

PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	INTESTINAL FAILURE AFTER NECROTIZING ENTEROCOLITIS – INCIDENCE AND RISK FACTORS IN A SWEDISH POPULATION-BASED LONGITUDINAL STUDY
AUTHORS	Sjoberg Bexelius, Tomas; Ahle, Margareta; Björling, Oscar; Elfvin, Anders; Ludvigsson, Jonas; Andersson, Roland

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Valeria Cohran Institution and Country: Division of Pediatric Gastroenterology, Hepatology and Nutrition. The Ann & Robert H. Lurie Children's Hospital of Chicago. Chicago, IL USA Competing interests: none
REVIEW RETURNED	17-Jun-2018

GENERAL COMMENTS	<p>This is a retrospective study examining the incidence and risk factors for Intestinal Failure in a Swedish population. Because of the large dataset, this work adds to the literature regarding a rare outcome, Intestinal Failure.</p> <ol style="list-style-type: none">1. Since the data can be extracted, I would like the diagnoses of the 16 non NEC IF patients included in one of the tables or the body of the manuscript.2. The gestational ages are broken down into categories. I would actually also like to see the mean/median gestational ages of the patients and controls within the different eras reported.3. Since you have follow up on the patients, it would be nice to include more about the IF patients including number of subsequent admissions and diagnoses at the time of discharge up to the end of the 2 year follow up period.4. The manuscript mentions the differences in IF in patients in US studies as compared to yours. The differences in accessibility to health care provided in the US may account for some of the differences between the reports.5. In the methods section, the authors mention that they separated the patients depending on the year into 4 quartiles. Clearly there are not a large number of patients who go on to develop IF except in the last quartile. Perhaps including more information on that cohort vs the others would be useful such as the mean/median gestational age, birth weight. Is it due to younger gestational age patients surviving to develop NEC as compared to the earlier years starting in 1987?
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REVIEWER	Reviewer name: Mikko Pakarinen Institution and Country: Children's Hospital, University of Helsinki, Finland Competing interests: No competing interests
REVIEW RETURNED	04-Jul-2018

GENERAL COMMENTS	<p>This is an elegant register based study on incidence and risk factors of intestinal failure among children with NEC. Although the subject is not a novel one, the study is well conducted and its major strength compared to previous studies lies in the use a matched control group. I think it is a useful addition to existing literature. I have few questions.</p> <p>The definition of intestinal failure seems rather arbitrary. It appears that patients with the diagnosis of "intestinal malabsorption" only were also classified as having intestinal failure. This needs to be clarified/explained. If this is the case, the incidence of intestinal failure is most likely gravely overestimated as many of the previous surgical NEC patients receive nutrient supplements without requiring parenteral support or having intestinal failure. I am not sure that the previous validation of the registry (ref 13) has specifically addressed this issue.</p> <p>Although overall mortality of NEC decreased over the study period, it would be probably more interesting to know whether there was a similar trend in surgically treated NEC.</p>
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REVIEWER	Reviewer name: Rachel Hilliam Institution and Country: The Open University, UK Competing interests: None
REVIEW RETURNED	18-Jul-2018

GENERAL COMMENTS	<p>The statistics used in this paper are appropriate and well explained. However there are a few cases where the wrong table of statistic is referenced and I will highlight these below.</p> <p>On page 7 it would be helpful if the criteria for matching was explained at this point, as this would help the reader understand what is matched and what isn't when looking at table 1. The matching is explained later in the paper (p10) so a re-ordering is needed here.</p> <p>Page 7 line 77 mentions exclusion due to lack of complete information in the MBR - I think this should be lacking information in SMB.</p> <p>p13 line 177 references table 4 for the Cox regression, this should be table 5.</p> <p>p18 line 198 the p-value in the table is $p < 0.01$ not $p < 0.001$.</p> <p>p18 line 200 in table 1 this is 2.2%, $n=197$ not what is quoted.</p> <p>p19, line 206, this should be table 5. I think you are referring to 15.9 with 95% CI (9.0, 28.3).</p> <p>As a general point confidence intervals should be stated as I have written these above, ie in brackets with a comma between the upper and lower limits (a, b) and not a-b.</p>
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	<p>p19, line 220 I think this reference should be HR = 6.1 with 95% CI (3.1, 12.1) and line 222 7.6 with 95% CI (2.6, 21.9).</p> <p>p22 line 237 is the supplementary table supplied the one you really meant to include, if so I'm not sure this table supports the preceding sentence.</p> <p>The subject of the paper is interesting and well written, if the references to the table are checked and corrected then this will be of interest to the readership of the journal.</p>
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VERSION 1 – AUTHOR RESPONSE

Comments to the Author

This is a retrospective study examining the incidence and risk factors for Intestinal Failure in a Swedish population. Because of the large dataset, this work adds to the literature regarding a rare outcome, Intestinal Failure.

