

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Population-based cohort study examining the association between splenectomy and empyema in adults in Taiwan
AUTHORS	Lin, Hsien-Feng; Liao, Kuan-Fu; Chang, Ching-Mei; Lin, Cheng-Li; Lai, Shih-Wei

VERSION 1 - REVIEW

REVIEWER	Henry Rice Professor of Surgery, Pediatrics, and Global Health Duke University Medical Center Durham, NC 27710 USA
REVIEW RETURNED	23-Nov-2016

GENERAL COMMENTS	<p>1) For the abstract and title page, I am not sure "holistic" is a term I would use to describe this study. To my mind at least, this does not enhance or help define this type of analysis.</p> <p>2) The rationale the study is a bit unclear. I get the sense the reason to study the effect of splenectomy on empyema risk is relatively empirical. I realize other studies have done similar types of analyses of impact of splenectomy on other infections, but this still seems a bit like a fishing expedition as written. Perhaps the authors could better describe why they chose this topic, which is actually quite interesting.</p> <p>3) I see that the authors limited this analysis to adults (> 20 years of age). Why? Overall children are at much higher risk of infectious complications following splenectomy-any reason not to include them in this analysis?</p> <p>4) The statistics seem appropriate, but should be reviewed by a statistician. My only question is whether Kaplan-Meier curve would enhance the comparison of the longitudinal risk of empyema in the study groups, but I would defer to a statistician.</p> <p>5) I may have missed it, but why is the follow-up time so short? Although 4-6 years of follow-up is actually quite good, is there value in longer follow-up? Is this related to the study design?</p>
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REVIEWER	Catalin Vasilescu Fundeni Clinical Institute, Bucharest, Romania
REVIEW RETURNED	24-Nov-2016

GENERAL COMMENTS	<p>Major compulsory revision 1: in this paper the information about the splenectomised patients is very scarce:</p> <ul style="list-style-type: none"> - We do not know why the patients were splenectomised? The cause of splenectomy could be the cause of the empyema, for example splenic abscesses are known to correlate with empyema. - We do not know how the patients were splenectomised, open surgery or laparoscopic surgery? Did all the patients undergo total splenectomy or were there partial splenectomised patients? Empyema correlates very well with open surgery for example. - How many of the splenectomised patients were vaccinated against encapsulated bacteria (especially <i>Streptococcus pneumoniae</i>)? I am almost certain that the lack of vaccination correlates with empyema. <p>Major compulsory revision 2: the authors underline that such a study does not permit to conclude a substantial causality. I agree, but once again the lack of information is the cause behind this limit. It would have been very interesting to know what kind of bacteria cause the empyema.</p>
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REVIEWER	Canan Baydemir Kocaeli University, Turkey
REVIEW RETURNED	25-Jan-2017

GENERAL COMMENTS	The paper is well designed. Table 1 should be reorganized (standard deviation parentheses are absent).
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REVIEWER	Peter Goldblatt UCL Institute of Health Equity United Kingdom
REVIEW RETURNED	30-Jan-2017

GENERAL COMMENTS	<p>General comments</p> <p>The overall relative risk of empyema of 2.56 is soundly based. However the increase in relative risk after correcting for confounders needs more explanation. In particular, it is not clear how much matching was undertaken for primary condition requiring treatment. Even if this was not medically appropriate, more indication of differences between cases and controls (than is provided on page 10) would be appropriate. Similarly, the extent of matching for combinations of comorbidity is unclear. Were exact matches undertaken based in the combination of ICD9 coded conditions listed on page 5?</p> <p>More emphasis is needed, in the abstract and conclusions, on the trend in relative risk. The long term risk is substantially below that of the figures quoted in the abstract (and the short term risk</p>
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	<p>correspondingly markedly higher).</p> <p>Detailed comments</p> <p>Page 2, lines 27 and 31</p> <p>The word "even" is inappropriate, given that the risk is higher after adjustment.</p> <p>Page 4, line 30 "performed" should be "underwent" as the patients are the subjects of the sentence</p> <p>page 5, line 47</p> <p>More emphasis needs to be given in the abstract, discussion and conclusion to the violation of the proportionality assumption.</p> <p>Page 7, line 6</p> <p>Does "found significantly" mean "found to be statistically significant". Please clarify.</p> <p>Page 7, lines 19 to 32</p> <p>It is unhelpful to simply give a list of factors associated with empyema. Including sex (male) with a list of diseases is confusing. Some explanation of the fact that the risks associated with the selected list are all lower than the overall risk is needed. Is this a statistical artifact of the method of calculation?</p> <p>Page 7 lines 45 to 55</p> <p>The relative risks of 4.52 and 8.23 are based on a different reference group (comorbidity free) than figures presented earlier. This should be explained more carefully and contextualised by drawing attention to the risk of 3.64 of empyema in those in the control group who have comorbidities.</p> <p>page 9, line 27</p> <p>The reference to "other comorbidities" is unclear. It seems to suggest that splenectomy is a comorbidity, when in fact it is a treatment that is the subject of the paper. Please clarify.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Henry Rice

