Standardising the elusive diagnosis of NEC in the premature infant- a practical score

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Abstract:

Objective

The perceived risk of necrotising enterocolitis (NEC) can result in overtreatment of the otherwise adapting preterm neonate. We aim to develop an assessment tool to aid the decision making in the management of preterm neonates at risk of NEC.

Method

An evidence-based assessment tool was designed bringing together clinical, laboratory and radiological signs commonly associated with NEC. A numerical score was awarded for each sign, with those more specific to NEC being graded higher. A multi-centre validation was conducted of the proposed assessment tool over three tertiary neonatal units.

Results

A total of 125 patients were included, 53 (42.4%) with a final diagnosis of NEC and 72 (57.6%) with an alternative diagnosis. The NEC group had a significantly higher total score compared to the non-NEC group; 15(2-28) vs. 4(1-9) ($p = <0.0001$). In ROC analysis, using a cut-off of eight, the assessment tool gave a sensitivity of 92.3% and a specificity of 90.4% for identifying NEC compared to an alternative diagnosis.

Conclusion

This comprehensive scoring system encourages a full assessment of the infant before deciding on withholding feeds, starting antibiotics, and transferring to a surgical centre. It is a safe objective measure to support a diagnosis of NEC in the presence of certain clinical signs.

Keywords:

Necrotising Enterocolitis, NEC, Preterm

Introduction:

Preterm neonates can have a wide variety of gastrointestinal problems in the first few months of life, with some conditions, such as necrotising enterocolitis (NEC) carrying a much higher morbidity and mortality than others [1,2]. It can be quite difficult, especially at the beginning of the disease process, to distinguish between the various diagnoses and therefore the decision on whether it is safe to continue feeds or not, or whether antibiotics are required, can be clinically challenging [1]. Withholding feeds and starting antibiotics when NEC is suspected may seem a simple and safe decision, but this paradigm needs to be challenged.

Recent research has shown that it is both safe and beneficial to establish enteral feeding early in preterm neonates [4, 5]. It reduces the period of Intravenous (IV) fluid administration and parenteral nutrition (PN) and has a positive effect on neurodevelopment and gut microbiome development [5-7]. With the concerns of missing a diagnosis of NEC, preterm neonates can end up having several episodes of withholding feeds which can disrupt enteral feeding patterns and establishment. It has also been suggested that repeated use of antibiotics in this cohort of patients with an immature gut may negatively affect the gut microbiome, potentially increasing the risk of developing NEC [7-10]. There is therefore a delicate balance to be achieved between over cautious treatment for possible NEC and missing the opportunity for early and effective treatment when the diagnosis of NEC is actually the correct one.

Several scoring systems have been developed around the diagnosis of NEC in the preterm neonate. The most well-known, and historically most widely used, is Bell's criteria which was developed in 1978, with one modification in 1987 [11, 12] Bell's criteria were designed to categorise NEC into three broad stages depending on disease eveity. It has been widely used for reporting and data collection purposes but there is an argument that it has become outdated and less clinically useful in recent years. Bell's stage I is highly likely to not represent a neonate with NEC but instead other conditions secondarily affecting the gut such as systemic sepsis.

There have been several scoring systems developed; GutCheck^{NEC} score looks at predicting overall risk of NEC [13] and others such as NeoNEEDS and PE-NE look more at the factors that influence the severity of NEC and the likelihood of requiring surgery [14,15]. There is, to the authors knowledge, no published scoring system aiming at supporting the clinician who is required to make a decision on stopping feeds and commencing antibiotic therapy. Our aim is to provide a tool based on a systematic approach to the symptoms, physical examination and investigation results that enables the clinician to be more likely to achieve the correct diagnosis and initiate the correct management. Our ultimate aim will be to see a reduction in unnecessary cessation of enteral feeds and antibiotic use and for many babies an unnecessary transfer to a surgical unit.

