Author's response to reviews

Title:Mortality following acute pancreatitis: social deprivation, hospital size and time of admission: record linkage study

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Author's response to reviews: see over
The Editor,
BMC Gastroenterology

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Dear Sir

Thank you for your e-mail. We are grateful for the thoughtful and insightful comments provided and have responded to each in detail below. We think they have improved the paper.

Please find uploaded a revised copy of the manuscript with all revisions denoted in blue font.

Yours sincerely

Dr Stephen E Roberts, reader in epidemiology and public health
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We are grateful for the thoughtful and insightful comments which we think have improved the manuscript. We have denoted all new text in blue font and would like to respond to the comments as follows:

Reviewer 1 report:

1. Acute pancreatitis (AP) related mortality is an important issue. Normally the 30 days mortality rate is reported, the authors focus on the 60 days mortality rate. Besides the general mortality, the authors also analyze the influence of five different factors for two main causes of AP (gallstones and alcohol). The strength of this study is that the data are linked with different databases. However the aetiology is known of by 35% of the total population. Major concern, it is not known/ discussed if the authors checked and corrected for unique cases (normally only 80% cases are really unique).
We report mortality rates at 60 days as the primary outcome measure but also report deaths at 30 days - in Table 1 and now in Table 2 – as a secondary outcome measure.

We have established reported the aetiology of acute pancreatitis in 70.5% of cases. In the remaining 29.5% of cases, the aetiologies were unknown or other minor aetiologies. Typically, In a substantial minority of cases, it is often not possible to determine the exact aetiology of the acute pancreatitis. Our figure of 70.5% established is comparable with some smaller case-note based studies - although lower than in others - but ours is one of few very large studies (>10,000 cases) that has established the aetiology in a high proportion of cases.

Based on specialist clinical consideration, we defined a unique case or attack of acute pancreatitis as a hospital admission for acute pancreatitis, providing that there was no previous admission for acute pancreatitis within the preceding 60 days (page 6, paragraph 3). We also report that 86% of the patients had one (unique) attack of acute pancreatitis over the 12 year study period (page 6, para 3).

We have also now reported analyses that are based on patients' first attacks of acute pancreatitis only (see response to point 2 below).

2. Another major concern is the fact that first attack AP's and recurrent AP's are not seperately analyzed (see p 7 definition of new cases).

As suggested, we now report mortality rates (with 95% confidence intervals) after including only the patients’ first attacks of acute pancreatitis (footnotes to Table 2). These mortality rates are not significantly different to those based on inclusion of patients' subsequent attacks of acute pancreatitis: for all cases of acute pancreatitis (6.4% when including subsequent attacks vs 7.3% when including first attacks only), for gallstone aetiology (5.1% vs 5.3% respectively) and for alcohol aetiology (3.1% % vs 3.9%). We have also repeated the investigations of the study factors on mortality after confining the analysis to first attacks of acute pancreatitis (see footnotes to Table 2). Confining these investigations to first attacks also did not make much difference to the study findings.

We have a preference for basing most of this study on acute pancreatitis that allows for subsequent attacks, as we have done consistently in previous studies. However, if the Editors would prefer the study to focus more on first attacks of acute pancreatitis we would be happy to oblige.

Minor concerns:
3. The five factors analyzed are very mixed from social deprivation to influence of EWTDs. To create a more easily to read manuscript the authors can probably skip some two of them. -the five factors analyzed should be discussed through the manuscript in the same order.

As suggested, we have now sequenced the ordering of the five study factors so that they are the same in the Results and Discussion sections.

We also appreciate this comment about the number of factors (five) included in the paper and have considered removing factors such as social deprivation and/or the week day of admission. Al though
we have a slight preference for retaining them, we would be happy to oblige with editorial preferences.

4.  -p 10 the percentage of total aetiology is not 100% but only 70.5%

Agreed, the total percentage of cases covered by the reported aetiologies adds up to 70.5%. As indicated, we have now clarified that the other 29.5% of cases were of other or unknown aetiologies (page 10, para 3).

5.   -p10 how can gallstones (in 13%) lead to death? This needs an explanation

In the methods section, we have now clarified that we report causes of death based on death certificate data from the official authority, the Office for National Statistics (page 9, para 3). Gallstones were certified in 38 cases (13% of cases) as the underlying cause of death rather than as the immediate cause of death. As indicated, we have now added a sentence that provides details of the immediate causes of death for these 38 cases (page 11, para 3). This shows that although gallstones were the underlying cause of death in 38 cases, the immediate cause of death was acute pancreatitis in most cases (30).

Please note that because of data provider confidentiality agreements, we have to refrain from listing specific causes of death in low numbers of cases (<5 cases).

We hope that this provides clarification. We would be happy to respond further if necessary and could provide a description of death certification procedures.

6.   -p14 study limitations: some should be added to the methods section, not in the discussion section. some cases were excluded.

As suggested, we have now added some of the study limitations from the Discussion section to the Methods section. In particular this includes text on the percentage of patients who were hospitalised once only during the study period (page 6, para 3) and death certification (page 9, para 3).

7.   -table 2, 3 and 4 have a great overlap, they should be shorter.

We appreciate this comment about the overlap of Tables 2, 3 and 4 (acute pancreatitis overall, gallstone aetiology and alcohol aetiology) and have now combined them more concisely into a single table (new Table 2).