Institution and Country: Professor of Surgery, Pediatrics, and Global Health, Duke University Medical Center, Durham, NC 27710 USA

Please state any competing interests: None declared

Please leave your comments for the authors below

This report by Lin et al is a very well constructed and performed epidemiologic analysis of the effect of splenectomy on the incidence of empyema in Taiwan. This group has used a large national administrative dataset unique to Taiwan to perform this analysis, which is an inherent strength of this study. This is of broad interest and of adequate quality for the readership of BMJ Open, and is worthy of publication. My only recommendations are relatively stylistic, but may improve the overall quality of this work.

1) For the abstract and title page, I am not sure "holistic" is a term I would use to describe this study. To my mind at least, this does not enhance or help define this type of analysis.

Response: We deleted the word " holistic ". Thanks for good comments.

2) The rationale the study is a bit unclear. I get the sense the reason to study the effect of splenectomy on empyema risk is relatively empirical. I realize other studies have done similar types of analyses of impact of splenectomy on other infections, but this still seems a bit like a fishing expedition as written. Perhaps the authors could better describe why they chose this topic, which is actually quite interesting.

Response: "The incidence of pleural infections diminished significantly during the first half of the 20th century because of the development of antibiotics. However, this trend changed at the end of the 20th century and, since the decade of the 1990s the incidence of empyema has tended to be increasing worldwide." "Despite the incidence of empyema has tended to be increasing worldwide, no study has evaluated the association between splenectomy and empyema." This point has been mentioned in section of introduction. Thanks for good comments.

3) I see that the authors limited this analysis to adults (> 20 years of age). Why? Overall children are at much higher risk of infectious complications following splenectomy-any reason not to include them in this analysis?

Response: In this study, we hope to focus on the adult population aged 20-84.

We made a crude analysis on empyema associated with splenectomy and other comorbidities among subjects aged 1-19 in below Table X. The crude HR of empyema was 8.52 for subjects with splenectomy (95% CI 2.57, 28.3), compared with non-splenectomy. Your good comments indicate a future research direction in pediatric population.

Thanks for good comments.

Table X. Hazard ratio and 95% confidence interval of empyema associated with splenectomy and other

comorbidities among subjects aged 1-19

Crude

Variable HR (95%CI)

Sex (male vs. female) 1.40 (0.38, 5.16)

Age (per one year) 1.31 (0.98, 1.74)

Baseline comorbidities (yes vs. no)

Splenectomy 8.52 (2.57, 28.3)

Alcohol-related diseases - -

Cancers - -

Chronic kidney diseases 139.8 (17.9, 1090.0)

Chronic liver diseases - -

Chronic obstructive pulmonary disease - -

Diabetes mellitus - -

4) The statistics seem appropriate, but should be reviewed by a statistician. My only question is whether Kaplan-Meier curve would enhance the comparison of the longitudinal risk of empyema in the

study groups, but I would defer to a statistician.

Response: We added Figure 1 to reveal the Kaplan-Meier cumulative incidence of pleural empyema for the splenectomy group and the non-splenectomy group (6.99% vs. 3.37% at the end of follow-up; $P < 0.001$). This point has been mentioned in section of results.

Thanks for good comments.

5) I may have missed it, but why is the follow-up time so short? Although 4-6 years of follow-up is actually quite good, is there value in longer follow-up? Is this related to the study design?

Response: This database includes the data since 2000 to 2011. The incidence of empyema at the end of 2011 was calculated. We think that the follow-up time seems not to be short.

Thanks for good comments.

All changes were underlined in blue.

Thanks for your very helpful comments.