Method:

A review of the current literature on NEC was undertaken and an assessment tool (NEC-T-Aid: Necrotising Enterocolitis Treatment Aid) was devised based around the most recent evidence on signs and symptoms suggestive of and specific to NEC. A four-part scoring system was developed consisting of; General clinical signs, Abdominal signs, Investigations and Abdominal x-ray findings. This can be seen in Figure 1. Designated scores for each clinical sign were decided upon according to specificity and sensitivity to NEC versus other NEC mimicking pathologies. The "NEC-T-Aid" score was reviewed and agreed upon by an expert panel comprising of neonatologists, surgeons and other relevant members of the multidisciplinary neonatal team. It was trialled out in several different neonatal units and reviewed and adjusted by the panel before the final version was agreed upon. It is designed so that the scores from each of the four categories can be combined to make a final score which is categorised as: 0-3 Normal/dysmotility, 4-7 Sepsis, 8-10 Suspected NEC and >10

confirmed NEC.

Five general clinical signs were chosen that highlight the sick, deteriorating neonate [1]. As these signs are not specific to NEC, one point was allocated to each, with a maximum score of only two points for this category (Figure 1). Six NEC associated abdominal signs were chosen [3]. It is important to note that abdominal distension in the presence of a soft, non-tender abdomen is not regarded as a specific sign of NEC especially in neonates who are on non-invasive respiratory support such as CPAP [16]. Therefore, in this part of the scoring system, points were only allocated if the abdominal distension had significantly worsened in the last 24 hours (clinician examination was used to determine abdominal distension rather than exact abdominal girth measurements). Increased gastric aspirates (>33% of last feed or >3.5ml single aspirate), vomiting (bilious or non-bilious) and blood in the stool are associated with NEC, however these are not specific and were therefore allocated one point each [17].

In a preterm neonate, under two weeks old, who is establishing enteral feed, bile-stained aspirates are likely to be a sign of functional dysmotility [18]. However, if a neonate has been tolerating full feeds for 48 hours and then develops bilious aspirates, it is mandatory to conduct a prompt and full assessment as this can indicate a potentially a more sinster pathology such as NEC. On the score, this was reflected with bilious aspirates being highlighted separately and being allocated a higher score of four, however only being allocated if the neonate had been previously tolerating full feeds for over 48 hours.

Five serological markers were chosen which have a good, although variable, sensitivity to NEC, but low specificity being markers of sepsis and increased inflammatory response [19]. These points should only be scored if the abnormal marker is new or worsening from the neonate's baseline.

The abdominal x-ray category consisted of four x-ray findings. Pneumatosis and pneumoperitoneum consistently had a greater association with NEC in the literature and therefore were given a higher score (eight points) compared to evidence of peritoneal fluid or bowel dilatation (one point) [20,21]. The category also included a yes/no question of whether the x-ray was normal or abnormal, allowing the person completing the form to highlight that although the x-ray did not fulfil any of the above criteria it was still not a normal x-ray, helping support management.

Validation of scoring system:

A multi-centre validation of the score was conducted over a six-year time period. Each unit received training on how to complete the form and a standardised teaching session on how to interpret abdominal x-rays in the preterm neonate, designed and later published by the investigators [21]. Three tertiary (level three) neonatal units in the UK took part in the validation of the score, with two centres collecting their data prospectively and one, retrospectively.

The scores were completed for neonates in whom the primary caregivers had concerns of clinical deterioration and feed intolerance and there was therefore a consideration of whether to stop feeds and start antibiotics. The primary caregivers who completed the scores were a mixture of neonatal doctors and advanced neonatal nurse practitioners. Neonates were then reviewed 6-24 hours later depending on clinical necessity and the clinicians were asked to complete a second scoring sheet at that time. Neonates born at over 37 weeks gestation and those with a congenital cardiac anomaly were excluded. Final diagnosis was confirmed two weeks after initial presentation. Confirmation of diagnosis was made either intra-operatively, on histology, or if the patient was not operated on, then by a consultant neonatologist.

Patients were divided into two groups, those with confirmed NEC and those with an alternative diagnosis. Data was analysed and compared in GraphPad Prism 9.0.2 using Mann-Whitney test,

Fisher exact test and a receiver-operative curve was performed. Data are presented as median (range) and number (percentage). A P value <0.05 was taken as statistically significant.

