal scan in 9 (22.5%) cases. None of the mothers had history of cocaine use in pregnancy. Growth restriction was noted in 18 (45%) cases. Significant perinatal asphyxia was not there in any cases. Only one subject had an umbilical cord pH <7.1 within first hour of birth. Hemodynamic resuscitation was required in the first week of life in 31 (77.5%) cases. HsPDA was diagnosed in 9 (22.5%) and were treated medically. No congenital cyanotic heart disease was noted. Early onset sepsis was diagnosed in 36 (90%) and; more than 4 days antibiotic therapy were received by 97.5% (n=39). Among these 72.5% (n=29) received triple antibiotic therapy. Late sepsis was diagnosed in 13 (32.5%) cases. None had a history of chorioamnionitis or multiple infections in first week of life before NEC. Histamine 2 receptor blockers were given to none.

On analysing the protective factors (Figure 3) for NEC, majority (n=29; 72.5%) received antenatal steroids. Standardized feeding guideline was followed in our unit. All subjects were kept nil per oral (NPO) during times of transfusion. Exclusive human milk enteral feeding were given in 77.5% (n=31) and probiotics were added to expressed breast milk (EBM) in 85% cases (n=34).

On comparing babies who developed NEC with those who did not develop NEC, newborns whose mothers did not receive antenatal steroids (55% vs 10%; *p*=0.003), late onset sepsis (66.7% vs. 22.5%;

p=0.01) were significant. NEC group had a more incidence of HsPDA compared to those who didn't (44% vs 16%) but this difference was not statistically significant (*p*=0.07). The gender, inborn status, twinning, gestational age, weight at birth, birth asphyxia, use of exclusive breast feeds, probiotics, inotrope use, triple antibiotic use, and early onset sepsis were not significantly different between two groups (Table 1 and Table 2). Comparison of risk factors between those who developed surgical NEC and medical NEC was done and there was no significant difference. The median age of development of NEC was 5 days (range 2 – 18days). 87.5% of cases who developed NEC had a high to very high risk score at 86 hours; while only 51.6% of non-NEC patients had high to very high risk score at 86 hours (*p*=0.07).

Table 1 Comparison of newborns who developed with those who did not develop NEC

Risk factor	No NEC (n=31)	NEC (n=9)	P value
Male n (%)	17 (54.8)	5 (55.6)	0.97
In born status n (%)	20 (64.5)	6 (66.7)	0.91
Multiple gestation n (%)	7 (22.6)	3 (33.3)	0.51
Growth Restriction n (%)	14 (45.2)	4 (44.2)	0.97
Weight at birth in gms			
<1000 n (%)	8 (25.8)	1 (11.1)	
1001-1500 n (%)	23 (74.2)	8 (88.9)	0.35
Gestational age			
<28 weeks	6 (19.4)	1(11.1)	
28-31 6/7 weeks	15 (48.4)	6 (66.7)	0.66
32-33 6/7 weeks	7 (22.6)	2 (22.2)	
>34 weeks	3 (9.7)	0 (0)	
Ante natal steroids	26 (83.9)	3 (33.3)	0.003
Exclusive human milk feeding	24 (77.4)	7 (77.8)	0.08
Probiotics	27 (87.1)	7 (77.8)	0.62
Hemodynamic resuscitation in 1st week	23 (74.2)	8 (88.9)	0.34
Hypertensive disease in mother	14 (45.2)	3 (33.3)	0.52
PDA hemodynamically significant	5 (16.1)	4 (44.4)	0.07
Triple antibiotic therapy	21 (67.7)	8 (88.9)	0.21
Initial antibiotic course >4 days	30 (96.8)	9 (100)	0.58
Early onset sepsis	27 (87.1)	9 (100)	0.25
Late onset sepsis	7 (22.6)	6 (66.7)	0.01