Reviewer: 2

Reviewer Name: Catalin Vasilescu

Institution and Country: Fundeni Clinical Institute, Bucharest, Romania

Please state any competing interests: None declared

Please leave your comments for the authors below

Dear editor,

Regarding the manuscript bmjopen-2016-015101 (Splenectomy correlates with increased risk of empyema: a population-based cohort study in Taiwan), I consider that the article is written in a good English language and the large sample size (13193 splenectomized patients) permits the authors to draw a conclusion. Moreover, I agree with the authors, this would be the first study to link splenectomy with empyema, but there are several revisions that should be done:

Major compulsory revision 1: in this paper the information about the splenectomized patients is very scarce:

- We do not know why the patients were splenectomized? The cause of splenectomy could be the cause of the empyema, for example splenic abscesses are known to correlate with empyema.

Response: We agree with your comments. Due to the inherent limitation of this insurance database, the underlying causes for splenectomy were not recorded. The cause of splenectomy could be the cause of the empyema, for example, splenic abscess. From a view of the good quality of the Taiwan medical system, it does not need to spend one month to confirm a diagnosis of empyema from the onset of empyema prodrome. In order to reduce the biased results, subjects who had an empyema diagnosis within one month after performing splenectomy were excluded from the study. Therefore, it is less possible that splenectomy could be the cause of the empyema. This point has been mentioned in section of limitation.

Thanks for good comments.

- We do not know how the patients were splenectomized, open surgery or laparoscopic surgery? Did all the patients undergo total splenectomy or where there partial splenectomized patients? Empyema correlates very well with open surgery for example.

Response: We agree with your comments. Empyema could correlate very well with open surgery. However, due to the same limitation, the splenectomized type was not recorded. We did not know how the patients were splenectomized, open surgery or laparoscopic surgery. Similarly, we did not know that patients underwent total splenectomy or partial splenectomy. This point has been mentioned in section of limitation.

Thanks for good comments.

How many of the splenectomised patients were vaccinated against encapsulated bacteria (especially *Streptococcus pneumoniae*)? I am almost certain that the lack of vaccination correlates with empyema.

Response: We agree with your comments. Lack of vaccination could correlate very well with empyema. However, due to the same limitation, we did not know how many of the splenectomized patients were vaccinated against encapsulated bacteria (especially *Streptococcus pneumoniae*). We could not investigate whether pneumococcal vaccination might decrease the risk of empyema among patients with splenectomy in Taiwan. This point has been mentioned in section limitation. Your good comment indicates a further research direction. Thanks for good comments.

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Major compulsory revision 2: the authors underline that such a study does not permit to conclude a substantial causality. I agree, but once again the lack of information is the cause behind this limit. It would have been very interesting to know what kind of bacteria cause the empyema.

Response: Due to the same limitation, causative pathogens were not recorded. We could not investigate what kind of bacteria would cause the empyema among patients with splenectomy. Lack of such information does not permit the present study to conclude a substantial causality. This point has been mentioned in section of limitation.

Thanks for good comments.

All changes were underlined in blue.

Thanks for your very helpful comments.

Reviewer: 3

Reviewer Name: Canan Baydemir

Institution and Country: Kocaeli University, Turkey

Please state any competing interests: -

Please leave your comments for the authors below

The paper is well designed.

Table 1 should be reorganized (standard deviation parentheses are absent).

Response: Parentheses have been added in standard deviation of Table 1.

Thanks for good comments.

All changes were underlined in blue.

Thanks for your very helpful comments.

Reviewer: 4

Reviewer Name: Peter Goldblatt

Institution and Country: UCL Institute of Health Equity, United Kingdom

Please state any competing interests: None declared

Please leave your comments for the authors below

General comments

The overall relative risk of empyema of 2.56 is soundly based. However the increase in relative risk after correcting for confounders needs more explanation. In particular, it is not clear how much matching was undertaken for primary condition requiring treatment. Even if this was not medically appropriate, more indication of differences between cases and controls (than is provided on page 10) would be appropriate. Similarly, the extent of matching for combinations of comorbidity is unclear.

Were exact matches undertaken based in the combination of ICD9 coded conditions listed on page 5? More emphasis is needed, in the abstract and conclusions, on the trend in relative risk. The long term risk is substantially below that of the figures quoted in the abstract (and the short term risk correspondingly markedly higher).

Response: We agree with your comments. Before analysis, however, it is very difficult to determine which factors should be included in the study to compare subjects with and without splenectomy. Thus, we reviewed the relevant literature and found some comorbidities which could be potentially related to empyema. To minimize the confounding effects caused by comorbidities, the splenectomy group and the non-splenectomy were matched with comorbidities. Except cardiovascular disease and hypertension, there was no significant difference in the prevalence of comorbidities studied between the splenectomy group and the non-splenectomy group (Chi-square test, $P > 0.05$ for all). Thanks for good comments.