Results:

A total of 125 patients had a score sheet completed between 2014 and 2020 across the three tertiary neonatal units. Basic demographics were; median gestation 26 (23-36) weeks, birthweight 776g (438-1890) and male:female ratio 73:52. Median age of presentation was 17 days (1-120) of life. Of the 125 preterm neonates, 55 (44.0%) were on full enteral feeds prior to the presenting episode with a median feed volume of 150 (0-200) ml/kg/day. The type of milk used for enteral feed was broken down into 79 (63.2%) receiving expressed breast milk (EBM), 16 (12.8%) EBM and milk fortifier, 8 (6.4%) hydrolysed or partially hydrolysed formula 3 (2.4%) non-hydrolysed formula and 19 (15.2%) on full PN.

The patients were divided into two groups; those with a final diagnosis of NEC (53/125, 42.4%) and those with an alternative diagnosis (72/125, 576%). There were no demographic differences between the NEC and non-NEC group (gestation; 27/40 (23-35) vs. 26/40 (23-36), p value = 0.24, birthweight; 783 (480-1880) vs. 773 (438-1890), p value = 0.38, day of life; 15 (3-120) vs. 17 (1-73), p value 0.37). Figure 2 shows the final diagnoses recorded in the non-NEC group, with non-gastrointestinal (GI) sepsis recorded as the most common (41/72, 56.9%). In 15/72 (20.8%) cases there was either no documentation of final diagnosis, or no cause for the neonatal deterioration was found. Feeds were stopped in 58/72 (805%) non-NEC cases and antibiotics started in 53/72 (73.6%), with 48/72 (66.6%) patients having both feeds withheld and antibiotics started. It was not documented how many of these had feeds restarted or antibiotics stopped at review within 24 hours of presentation. This was in comparison to the NEC group where 49/53 (92.4%) of patients had both feeds held and antibiotics started at initial review, increasing to 53/53 (100%) at subsequent review.

All 125 patients had an initial score completed at time of presentation. The overall median total score for the initial review was 6 (1-28), with a significant difference between the NEC: 15 (2-28) and Non-NEC: 4 (1-12) group p = < 0.0001 (Figure 3). Using a cut-off of eight and above, sensitivity was 92.3 [95% CI 81.5-97.9] % and specificity was 90.4 [95% CI 81.2-96.1] %; with a positive likelihood ratio of 9.6 [95% CI 4.7-19.6] and a negative likelihood ratio of 0.09 [95% CI 0.03-0.22], the receiver-operator curve is shown in Figure 4.

For the initial score the breakdown of individual components can be seen in Table 1. Clinical signs between the two groups were not significant with both groups having a high incidence of worsening desaturations/bradycardias (33/53 vs. 40/72, p = 0.469) and increasing ventilation settings (20/53 vs. 20/72, p = 0.251). Abdominal signs were more common in the NEC group with a significant difference seen with worsening abdominal distension (33/53 vs. 33/72, p value = 0.045) and the presence of bilious aspirates after the neonate had been previously tolerating full feeds for 48 hours (16/53 vs. 1/72, p = <0.0001). There was also a significant difference in all serological markers in the NEC group compared to the non-NEC group with metabolic derangement (high lactates, electrolyte disturbances etc.) and worsening CRP having the largest difference (Table 1). As expected, perforation and pneumatosis were significantly more commonly seen in the NEC group (perforation; p = 0.0006, pneumatosis; p = <0.0001).

Only one of the three units recorded a second score within 6-24 hours, making a total of 39/125 (31.2%) patients having two complete scores. A sub-analysis was completed for these patients comparing the first and the second score for (a) NEC, (b) non-NEC, (c) neonates with a score of eight and above on the first score and (d) neonates with a score below eight on the first score. There was no significant difference in any of those four groups with Figure 5 showing median and range.