8.   -the five factors analyzed should not be mentioned as prognostic factors in the text of the different tables, this is not the correct term and even misleading.
As suggested, we have removed the term “prognostic” from “prognostic factor” throughout the manuscript.

Reviewer 2 report

This manuscript is a register study. The questions posed by the authors are well defined and methods are appropriate and well described. It fulfills the standards for reporting and I find the discussion and conclusions well balanced and adequately supported by the data. I think limitations of the work overall are clearly stated and acknowledgement are clearly stated. The title convey the findings and the writing is more than acceptable.

Minor Essential Revisions:

1. Study strength and limitations:
This is a pure register study with the problems it can bring. The strength is the size of study. Unfortunately, the register lacks information about alcohol intake, tobacco use, BMI, severity of acute pancreatitis and treatment. The last is mentioned in the discussion but I would recommend that you also mention the other lacks of information. I am impressed that you are able to distinguish between the different aetiologies by using the DRG-codes alone. Have you validated this?

As suggested, we have now added in the study limitations section that the study did not have information on alcohol consumption, tobacco use and body mass index (page 15, para 2). We had previously commented that information was not available on case severity and treatment.

Although we have not to date formally validated the ICD-10 codes for acute pancreatitis (from case notes) we have used them in previous studies published in Aliment Pharmacol Ther (references 7 and 17 in the reference list in the paper). However, we have previously validated ICD-10 codes as the principal diagnosis for inpatient admissions for other GI disorders (Crohn’s Disease and ulcerative colitis). We have now included these validation results along with those for the study death ascertainment and record linkage methodology used. These were respectively >90%, >98% and >99.8% accurate (page 15, para 1).

2. Deprivation:
It is surprising that social deprivation is not significantly correlated with mortality. How is the deprivation calculated exactly? Which register has been used to make this scale and how is this parameter validated? Is the parameter only based on the postcode or could you supply with information from any social registers?

We have expanded the Methods section to provide further details of how social deprivation (WIMD) is calculated (page 7, para 2). WIMD is based on several (social register based) components of social deprivation (including income, employment, education and housing, etc) that are weighted and assigned to postcode residential areas. We also provide a reference that provides further details of the methodology used (reference 26). WIMD has been used extensively in publications in many international Medline journals in recent years (a few of these references are provided on page 7, para 3). WIMD was designed to be compatible with the even more widely published English
measure of social deprivation (IMD; page 7, para 2). It is also regarded widely as the best and most published measure of social deprivation available for the study population.

3. Month of admission and recruitment of junior doctors each August The hypothesis: “EWTD is bad for the patients and leads to a higher mortality”. Do you only recruit new young doctors in August? In my country we recruit new doctors all year around so it would not be possible to test this hypothesis by comparing the different months. Could the drop in working hours per week not be a positive thing for the patient? It might lead to a more enthusiastic and awake doctor if the doctor haven't been to work 60 hours this week... You might mention this part of the discussion too in the manuscript. You find a higher mortality for alcoholic pancreatitis in August-October. This finding do not have to be connected to the recruitment of young doctors. It could be related to a higher alcohol intake these months.

We appreciate these comments and have further clarified that the recruitment of newly qualified junior doctors in Wales occurs almost always during August (page 8, para 2). However, we have further investigated other rotation or ‘swap over’ months for junior doctors in April and December (page 13, para 1) and have compared all months of the year in Figure 1.

As suggested, we have commented that EWTD reductions over time in working hours should have a positive impact on reducing fatigue among junior doctors and patient care (page 19, para 1). Also, as suggested, we have commented that the higher mortality during the months from August to October among patients with acute pancreatitis of alcohol aetiology may be linked to higher alcohol consumption and case severity - especially as mortality was highest for alcohol aetiology during the holiday month of August (page 18, para 1).

4. Analysis
In figure 3 you have not defined the red and green box-plots. Is it August?

For Figures 2, we have defined the Red columns as denoting “the two European Working Time Directives in August 2004 and August 2009) and the Green columns as denoting “the recruitment of newly qualified junior doctors in August each year” (footnotes to Figure 2, page 13).

5. Underlying cause of death
p. 10: gallstone is stated as the cause in 13% How can that be true?

Please see the response to the similar point raised by Reviewer 1 (point 5 above).

6. Mortality according to size of hospital:
You are surprised to find a higher mortality in the largest hospitals. In my country, patients are distributed to the different hospitals by a specific pre-hospital selection. The doctor that sends the patient to the hospital sets a hypothetic diagnosis. He/she contacts a ”central distribution center” and then the most ill patients with a specific diagnosis are distributed to the largest hospitals
while patients less ill and with other diagnosis are send to smaller hospitals. If this is also the case in UK, it might explain some of the results.

We appreciate these comments too. As indicated, we have now commented in the Discussion that, unlike some other countries, pre-admission triage according to the severity of acute pancreatitis is not usually implemented in our study population (page 16, para 3). We have also reported on hospital transfers, including transfers from Emergency Departments as well as inpatient transfers (page 11, para 3). However, these amounted to only 267 transfers out of the 10,589 cases (2.5%). Only 95 patients (0.9%) were transferred to the four large specialist centres with a mortality rate of 20% based on 19 deaths (page 12, para 2).

We would be happy to respond to any further comments if necessary.