Detailed comments

Page 2, lines 27 and 31

The word "even" is inappropriate, given that the risk is higher after adjustment.

Response: We deleted the word " even ". Thanks for good comments.

Page 4, line 30 "performed" should be "underwent" as the patients are the subjects of the sentence

Response: We revised " performed " into " underwent ". Thanks for good comments.

page 5, line 47

More emphasis needs to be given in the abstract, discussion and conclusion to the violation of the proportionality assumption.

Response: In our study, the risk of empyema in the splenectomy group was higher in the first 5 years of follow-up than after 5 years (incidence rate ratio 2.87 vs 1.72). However, the risk of empyema still existed in the splenectomy group even after 5 years. These findings are compatible with previous studies showing that the majority of severe infections occur within the first 3 years after splenectomy, and, although the risk declines over time, the risk might last for more than 5 years after splenectomy. We added Figure 1 to reveal the Kaplan-Meier cumulative incidence of pleural empyema for the splenectomy group and the non-splenectomy group (6.99% vs. 3.37% at the end of follow-up; $P < 0.001$).

Thanks for good comments.

Page 7, line 6

Does "found significantly" mean "found to be statistically significant". Please clarify.

Response: Yes, found to be statistically significant. We have revised it.

Thanks for good comments.

Page 7, lines 19 to 32

It is unhelpful to simply give a list of factors associated with empyema. Including sex (male) with a list of diseases is confusing. Some explanation of the fact that the risks associated with the selected list are all lower than the overall risk is needed. Is this a statistical artifact of the method of calculation?

Response: We have deleted a list of factors associated with empyema. Though these comorbidities were found to be associated with empyema, to minimize their confounding effects, we made a further analysis, even in absence of any comorbidity, patients with splenectomy still had a higher hazard of empyema (HR 4.52). These results indicate that not requiring the presence of comorbidity, splenectomy may have a unique role on risk of empyema. This point has been mentioned in section of discussion.

Thanks for good comments.

Page 7 lines 45 to 55

The relative risks of 4.52 and 8.23 are based on a different reference group (comorbidity free) than figures presented earlier. This should be explained more carefully and contextualised by drawing attention to the risk of 3.64 of empyema in the those in the control group who have comorbidities.

Response: The HR was not confounded by comorbidities studied because there was no significant difference in the prevalence of comorbidities between the splenectomy group and the non-splenectomy group. It means the increased hazard of empyema in patients with splenectomy cannot be totally attributable to the effect of comorbidities. In further analysis, even in absence of any comorbidity, patients with splenectomy still had a higher hazard of empyema (HR 4.52). These results indicate that not requiring the presence of comorbidity, splenectomy may have a unique role on risk of empyema. These findings are compatible with the literature that patients with splenectomy are not only more prone to suffer severe life-threatening infection due to the immunocompromised condition caused by splenectomy, but also at an increased hazard of developing empyema. This point has been mentioned in section of discussion.

VERSION 2 – REVIEW

REVIEWER	Henry Rice Duke University Medical Center Durham, North Carolina, USA
REVIEW RETURNED	07-Mar-2017

GENERAL COMMENTS	All shortcomings addressed adequately. Still requires formal review by statistician.
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REVIEWER	Canan BAYDEMIR Kocaeli University Medical Faculty Biostatistics and Medical Enformatic Dep. TURKEY
REVIEW RETURNED	21-Mar-2017

GENERAL COMMENTS	It is well designed paper.
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REVIEWER	Peter Goldblatt UCL institute of Health Equity United Kingdom
REVIEW RETURNED	13-Mar-2017

GENERAL COMMENTS	<p>My comment "the increase in relative risk after correcting for confounders needs more explanation." This comment reflected the increase in risk from 2.52 to 2.89 after adjustment for confounders (Table 3). I can find nothing in the revised text that explains this phenomenon atht would normally be regarded as counter-intuitive.</p> <p>My comment "More emphasis is needed, in the abstract and conclusions, on the trend in relative risk." This comment reflected the reduction in the incidence rate ratio (IRR) between splenectomy and non-splenectomy from 2.87 to 1.73.after 5 years (Table 2). This renders the average for the study period of 2.56 fairly meaningless. Had the study had an even longer follow up, this average would have gone down further. I can find no reference to this in the revised abstract or conclusions.</p>
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	<p>My comment "The word "even" is inappropriate". this referred to the sentence "Even in the absence of comorbidities, the risk remains high". While the authors have removed "even" in the abstract, as suggested. However the word "even" is still present in similar sentences on page 10 line 40 and page 12 line 40. these occurrences of the same or similar phrases are equally inappropriate to the context.</p> <p>My comment "performed splenectomy" should be "underwent splenectomy". This is unchanged on page 4 line 43.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Henry Rice

