Author's response to reviews

Title: The impact of comorbidity and stage on ovarian cancer mortality: A nationwide Danish cohort study

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Author's response to reviews: see over
RE: Manuscript Number: 4588257221616513
‘The impact of comorbidity and stage on ovarian cancer mortality: A nationwide Danish cohort study’
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Thank you very much for giving us the opportunity to revise the manuscript. We have gone through the constructive comments from the reviewers and we have revised the manuscript accordingly.

Our response to the comments is as follows:

Reviewer Laurie Elit:

1. In the abstract the authors assume that patients with comorbidities experience a delay in diagnosis and this is the reason for their poor outcome. This assumption is not evaluated in the manuscript. In fact the manuscript is more balanced. The discussion points this out as one possible explanation. Thus this assumption should be removed from the abstract. This paper mainly shows that those with more comorbidities have a worse prognosis when diagnosed with ovarian cancer. Other reasons for a poorer outcome include: compromised immunity, poorer reserve ect. In fact, patients with more comorbidities may actually be diagnosed earlier because they have such a close relationship with the health care system. The author also assumes that ovarian cancer progresses from Stage 1 to 4. This point is also subject to discussion as, there is a school of thought that stage 1 (localized) and stage 3 (multifocal) may be different forms of the disease.

Ad 1. We agree that the concept “delay in diagnosis” has not been evaluated. We found that the presence of severe comorbidity was associated with an advanced stage of ovarian cancer which we suggested could be interpreted as a delay in diagnosis. We acknowledge that we by that have assumed that ovarian cancer progresses from Stage 1 to 4.

We have, therefore, rephrased the sentence “If patients with comorbidities are diagnosed with advanced stages, this would explain the poor survival observed among ovarian cancer patients with severe comorbidity”. Page 2 lines 3 to 5

And we have added “Patients with comorbidities may experience a delay in diagnosis or they may actually be diagnosed earlier because they have a close relationship with the health care system. We found that the presence of severe comorbidity was associated with an advanced stage of ovarian cancer. If ovarian cancer progresses from Figo-stage I to IV this could suggest a delay in diagnosis. It has, however, been suggested that stage I and stage III may be different forms of the disease (reference). Please see page 12 lines 7 to 11
2. It would be interesting to know the 1 and 5 yr survival of patients without out cancer and the comorbidity scores of interest and to what degree the diagnosis of ovarian cancer changes these figures.

Ad 2. We agree that this is a very interesting question, however our study-population were patients with ovarian cancer, and therefore we had no patients without cancer included.

Reviewer René Scheiden:

1. As mentioned in the title of the manuscript, the study focused on comorbidity, tumour-stage and mortality.
- The authors state that “comorbidity is an important predictor of prognosis in patients with chronic diseases including cancer” and that “among women with ovarian cancer, the presence of comorbidity may substantially influence the diagnostic work-up, after treatment efficacy and affect survival”. Analysing the results of the present study, these statements are absolutely justified. Because, comorbidity is a central parameter in this study, it seems important and necessary to define more precisely in the “Methods-chapter cf. page 7, line 3 and page 7, line 7-9”, the terms of “moderate and severe comorbidity” and give for each category as many as possible examples issued from the Danish Hospital Discharge Registry.

Ad 1. No recorded comorbidity, moderate and severe comorbidity is already defined as Charlson scores (0, 1-2 and 3+) please see page 7 lines 4 to 6.

We have presented the prevalence of the different comorbid diseases included in the Charlson comorbidity index in a table below. We think that this may be too extensive for the paper. We are of course willing to add this table to the paper if the editor disagrees with us.
Comorbid conditions in the 5,213 ovarian cancer patients

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Total</th>
<th>Charlson score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarct</td>
<td>113 (2.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>117 (2.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>112 (2.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>229 (4.4%)</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>17 (0.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>232 (4.5%)</td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>137 (2.6%)</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>180 (3.5%)</td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>47 (0.9%)</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes type 1 or type 2</td>
<td>124 (2.4%)</td>
<td>1</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>8 (0.2%)</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td>39 (0.8%)</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
<td>50 (1.0%)</td>
<td>2</td>
</tr>
<tr>
<td>Any tumour (not ovarian cancer)</td>
<td>490 (9.4%)</td>
<td>2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>9 (0.2%)</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>13 (0.3%)</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>11 (0.2%)</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic solid tumour</td>
<td>160 (3.1%)</td>
<td>6</td>
</tr>
<tr>
<td>AIDS</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

2. Also for those who are not experts in this field it might be of interest to define the terms “absolute survival and relative mortality rate ratios (MMRs)”.

Ad 2. We have defined the term absolute survival. We have added “absolute survival was defined as the proportion of the patients who were still alive one- or five-years after diagnosis” see page 8 lines 7 to 9. We believe that the term mortality rate ratio is defined in the text already – please see page 8 lines 1 to 2, and 9 to 11.
3. The authors state that the Danish Cancer Registry also contains information on histological types (page 6, line 4). Why was it not possible to separate FIGO-stage II from FIGO-stage III tumours? (cf. page 5, line 19-20).