Table 2 Comparison of various parameters between patients with and without NEC

	Developed NEC	N	Mean	Std. deviation	Std. error mean	P value
Gestational age in days	Yes	9	211.33	13.019	4.34	0.56
	No	31	215.03	17.423	3.129	
Birth weight in gms	Yes	9	1193.33	169.466	56.489	0.79
	No	31	1162.84	225.045	40.419	
Score 72 hrs	Yes	8	35.38	4.373	1.546	0.45
	No	31	33.35	7.153	1.285	
Score 86 hrs	Yes	8	37.88	6.01	2.125	0.12
	No	31	33.19	7.661	1.376	
Score 7 days	Yes	8	39.75	6.585	2.328	0.05*
	No	30	32.47	9.584	1.75	
Score 14 days	Yes	7	40.71	7.675	2.901	<0.001*
	No	25	28.32	6.669	1.334	
Score 21 days	Yes	7	38.43	5.563	2.103	0.02*
	No	18	31.17	7.115	1.677	
Score 28 days	Yes	7	38.86	5.64	2.132	0.04*
	No	13	32.15	6.902	1.914	

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A comparison of scores at various time points between suspect NEC (Stage 1A, 1B) and confirmed NEC (Stage 2A, 2B, 3A and 3B) and medical and surgical NEC were also performed. The scores were not significantly different at any time point (Table 3 and Table 4).

Table 3 Comparison of scores at various time points between patients with suspect and confirmed NEC

	NEC	N	Mean	Std. deviation	Std. error mean	P value
Score 72 hrs	1	3	34.67	7.572	4.372	0.752
	2	5	35.8	2.049	0.917	
Score 86 hrs	1	3	34.67	7.572	4.372	0.273
	2	5	39.8	4.712	2.107	
Score 7 days	1	3	34.67	7.572	4.372	0.88
	2	5	42.8	4.025	1.8	
Score 14 days	1	3	37.33	9.452	5.457	0.358
	2	4	43.25	6.185	3.092	
Score 21 days	1	3	35.33	7.095	4.096	0.231
	2	4	40.75	3.403	1.702	
Score 28 days	1	3	35.33	7.095	4.096	0.168
	2	4	41.5	2.887	1.443	

1= Suspect NEC; 2= Confirmed NEC

Table 4 Comparison of scores at various time points between patients with medical and surgical NEC

	Medical/ surgical NEC	N	Mean	Std. deviation	Std. error mean	P value
Score 72 hrs	Medical	7	35.57	4.685	1.771	0.764
	Surgical	1	34	.	.	
Score 86 hrs	Medical	7	38.43	6.268	2.369	0.533
	Surgical	1	34	.	.	
Score 7 days	Medical	6	37.67	6.022	2.459	0.127
	Surgical	2	46	4.243	3	
Score 14 days	Medical	6	39.67	7.84	3.201	0.426
	Surgical	1	47	.	.	
Score 21 days	Medical	6	37.83	5.845	2.386	0.538
	Surgical	1	42	.	.	
Score 28 days	Medical	6	38.33	5.989	2.445	0.595
	Surgical	1	42	.	.	

The specificity and sensitivity for cut off >32 (as described in the original study by Gephart et al[8]) at 86 hours was calculated. 23/40 (57.5%) cases had score >32. Out of this, 8 patients developed NEC. Only 1/17 (5.9%) patients with score <32 developed NEC. This translates to a sensitivity, specificity, positive predictive value/ PPV and negative predictive value/NPV of 88.9%, 51.6%, 34.8% and 94.1% in predicting NEC. 6/23 with score >32 developed medical NEC and 2/23 developed surgical NEC. 1/17 with score <32 developed medical NEC, while none developed surgical NEC. The sensitivity and specificity was 85.7% and 48.5% (PPV – 26.1%, NPV – 94%) respectively for medical NEC and 100% and 44.7% (PPV – 8.7%, NPV – 100%) respectively for surgical NEC (Table 5).