Discussion:

NEC remains a leading cause of morbidity and mortality in the preterm neonate [1,2]. Due to diagnostic challenges distinguishing between NEC and non-NEC pathologies, NEC is commonly over-diagnosed and preterm neonates are subjected to unnecessary cessation of feeds and antibiotic treatment. We present a novel assessment tool that gives the clinician the evidence to support the decision about feeds, antibiotics and diagnosis of NEC on a specific case, on the spot. With a cut-off of eight and above the score has a sensitivity of 92.3% and a specificity of 90.4% to differentiate between NEC and alternative, clinically distinct pathologies Therefore, with the use of this novel assessment tool, which includes a quick but comprehensive examination of the neonate, it is possible to safely continue feeds and hold off starting antibiotics with a score of below eight.

Abnormal intestinal microbiomes have been described as a potential risk factor for NEC [6,7]. The use of empirical antibiotics can disturb normal intestinal colonisation, hence may actually increase the risk of NEC [10]. In addition to this it has been documented that prolonged or repeated courses of antibiotics are associated with an increased odds ratio of developing NEC, although this may be cofounded by the fact that antibiotics are given to the more unwell neonates and it is these neonates who are at a higher risk of NEC [8].

We are also seeing an increasing amount of literature in support of early and effective enteral feeding for preterm neonates [4-6]. Repeated cessation of feeds for suspected NEC can interrupt this and prolong the time to achieve full enteral feeds, potentially even further increasing the risk of developing NEC [10]. In this cohor almost 70% of patients who did not have NEC still had both their feeds stopped and antibiotics started. This is likely to be clinically appropriate for some in this group (for example; incarcerated inguinal hernia, severe sepsis) however the majority may not have required this intervention. It is therefore important to correctly identify which neonates have NEC and which do not, so as not to subject preterm neonates to unnecessary treatment and delayed establishment of enteral feeds.

Bell's criteria has long been the 'go-to' scoring system for NEC, however increasingly is being felt to be outdated and less clinically useful [22]. The different stages (I, IIa, IIb, IIIa and IIIb) are becoming less relevant with our increasing knowledge of NEC and the overlap with other NEC mimicking pathologies (e.g. feed intolerance, SIP). Most specifically Bell's stage I (*Temperature instability, apnea, bradycardia, gastric residuals, mild abdominal distention, normal motility or perhaps mild ileus, with occult positive stools)* could actually be contributing to the over diagnosis and treatment of NEC as it describes many symptoms seen in the unwell neonate, not specifically one with developing NEC. For this reason, Bell Stage I is being used less and less in both clinical and research environments. The authors would advocate that the use of Bell's stage I should be abandoned all together and any use of Bell's stages II and III be confined for audit purposes rather than to aid in decision making.

The "NEC-T-Aid" assessment tool presented here is divided into four sections; clinical signs, abdominal signs, serological markers and x-ray findings. The idea is that it prompts the person reviewing the neonate to complete a comprehensive assessment of the case including investigations, which although is standard practice, can differ in approach and completeness from person to person. Use of the score is aimed to prevent the practice of withholding feeds without examining the infant, which may happen in busy settings or with less-experienced doctors.

Studies have suggested that analysis of vital signs can help to evaluate for impending NEC, with subtle changes being present prior to the more obvious deterioration of the neonate [23]. However, these clinical signs are not specific to NEC and are therefore unlikely to be useful in distinguishing NEC from other NEC-mimicking pathologies [24, 25]. In Table 1 it can be seen that that the rate of general clinical signs was similar in both groups, therefore supporting that they should be used in the

overall assessment of the clinically unwell neonate but not as a clinical marker of NEC on their own.

What we have seen with our cohort of patients, which is mirrored in the literature, is that abdominal signs and serological markers along with changes on abdominal x-rays were all consistently higher in neonates with NEC compared to those with an alternative diagnosis [16, 20, 25-28].

We have seen in previous studies that abdominal signs such as abdominal distension, abdominal wall discolouration and higher gastric residuals are associated with NEC compared to controls [2]. Bilious aspirates in neonates who have been previously fully fed for at least 48 hours have a higher association with NEC and this is clearly seen in this study with only one neonate in the non-NEC group fulfilling the criteria for this point to be awarded ($p = <0.001$).