1. Since the data can be extracted, I would like the diagnoses of the 16 non NEC IF patients included in one of the tables or the body of the manuscript.

Response: We have added this information as requested on Page 16, in paragraph “Incidence and distribution of risk factors for intestinal failure in the study cohort

“ The commonest diagnoses has been included in Table 4, e.g. patients with a birth weight lower than 1500 g corresponding to P07.0/1x.

“The commonest main diagnosis in IF patients without previous history of NEC (reference cohort) was very and extreme prematurity, P07.2/3 (n=9); very/extreme low birth weight P07.0/1 (n=11) and light for gestational age (P05x; n=9). These are shown categorised in Table 4. Other diagnoses included neonatal skin infection P39.4 (n=1), and hematemesis, K92.0 (n =1).

2. The gestational ages are broken down into categories. I would actually also like to see the mean/median gestational ages of the patients and controls within the different eras reported.

Response: Ok thank you, we have added this data in Table 2.

3. Since you have follow up on the patients, it would be nice to include more about the IF patients including number of subsequent admissions and diagnoses at the time of discharge up to the end of the 2 year follow up period.

Response: We have added number of admissions broken down in those who develop IF depending on their cohort. Given the scope of the article we haven't included all the diagnoses, but most diagnoses relates to infection, nutritional problem secondary to their underlying prematurity (data not shown).

We have added a comment in result section in the last paragraph (page 21) regarding number of subsequent admissions:

The number of admissions among cases with IF varies depending on whether they had NEC or belonged to the reference group, i.e. there was a mean of 9 admissions (range 2-41) among the reference cohort compared to 6 (range 1-28) in the NEC cohort.

4. The manuscript mentions the differences in IF in patients in US studies as compared to yours. The differences in accessibility to health care provided in the US may account for some of the differences between the reports.

Response: Yes, we completely agree. We have access to medical records from the entire country including non-tertiary centres wherever the patients follow up might take place. This could account for some of the difference in incidence of IF as suggested by the reviewer. The generalisation of the results may then be limited but we believe the internal validity of our results restricted to the Swedish population is sound.

5. In the methods section, the authors mention that they separated the patients depending on the year into 4 quartiles. Clearly there are not a large number of patients who go on to develop IF except in the last quartile. Perhaps including more information on that cohort vs the others would be useful such as the mean/median gestational age, birth weight. Is it due to younger gestational age patients surviving to develop NEC as compared to the earlier years starting in 1987?

Response: It is a very good question and something we have given a lot of thought. We believe that part is due to the improved survival of extreme preterm infants in general due to improved supportive care and intensive care that has developed over time. Also the use of Parental nutrition may affect the incidence as does change in treatment. It is difficult to know for sure. We have added the following section in the discussion section on page 22 of the manuscript:

The mean gestational age in weeks among infants born in 1987-2003 was 32.6 (median of 32 weeks) compared to 29.7 (median of 28 weeks) in 2007-2009. Thus the population is indeed more premature and more prone to complications such as NEC and secondary IF.

Moreover, the birth weight differs significantly depending on birth cohort, e.g. 17% of infants born between 2007-2009 had a birth weight less than 750g compared to 6.5% in 1987-1993. The proportion of infants with a birth weight more than 2500 g was 16.5% in 2007-2009 compared to 39% in 1987-1993.

In discussion section, p15 line 247-250; "Possibly, treatment of NEC has been more successful over time in increasing survival, but at the same time causing long-term complications such as IF. In fact, neonatal mortality dropped from 20.6% from 1987-1997 to 10.4% for the birth cohort in 2007-2009, supporting this notion (Table 2)."

Reviewer: 2

Comments to the Author

This is an elegant register based study on incidence and risk factors of intestinal failure among children with NEC. Although the subject is not a novel one, the study is well conducted and its major strength compared to previous studies lies in the use of a matched control group. I think it is a useful addition to existing literature. I have few questions.

The definition of intestinal failure seems rather arbitrary. It appears that patients with the diagnosis of "intestinal malabsorption" only were also classified as having intestinal failure. This needs to be clarified/explained. If this is the case, the incidence of intestinal failure is most likely gravely overestimated as many of the previous surgical NEC patients receive nutrient supplements without requiring parenteral support or having intestinal failure. I am not sure that the previous validation of the registry (ref 13) has specifically addressed this issue.

Although overall mortality of NEC decreased over the study period, it would be probably more interesting to know whether there was a similar trend in surgically treated NEC.

Response: The reviewer is correct in that a uniform definition for paediatric IF is difficult.

We have used a combination of criteria as outlined in the methods section – as a combination between diagnosis of intestinal malabsorption and use of procedural code parenteral nutrition.