Institution and Country: Duke University Medical Center, Durham, North Carolina, USA

Please state any competing interests: None declared

Please leave your comments for the authors below

All shortcomings addressed adequately. Still requires formal review by statistician.

Response: The fourth author Miss Cheng-Li Lin is a statistician. She conducted the data analysis and participated in the data interpretation. Thanks for good comments.

Reviewer: 4

Reviewer Name: Peter Goldblatt

Institution and Country: UCL institute of Health Equity, United Kingdom

Please state any competing interests: None

Please leave your comments for the authors below

The authors have, in general, provided good responses to my comments on the previous draft. However not all of these responses are reflected in the redrafted paper.

My comment "the increase in relative risk after correcting for confounders needs more explanation." This comment reflected the increase in risk from 2.52 to 2.89 after adjustment for confounders (Table 3). I can find nothing in the revised text that explains this phenomenon that would normally be regarded as counter-intuitive.

Response: "The phenomenon that would normally be regarded as counter-intuitive and the reason were unclear. It may be due to some comorbidities which could be potentially related to empyema should be included in the study, but we lose them. Future studies are needed to explain this phenomenon." This point has been mentioned in section of discussion. Thanks for good comments.

My comment "More emphasis is needed, in the abstract and conclusions, on the trend in relative risk." This comment reflected the reduction in the incidence rate ratio (IRR) between splenectomy and non-splenectomy from 2.87 to 1.73 after 5 years (Table 2). This renders the average for the study period of 2.56 fairly meaningless. Had the study had an even longer follow up, this average would have gone down further. I can find no reference to this in the revised abstract or conclusions.

Response: "The incidence rate ratio between splenectomy and non-splenectomy from 2.87 reduced to 1.73 after 5 years, but the risk of empyema still existed in the splenectomy. Future studies are

needed to confirm that if the study had an even longer follow up, this average would have gone down further." This point has been mentioned in section of abstract and conclusions. Thanks for good comments.

My comment "The word "even" is inappropriate". this referred to the sentence "Even in the absence of comorbidities, the risk remains high". While the authors have removed "even" in the abstract, as suggested. However the word "even" is still present in similar sentences on page 10 line 40 and page 12 line 40. these occurrences of the same or similar phrases are equally inappropriate to the context.

Response: We deleted the word " even ". Thanks for good comments.

My comment "performed splenectomy" should be "underwent splenectomy". This is unchanged on page 4 line 43.

Response: We revised " performed " into " underwent ". Thanks for good comments.

All changes were underlined in blue.
Thanks for your very helpful comments.

Reviewer: 3

Reviewer Name: Canan BAYDEMIR

Institution and Country: Kocaeli University Medical FacultyBiostatistics and Medical Enformatic Dep.
TURKEY

Please state any competing interests: None declared

Please leave your comments for the authors below

It is a well-designed paper.

VERSION 3 - REVIEW

REVIEWER	Peter goldblatt UCL Institute of Health Equity, united Kingdom
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	<p>1) The two sentences added to the final paragraph of the abstract and conclusion have unfortunately raised more issues than they answer.</p> <p>At a minor drafting level the first new sentence, which should be amended to "The incidence rate ratio.....reduced from 2.87 to 1.73....", is confusing because the previous sentence in the paragraph refers to a "2.89-fold increased risk". For clarity the latter should be amended to a "hazard ratio of 2.89" to avoid confusion with the 2.87 IRR in the new sentence.</p> <p>Mor substantially the second new sentence suggests that with "even longer follow up this average would have gone down further".</p>
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	<p>However close scrutiny of the study design indicates that some subjects had 12 years of follow up (January 1, 2000 to December 31, 2011) while others had only one year of follow up (December 31, 2010 to December 31, 2011). So this sentence suggests that the results presented are a curious weighted average of a time-dependent variable (risk of an empyema diagnosis with time from splenectomy). Addressing this issue does not require a further study - it requires a time dependent hazard model to estimate the shape of the risk curve between one month and 12 years. Because of the study design, the confidence interval will widen with length of follow up as the sample available for analysis decreases. But that does not preclude estimating a non-linear regression line with length of follow up.</p> <p>Rather than undertaking this analysis, the authors could simply replace the need for further studies with "further analysis of the data" being required to determine the pattern of risk over time.</p> <p>2) A further issue raised by this sentence and by the new sentences on the the apparent raised risk among those with splenectomy only (page 11), is the rate of attrition in the sample over time. The numbers lost (by time period) from death and withdrawal from insurance, in particular, should be given in a table. It may, for example be, that those with co-morbidity are more likely to die early or withdraw from insurance - before they can be diagnosed with empyema. The reader needs to be reassured that the attrition rate for these reasons is too small to impact on risk - or its change over time.</p>
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VERSION 3 – AUTHOR RESPONSE