Table 5 Sensitivity, specificity, positive and negative predictive value of a score >32 at 86 hours in predicting NEC

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
All cases	88.90%	51.60%	34.80%	94.10%
Medical NEC	85.70%	48.50%	26.10%	94.10%
Surgical NEC	100%	44.70%	8.70%	100%

The median duration of hospital stay was not significantly different between patients who developed NEC and those who did not (34 days vs 32 days; p=0.88). Coagulopathy was significantly more frequent in patients with NEC (100% vs. 48.4%; p=0.006). The frequencies of various complications (Hyaline membrane disease (p=0.67), sepsis (p=0.65), meningitis (p=0.16), shock (p=0.27), anemia (p=0.28), bronchopulmonary dysplasia (p=0.09), apnea (p=0.16), jaundice (p=0.32), pulmonary hemorrhage (p=0.9), intraventricular hemorrhage (p=0.64), retinopathy of prematurity (p=0.16) or pneumothorax (p=0.43)) were not significantly different between two groups.

Discussion

NEC was diagnosed 17% of our babies, which was high compared to 5% reported in very low birth weight babies and 10% in extremely low birth weight babies.[5,6] The prevalence was similar in the studies from In the United States, a study conducted using data from the National Institute of Child Health.[7] In a previous study from PGIMER Chandigarh, NEC was diagnosed in 77 out of 2200 (5.2%) newborn admitted in NICU over a period of 4 years. The frequency in VLBW babies was 5.7%.[8] However, in a study from new born tertiary centre

from Ankara, Turkey, 12.6% of VLBW babies developed NEC.[9] The high frequency of NEC in our cohort is likely due to selection bias. Our centre being a tertiary care centre receives sick new born.

Moreover, the total number of patients and the period of study were also less for any definite conclusions.

The median age of development of NEC was 5 days (range 2-18 days). In the study by Narang et al, the mean age at presentation was 4.9 days and majority of cases presented during the first 14 days which is similar to our study.[8] Buch et al reported a mean age of 5.2 days and 81% of cases presented within first week of life. They noted that most severe cases presented early.[10] However, we did not find such a trend. Two patients in stage 3 developed NEC on day 18, one child with 1A developed NEC on day 12, while others developed NEC between day 2 and day 8.

Stage 1, 2 and 3 NEC was diagnosed in 34%, 44% and 22% cases respectively. The frequencies were 51.1%, 30.3% and 18.6% respectively in the Chinese cohort.[11] In the Korean cohort, a much higher percentage of 53% required surgical intervention.[12]

The mortality rate in our cohort of NEC was 33% (3/9). Walther et al reported a mortality of 21.9%[20] while, Atasay reported a mortality of 16.5%.[9] Kanto Jr et al reported a survival of 68% in medically treated and 48% in surgically treated NECs.[21] Generally the morality rate is higher in patients requiring surgical intervention.[21–24]

Overall various studies reports and improvement in the survival over last decade in both medically and surgically treated patients.[23] In our cohort the stage of NEC in three children who died were 2B in two cases and 3A in one. The mortality also depends on the stage of NEC. In the study by Buch et al, the mortality ranged from 45% for stage I, 20% for stage II and 67% for stage III.[10] In our study, the mortality in stage I was 0%, while it was 50% each in. stage II and III.

Several risk factors have been identified for the development of NEC. Lack of antenatal steroid usage,late sepsis and HsPDA were more frequent in cases with NEC. However, gender, inborn status, twinning, gestational age, weight at birth, birth asphyxia, use of exclusive breast feeds, probiotics, inotrope use, triple antibiotic use, and early onset sepsis were not significantly different between two groups. In Youn et al[12] study, birth weight and gestational age were significantly lower and frequency of sepsis and PDA were significantly higher in NEC patients. But contrary to our study, antenatal steroids did not show a difference between two groups in that study. In the study by Buch et al, NEC cases had significantly more frequent incidence of hypothermia, respiratory acidosis, respiratory distress, polycythemia, sepsis, enteral feeding and asphyxia.[10] Walther et showed that only sepsis and birth weight were significantly associated with NEC.[13]

Maternal pregnancy-induced hypertension is a well-recognised risk factor for NEC.[14] 42.5% of the entire cohort and 33% of patients who developed NEC had pregnancy induced hypertension in the mother. Maternal cocaine abuse is a well-known risk factor for NEC;[15] however was not seen in any our cases. Abnormal Doppler flow was detected in antenatal scan in 9 (22.5%) cases and 33% (3/9) of cases with NEC of which two died. In one of the studies,[16] absent or reverse end diastolic frequencies in the umbilical arteries showed a positive predictive value of 52.6% and mortality of 50%.