We agree that many premature infants would have been treated with periods of parental nutrition and that is why we included a limit of more than 14 days and a readmission criteria to single out cases that needed long term PN for adequate nutrition suggested by Pironi et al, 2016 (reference 5). Over time it is possible that the increased use of TPN or prolonged period of TPN would over-estimate the incidence of IF and we have commented on this in the manuscript extensively and indeed using different lengths of TPN treatment would affect the estimation of IF as commented in reference 9. However given the small absolute number of IF the risk is quite small. Also the effect on our risk estimates would be non-differential, as no difference in use of TPN among cases with NEC or without is expected.

We agree that additional validation of Swedish Patient Register is warranted and we have commented in the manuscript that a manual chart review to validate cases of IF would be ideal but not possible given our data set and limitation in retrospectively accessing and identifying individual case notes.

In our data the proportion of cases who underwent surgery I likely underestimated, making sub-analysis that the reviewer suggests more difficult but we agree that it would be very valuable.

In discussion the following passage is included, line 254-257

Moreover, the risk of IF varied over time, with the highest risk occurring for infants born during 2007-2009, a finding that is yet to be explained. One reason could be increased registration of TPN as a procedural code and/or increased usage of TPN.

Reviewer: 3

The statistics used in this paper are appropriate and well explained. However there are a few cases where the wrong table of statistic is referenced and I will highlight these below.

On page 7 it would be helpful if the criteria for matching were explained at this point, as this would help the reader understand what is matched and what isn't when looking at table 1. The matching is explained later in the paper (p10) so a re-ordering is needed here.

Response: Thank you, we have re-ordered this as suggested by the reviewer

“The individuals with NEC and the reference individuals without NEC were matched for GA in days (categorized as degree of prematurity) and birth year” has now been moved to page 7 and corresponding entry on page 10 has been deleted.

Page 7 line 77 mentions exclusion due to lack of complete information in the MBR - I think this should be lacking information in SMB.

Response: We have double checked but the information is collated from the Medical Birth Register (MBR)

p13 line 177 references table 4 for the Cox regression, this should be table 5.

Response: Changed.

p18 line 198 the p-value in the table is $p < 0.01$ not $p < 0.001$.

Response: Amended

p18 line 200 in table 1 this is 2.2%, n=197 not what is quoted.

Response: I am sure the reviewer is right, but I couldn't find the line in Table 1. If this can be clarified we will amend the manuscript accordingly.

p19, line 206, this should be table 5. I think you are referring to 15.9 with 95% CI (9.0, 28.3).

Response: We agree that the table should be Table 5. However, we are referring to adjusted Hazard ratio using the multivariable analysis corresponding to HR=13.2 with 95% CI (7.3, 23.8)

As a general point confidence intervals should be stated as I have written these above, i.e. in brackets with a comma between the upper and lower limits (a, b) and not a-b.

p19, line 220 I think this reference should be HR = 6.1 with 95% CI (3.1, 12.1) and line 222 7.6 with 95% CI (2.6, 21.9).

Response: OK, we have amended the format for reporting hazard ratio as suggested by the reviewer.

p22 line 237 is the supplementary table supplied the one you really meant to include, if so I'm not sure this table supports the preceding sentence.

Response: We have double checked this reference to the appropriate table.

Finally to support our results we have included a figure 3; a Kaplan-Meier survival table indicating time to event of intestinal failure divided by type of cohort, i.e. NEC vs. reference cohort.

Response: In the result section we have inserted the following

As shown in Figure 3, there is a clear difference in incidence of IF in between the NEC and reference cohort and that most cases occur within the first year of follow up from study start.

The subject of the paper is interesting and well written, if the references to the table are checked and corrected then this will be of interest to the readership of the journal.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Rachel Hilliam Institution and Country: The Open University, UK Competing interests: None
REVIEW RETURNED	28-Sep-2018

GENERAL COMMENTS	<p>The line in the original table 1 is as follows Abdominal surgery No 3582 (98.0) 523 (72.6) Yes 74 (2.0) 197 (27.4)</p> <p>Whereas on p18 you quote "Individuals with NEC more frequently underwent abdominal surgery (21.8%, n=157 199 compared with reference individuals (2.2%, n=82), p<0.01 (Table 1). "</p> <p>These two need to match, I'm not sure which is wrong, so worth going back to check.</p> <p>What you have quoted</p>
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VERSION 2 – AUTHOR RESPONSE

Thank you for the review of our manuscript and the positive response. We have re-reviewed all of the results and updated the manuscript and tables accordingly.

As the reviewer pointed out, there was a discrepancy between the result in the table regarding proportion of patients undergoing surgical procedures. After cross checking we have updated the tables with the most recent and accurate result. As a result, the table 5 outlining hazard ratio also have been corrected.

Many thanks for given us the opportunity to resubmit our manuscript and await your final decision.