Ad 3. In the Danish Cancer Registry stage was classified either using the FIGO classification or as either local, regional spread, or distant metastasis. For tumours categorized as regional spread, we were unable to determine whether it was FIGO-stage II or FIGO-stage III tumour. We therefore categorized the ovarian cancer cases into four groups, as previously done by Kjaerby-Thygesen et al. (Acta Obstet. Gynecol. Scand. 2005): (a) localized tumours/FIGO-stage I tumours; (b) tumours with regional spread/FIGO-stage II and III tumours; (c) tumours with distant metastases/FIGO-stage IV tumours; and (d) tumours with unspecified stage.

We have rephrased the sentence to “For tumours categorized as regional spread, we were unable to determine whether it was a FIGO-stage II or FIGO-stage III tumour, therefore we used the scheme of Kjaerby-Thygesen…” Please see page 5 lines 17 to 19

MINOR ESSENTIAL REVISIONS:

4. page 5, line 22: tumours with regional “pelvic” spread...

Ad 4. We included both stage II and II in these tumours with regional spread, it is therefore both pelvic spread and “abdominal” spread.


Ad 5. We apologize and have changed it to 1995 on page 6 line 3

6. page 9, line 12+13: Among patients with severe comorbidity, 42% had distant metastases/FIGO IV, compared to 28% of patients without comorbidity.

In table 1, line 19: Distant metastases/FIGO IV // comorbidity 0:27% versus comorbidity 3+:38%?

Ad 6. When computing the prevalence ratio we only used information on patients for whom information on stage was available. Therefore we have rephrased the sentence to “An association between comorbidity and advanced stage, for whom information on stage of disease was available, was found only among patients with severe comorbidity.” Please see page 9 lines 6 to 7

DISCRETIONARY REVISIONS:

a. page 4, line 14-17: However...
The two sentences are not important in the context of the present study. I would delete them.
Ad a. We would prefer to keep this information because it is the reason why we conducted an additional study. We have, however, shortened the sentences:

However, the study was limited by lack of information on the stage of cancer and by our inability to exclude patients with borderline tumours. Page 4 lines 15 to 16

b. page 5, line 5+6: Use of date...
This sentence should be part of the “Method chapter”, perhaps in a paragraph with a statement on the different histological types of ovarian cancers evaluated in the present study (cf. WHO classification) at page 6, line 4

Ad b. We agree and have deleted the sentence. Since we do not address the histological types of ovarian cancers we have not stated this further.

c. page 5, line 19: Since we could not classify tumours with regional spread as either FIGO-stage II or III tumours... we used ...
Why?

Ad c. Please see the answer to question 3

d. page 12, line 2+3: When applied to administrative data, misclassifications of comorbidity may occur.
Why?

Ad d. When applied to administrative data information on comorbidity is based on ICD-codes. The comorbid diseases may be coded with different accuracy in the different administrative registries and misclassifications occur in most registries. The Charlson index has been shown to have a high specificity, but a more variable sensitivity when compared with diagnoses abstracted from the medical charts (please see Wilchesky et al. Validation of diagnostic codes within medical services claims. J Clin Epidemiol 2004;57:131-41)

We have rephrased the sentences “When applied to administrative data information on comorbidity is based on ICD-codes. The comorbid diseases may be coded with different accuracy in the different administrative registries and misclassifications occur in most registries. The Charlson index has been shown to have a high specificity, but a more variable sensitivity when compared with diagnoses abstracted from the medical charts.” Page 11 line 22 to page 12 line 1

e. page 12, line 6: However, since comorbidity was independently recorded before the cancer diagnosis ...
Since when?

Ad e. We have rephrased the sentence to “However, because comorbidity was independently recorded before the cancer diagnosis …” page 12 line 4
As stated on page 6 line 21 “We obtained 18 to 26 years of hospitalization history for each patient, depending on date of diagnosis, and used this information to compute the Charlson Comorbidity Index”

f. page 14, line 2: This may explain …  
This may also explain …

Ad f. We have rephrased the sentence to “This may also explain …”

Reviewer Patricia Tai:

Minor Essential Revisions

1. p10. 5th line: MMRs is a typo.

Ad 1. We apologize and have corrected it to MRRs

2. p12. middle of 2nd paragraph: "One reason this study did not find an association may be its adjustment for residual tumour, which may be an intermediate factor in the causal pathway between comorbidity and survival." Please explain this a bit more.

Ad 2. To explain the phrase, we have rephrased the sentence to “One reason this study did not find an association may be its adjustment for residual tumour. Presence of a residual tumour is related to the aggressiveness of surgery and if comorbidity results in less aggressive surgery, residual tumour may be an intermediate in the causal pathway from comorbidity to death. In this situation, adjustment for residual tumour would be inappropriate. The effect of comorbidity on mortality may be mediated to a large degree by higher volume of residual tumour.” Please see page 12 lines 19 to 24

3. p12. "Similarly, an American hospital-based study reported an age-” needs to have a ”,“ after age-.

Ad 3. We have added a “,” and corrected it to “…age-, stage- ….. “