Growth restriction was noted in 18 (45%) all cases and 44% of cases with NEC. Studies have shown a significant association between birth weight and risk of development of NEC.[17,18] Even in our study, the birth weight was lower in children who developed NEC (mean birth weight - 1193 vs 1162 gms); however the difference was not statistically significant. 5-minute Apgar scores of <7 is was reported as a significant factor for the development of NEC,[17,19] however none of the cases in the current study had lower APGAR score or other features of perinatal asphyxia.

Similarly, higher umbilical cord artery base deficit is a risk factor for the development of NEC.[17] Only one subject in the entire had an umbilical cord pH <7.1 within first hour of birth and that child developed NEC. Hemodynamic resuscitation was required in the first week of life in 31 (77.5%) cases in the entire cohort and 8/9 (89%) cases who developed NEC.

PDA whether treated using indomethacin or not is an independent factor of NEC.[20] HsPDA was diagnosed and treated with injection paracetamol in 9 (22.5%) all NBs and 3/9 (33%) of infants with NEC in our study. Congenital cyanotic heart disease is another risk factor commonly associated with NEC;[21] however was not noted in any of our cases.

Both sepsis and prolonged antibiotic therapy has been shown to be a risk factor for the development of NEC in a multivariate analysis.[22] Early onset sepsis, more than 4 days antibiotic therapy and triple antibiotic therapy were present in 90%, 97.5% 72.5% of cases respectively. Late sepsis was diagnosed in 32.5% cases. 100% of the cases who developed NEC in our cohort had early sepsis and prolonged antibiotic therapy. Late sepsis was present in 6/9 (66.7%) cases with NEC.

72.5% of the all cases had received antenatal steroids; but only 33% of kids who developed NEC received antenatal steroids. This difference was statistically significant. Standardized feeding guideline was always followed. Nearly all neonates received exclusive human milk enteral feeding with probiotics.

GutCheck^{NEC} scoring system is a composite scoring system developed to predict the risk of development of NEC in new born.[4] Different weightages are assigned to various risk factors. We prospectively assessed its utility in predicting NEC in our new born cohort. The score ranges from 0-58. In our cohort, the median (IQR) scoring at 72 hrs, 86 hrs, 7 days, 14 days, 21days and 28 days were 34 (31, 38), 34 (30, 39), 34 (26, 43), 31 (23, 35), 35 (23, 38), 35 (30, 40) respectively. The median risk for developing NEC was high (33-36) on all days except day 14, when it was moderate (20-32). The median age of development of NEC was 5 days (range 2-18 days). Hence, the utility of the score was assessed at 86 hours. 87.5% of cases who developed NEC had a high to very high risk score at 86 hours; while only 51.6% of non-NEC patients had high to very high risk score at 86 hours (p=0.07). In the original study which described GutCheck^{NEC} scoring system, for a cut-off point score >32, the sensitivity ranges from 55% for medical NEC and 79% for surgical NEC The specificity for cut off >32 was 75% for both medical and surgical NEC.[8] In our cohort, the sensitivity was 88.9% and specificity was 51.6% in predicting NEC (both medical and surgical). The sensitivity and specificity was 85.7% and 48.5% respectively for medical NEC and 100% and 44.7% respectively for surgical NEC.[4]

Conclusion

NEC is a very serious disease with high mortality and long term complications. The implementation of a scoring system GUTCHECK can help in early prediction of NEC.87.5% of cases who developed NEC had a high to very high risk GUTCHECK score at 86 hours. For a cut-off point score >32 at 86 hrs, the GutCheck^{NEC} scoring system showed sensitivity of 88.9% and specificity of 51.6% in predicting NEC (both medical and surgical).

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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