There were universally more frequent rates of abnormal serological analysis in the NEC group compared to the non-NEC cohort (acidosis, metabolic derangement, raised WBC and CRP and low platelets) (Table 1). In the wider literature they have not yet proven to have accurate sensitivity or specificity over other pathologies, however we propose that they have an important role in the overall assessment of the clinically unwell neonate. There has been a suggested correlation between worsening serological markers (in particular abnormal WCC and low platelet counts) and neonates requiring surgical intervention for NEC compared to those successfully managed conservatively [27].

The use of imaging to diagnose NEC is a frequently discussed topic. Imaging modalities available at present are limited to X-ray or Ultrasound (US). The role of US, although showing promise as an imaging adjunct, has not yet been seen to be of diagnostic benefit over X-ray [25] and was therefore not included in our assessment tool. This may be partially due to the limited experience of neonatal units with this modality and access to paediatric radiologists out of hours. There is agreement that X-ray use for the diagnosis of NEC is of importance, however the exact timings and number of x-rays required is still debated [28]. Subtle radiological signs can occur before clinical signs and may progress ahead of obvious clinical deterioration, suggesting an important role in clinical decision making. However, it must be noted that some hallmark features, such as pneumatosis, may be transient and neonates who have perforated do not always present with pneumoperitoneum on x-ray. Given that x-ray standardisation of interpretation was key for the success of the score, the participating units were trained on a systematic approach designed and later published by the investigators [21]. The authors advocate that anyone planning to use this score clinically, should do so in conjunction with this published standardised interpretation of abdominal x-rays.

All three units that participated in this multi-centre validation project were asked informally (not via structured questionnaire) for comments on how they found using the score. All centres reported an observed improvement in standardised and structured assessments of these clinically unwell neonates. There were several comments from more junior members of the team on how it helped support their decision making, especially overnight, even if they did not feel confident to continue feeds initially, it allowed a clear time frame for review and a justification for restarting feeds and stopping antibiotics much earlier than they would have done before. This really highlights the aim of this score as a tool to be used as part of the overall clinical assessment and to encourage early review and consideration of whether the correct management has been started. It should be used in conjunction with senior clinical advice or review, regardless of the hour, to aid decision making.

We aimed for all centres to repeat a second score in the first 12 hours, but this was difficult to achieve. Good neonatal clinical practice would suggest that any infant in whom feeds have been withheld should be reviewed within the next 6 to 12 hours. We would therefore still stress the importance of repeating the score and using the change in trend to guide management.

Limitations of this study:

Despite this being a multi-centre validation, only three neonatal units participated, all of which

were tertiary centres and one centre collected the data retrospectively rather than prospectively. There had been a hope to have several more centres included wth a mixture of level two and three centres, however due to the COVID-19 pandemic this was not possible. Nevertheless, we feel that with a total of 125 patients, with no demographic difference between the two compared groups we have a large enough cohort of patients to validate the score for use in clinical practice.

Conclusion:

We present here a multi-centre validated assessment tool that is safe and practical to use to assess the neonate in whom enteral feeds are about to be stopped and decide safely whether this is necessary or not. It allows a structured, standardised and validated guide for medical staff on the neonatal unit to use at any time of day to aid clinical management based on clinical signs and symptoms. It could aid in identifying neonates with whom it is safe to continue feeds and therefore avoid unnecessary treatment. Further prospective assessment is needed to determine whether it decreases the over-diagnosis of NEC and initiation of unnecessary treatment.

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Conflicts of interest

None

Figure 1: Final version of Necrotising Enterocolitis Treatment Aid (NEC-T-AID)

Figure 2: Bar graph showing the range of diagnoses in non-NEC group (n=72)

(GI=gastro-intestinal, CMV=cytomegalovirus, ICP=intra-cranial pressure, IVH=intraventricular haemorrhage)

Figure 3: Median total score in NEC (n=53) and non-NEC (n=72) groups

Figure 4: Receiver-operator characteristics curve comparing NEC (n=53) and non-NEC (n=72) groups

Figure 5: Comparison of first score and second score for (a) NEC group, (b) non-NEC group, (C) First score equal or above eight, (d) First score below eight