All questions raised by Reviewer 4 are too difficult to be answered.
 Would you please make a decision omitting Reviewer 4's comments?

VERSION 4 – REVIEW

REVIEWER	Peter Goldblatt UCL Institute of Health Equity United Kingdom
REVIEW RETURNED	11-Jun-2017

GENERAL COMMENTS	<p>The major concerns and potential contradictions in the study have largely been dealt with in this revision. There are still minor issues with language, that require proof reading - but the general standard is acceptable for publication.</p> <p>My main concern is with the clarity of the conclusion in the abstract and in the final paragraph of the discussion. This jumps between the results in Tables 1 to 4 in an unhelpful way. My reading of the discussion is that the authors should consider reordering something along the following lines (subject to them agreeing that this is an accurate reflection of their findings, of course):</p>
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	<p>"We conclude that the incidence rate ratio between splenectomy and non splenectomy reduced from 2.87 in the first 5 years of follow up to 1.73 in the period after 5 years. Future studies are needed to confirm that if the study had an even longer follow up, this average would have gone down further.</p> <p>Patients with splenectomy in the study had an overall hazard ratio of 2.89 after adjusting for age, sex and comorbidities identified from previous literature (including alcohol related disease s, cancers, chronic kidney diseases, chronic liver diseases, chronic obstructive pulmonary diseases, and diabetes mellitus. Even in the absence of these comorbidities the risk remains high."</p>
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VERSION 4 – AUTHOR RESPONSE

Reviewer: 4

Reviewer Name: Peter Goldblatt

Institution and Country: UCL Institute of Health Equity, United Kingdom

Please state any competing interests: None declared

Please leave your comments for the authors below

The major concerns and potential contradictions in the study have largely been dealt with in this revision. There are still minor issues with language, that require proof reading - but the general standrad is acceptable for publication.

Response: The manuscript has been revised for English grammar by an English-speaking person. Please see the attached proof. Thanks for good comments.

My main concern is with the clarity of the conclusion in the abstract and in the final paragraph of the discussion. This jumps between the results in Tables 1 to 4 in an unhelpful way. My reading of the discussion is that the authors should consider reordering something along the following lines (subject to them agreeing that this is an accurate reflection of their findings, of course):

"We conclude that the incidence rate ratio between splenectomy and non splenectomy reduced from 2.87 in the first 5 years of follow up to 1.73 in the period after 5 years. Future studies are needed to confirm that if the study had an even longer follow up, this average would have gone down further.

Patients with splenectomy in the study had an overall hazard ratio of 2.89 after adjusting for age, sex and comorbidities identified from previous literature (including alcohol related disease s, cancers, chronic kidney diseases, chronic liver diseases, chronic obstructive pulmonary diseases, and diabetes mellitus. Even in the absence of these comorbidities the risk remains high."

Response: We have revised the conclusion in the abstract and in the final paragraph of the discussion to " The incidence rate ratio between the splenectomy and non-splenectomy groups reduced from 2.87 in the first 5 years of follow-up to 1.73 in the period following the 5 years. Future studies are required to confirm whether a longer follow-up period would further reduce this average ratio. For the splenectomy group, the overall HR of developing empyema was 2.89 after adjusting for age, sex, and comorbidities, which were identified from previous literature (including alcohol-related disease, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus). The risk of empyema following splenectomy remains high despite the absence of these comorbidities." Thanks for good comments.

VERSION 5 - REVIEW

REVIEWER	Peter Goldblatt UCL Institute of Health Equity United Kingdom
REVIEW RETURNED	22-Jul-2017

GENERAL COMMENTS	The authors have now taken account of all my comments
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