Table 1: Comparison of individual score components for NEC (n=53) and non-NEC (n=72) groups. Data analysed using Fisher exact Test and displayed as number (percentage). P value < 0.05 taken as significant (*)

Table 1:

	NEC Group (n=53)	Non-NEC Group (n=72)	P value
Desaturation/Bradycardia	33 (62.2)	40 (55.5)	0.4693
Tachycardia	16 (30.1)	15 (20.8)	0.2953
Apnoea	15 (28.3)	12 (16.6)	0.1297
Temperature instability	8 (15.1)	3 (4.1)	0.0524
Ventilation increase	20 (37.7)	20 (27.4)	0.2512
Abdominal distension	33 (62.2)	33 (45.8)	0.0449*
Abdominal tenderness	16 (30.8)	22 (30.1)	>0.9999
Increased aspirates	17 (32.1)	14 (19.4)	0.0982
Vomiting	12 (22.6)	8 (11.1)	0.0908
Bloody stool	9 (16.9)	8 (11.1)	0.4307
Bilious aspirates	16 (30.2)	1 (1.3)	<0.0001*
Acidosis	25 (47.1)	16 (22.2)	0.0033*
Metabolic derangement	33 (62.2)	9 (12.5)	<0.0001*
Raised white blood cells	30 (56.6)	24 (33.3)	0.0111*
Raised C-Reactive protein	38 (71.7)	13 (18.1)	<0.0001*
Low/falling platelets	23 (43.3)	12 (16.6)	0.0010*
Perforation	10 (18.8)	1 (13)	0.0006*
Pneumatosis	30 (56.6)	0 (00)	< 0.0001*
Peritoneal Fluid	3 (5.6)	1 (1.3)	0.3104
Bowel dilatation	31 (58.5)	50 (69.4)	0.3451
Normal X-ray	0 (0.0)	14 (19.4)	0.0003*

References:

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4) SIFT Investigators group. Early enteral feeding strategies for very preterm infants: current

Date and Time submitted to REDCAP: REDCAP ID:

NEC-T-Aid
Necrotising Enterocolitis Treatment Aid

Patient Hospital No:	**Date:** **Time:**
DOB:	**Days of Life:**
Gestational Age:	
Birth Weight:	**Feed Type:**
Gender:	**Feed Volume:**

To complete the form please input the numerical score awarded into the corresponding empty box (not just a tick). If a sign is not present please input a 0 (zero).

General signs (changes within the last 12 hours)	Max score 2	
Increased frequency of desats/bradys	1	
Tachycardia (in the absence of inotropes)	1	
Apnoea	1	
Temperature instability	1	
Sudden increase in ventilation settings	1	

Abdominal signs	Max score 8	
Worsening abdominal distension/discolouration	2	
Abdominal tenderness	1	
Increased aspirates >(33% of last feed), or >3.5ml single aspirate	1	
Vomiting	1	
Visible blood in the stool	1	

<u>Bilious Aspirates</u> ONLY score if previously tolerating full feeds for 48 hours	4	

Investigations	Max score 4	
New/worsening Metabolic acidosis	1	
New/worsening Metabolic changes (high lactate/high glucose/low sodium etc.)	1	
WCC suggestive of sepsis	1	
High/worsening CRP	1	
Low/falling platelets	1	

Abdominal X-ray*	All relevant	
Evidence of perforation	8	
Evidence of pneumatosis	8	
Evidence of peritoneal fluid	1	
Bowel dilatation	1	
Normal x-ray	Yes/No	

***Please see supporting document for further details**

TOTAL SCORE	

Date and Time submitted to REDCAP: REDCAP ID:

NEC-T-Aid
Necrotising Enterocolitis Treatment Aid

Assessment	Signs	Score and Range		Management
		Max score	Range	
Normal/ dysmotility	Clinical abdominal investigations AXR	3	0 - 3	No need for Abx If feed intolerance: omit feeds as needed Monitor closely
Sepsis	Clinical abdominal investigations AXR	7	4 - 7	Abx as per local guideline (no need for Metronidazole) Feeds as appropriate
Suspected NEC or NEC alert	Clinical abdominal investigations AXR	10	8 - 10	Consider Triple Abx Consider NBM 48 hours Daily bloods Repeat AXR Re assess after 6hrs Inform Surgeons
Confirmed NEC	Clinical abdominal investigations AXR	11	>10	Triple Abx NBM 7 days Daily bloods Repeat AXR as appropriate Refer to surgeons

If management differed to that suggested on this score, please comment below:

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_____

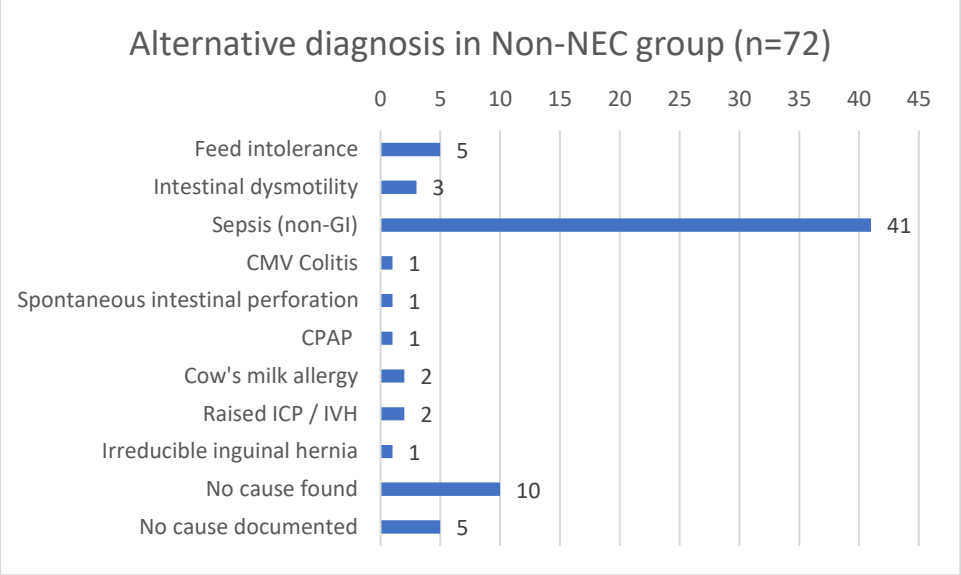


Figure 2: Bar graph showing the range of diagnoses in non-NEC group (n=72)

(GI=gastro-intestinal, CMV=cytomegalovirus, ICP=intra-cranial pressure, IVH=intraventricular haemorrhage)

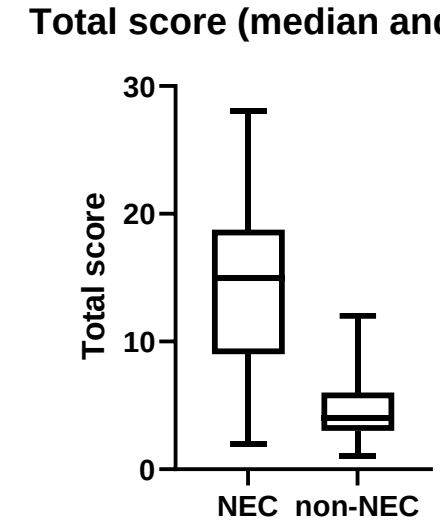
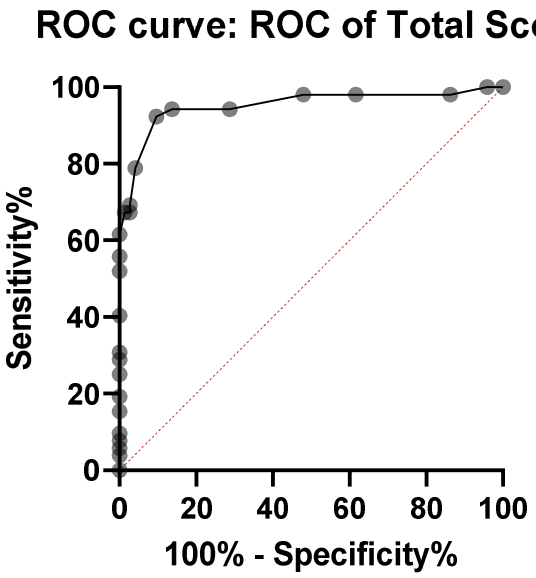
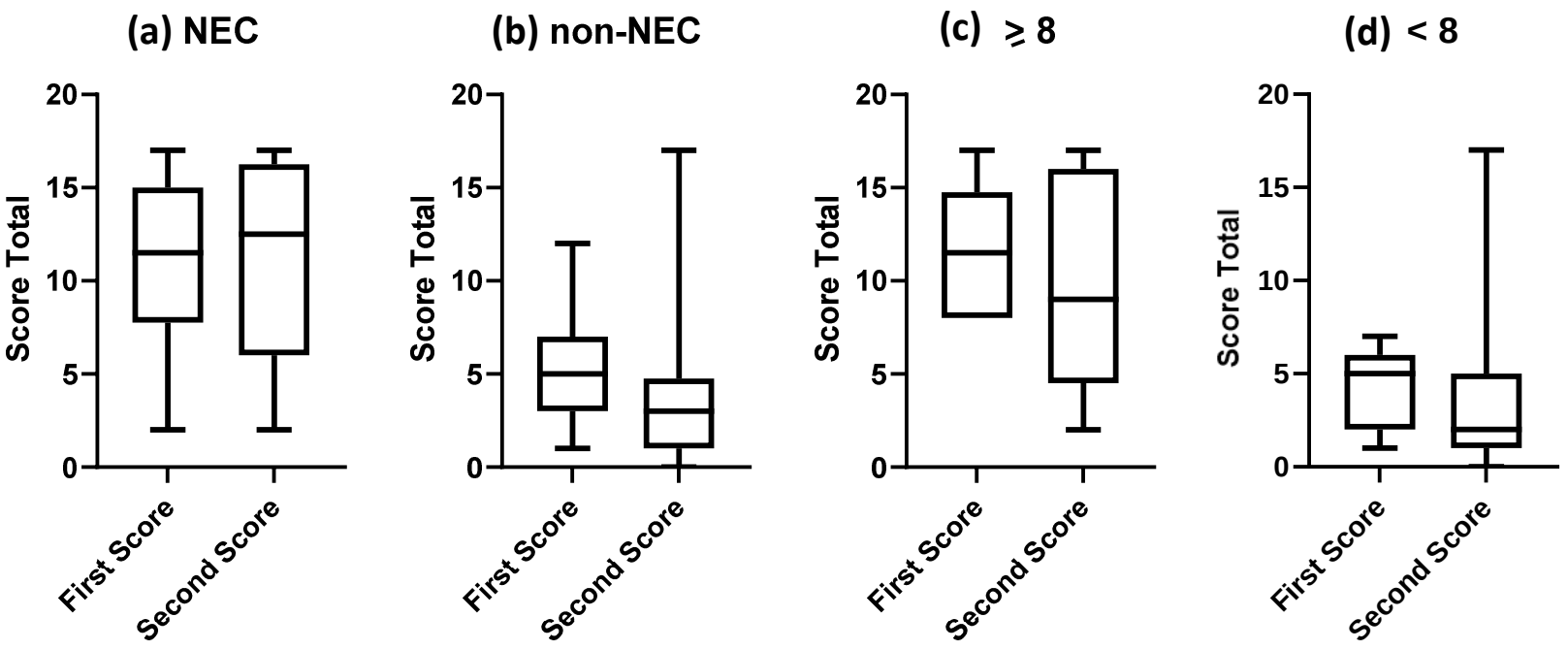

Total score (median and range)
Total score
30
20
10
0
NEC
non-NEC

Fig 3


ROC curve: ROC of Total Score
Sensitivity%
100
80
60
40
20
0
0
20
40
60
80
100
100% - Specificity%


(a) NEC
(b) non-NEC
(c) ≥ 8
(d) < 8
Score Total
20
15
10
5
0
First Score
Second Score