PEER REVIEW HISTORY

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ARTICLE DETAILS

| TITLE (PROVISIONAL) | Pre-hospital care for ovarian cancer in Catalonia. Could we do better in primary care? Retrospective cohort study |
|---------------------|----------------------------------------------------------------------------------------------------------|
| AUTHORS             | Vela-Vallespin, Carmen; Manchon-Walsh, Paula; Aliste, Luisa; Borras, Josep M.; Marzo-Castillejo, Mercè |

VERSION 1 – REVIEW

| REVIEWER            | Long, Joanna                                                                 |
|                     | University of Birmingham, Institute of Applied Health Sciences                 |
| REVIEW RETURNED     | 03-Feb-2022                                                                  |

GENERAL COMMENTS

Thank you for writing this really interesting and valuable piece of research. This retrospective quasi-population-based cohort study looked at data from primary and secondary care clinical histories and care processes in the 18 months leading up to diagnosis. Results suggested survival in EOC is not associated with diagnostic pathways or pre-hospital health care, but it is influenced by stage at diagnosis, tumor histology, administration of primary cytoreduction plus chemotherapy, and patient age. This is important in the context of this study as Spain does not have early referral to cancer pathways (as in the case in the UK TWW). I have reviewed this study and aside from minor spelling/grammatical issues I suggest this study should be accepted.

My only comment is whether you have been able to look at the differences in standard vs radical/ultraradical surgery in this cohort, if applicable? Or if there are any differences in terms of surgical complexity scores, if recorded?

| REVIEWER            | Zhang, James                                                                |
|                     | University of Chicago, Medicine                                              |
| REVIEW RETURNED     | 13-Feb-2022                                                                  |

GENERAL COMMENTS

This study aimed to assess the impact of pre-hospital factors (diagnostic pathways, first presentation to healthcare services, intervals, participation in primary care) on 1- and 5-year survival in people with epithelial ovarian cancer (EOC). The analysis has been carefully carried out with several important contributing factors evaluated. There are a few conceptual, methodological, and presentational issues that require clarification.

1. Cancer stage. The cancer stages have been combined into two groups with I and II, and III and IV, respectively, likely due to small sample size (Table 1). However, this variable was not presented in the results in univariate or multivariate analysis (Table 5). (It appeared in the Supplementary Table 1.) Given cancer stage is a
key driving factor for survival (and it seemed to have some

difference in Table 1), a more organized/streamlined
discussion/presentation of the stage and its association with the
diagnostic pathways may help readers to better understand the
prognostic value of pre-hospital factors in addition to cancer stage
in EOC.

2. Clinical outcomes. The study assessed both 1- and 5-year
survivals (Abstract) but only results on 5-year survival were
reported in the Abstract. What kind of difference these two
measurements make in understanding the role of pre-hospital
factors? A more thought-out discussion/presentation in this line will
likely benefit the readers in understanding the conceptual
framework of the impact of the pre-hospital factors.

3. Statistical analysis and results reporting. One major finding is
that most of the variables were not statistically significant
(Abstract). The wording may need to be modified to present clearly
that this is the case, for example, “Patients whose first contact did
not involve primary care had a slight disadvantage (HR 1.39, 95%
CI 0.93, 2.09) compared to those who did go through this service.
Diagnostic pathways involving referral to elective gynecological
care from specialists other than family physicians (HR 0.80, 95%
CI 0.51, 1.26) and self-presentation to emergency services (HR
0.82, 95% CI 0.52, 1.31) had a small advantage over patients
referred from family physicians, although the difference was not
statistically significant” (Abstract, Results). Perhaps using some
wording more neutral than “had a small advantage” or “had a slight
disadvantage”.

4. Conclusion. “Survival in EOC is not associated with diagnostic
pathways or pre-hospital health care, but it is influenced by stage
at diagnosis, tumor histology, administration of primary
cytoreduction plus chemotherapy, and patient age.” (Abstract,
Conclusions). The effects of stage, age etc. were not reported in
the Results in the Abstract hence should not appear here unless
the authors add the information in the Results in the Abstract. It is
not surprising that the diagnostic pathways or pre-hospital health
care were not statistically significant given the complex fabric of
interactions among those variables and possible measurement
errors, but a more nuanced discussion in this line may help
advance the research in the right direction.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Joanna Long, University of Birmingham
Comments to the Author:
Thank you for writing this really interesting and valuable piece of research. This retrospective quasi-
population-based cohort study looked at data from primary and secondary care clinical histories and
care processes in the 18 months leading up to diagnosis. Results suggested survival in EOC is not
associated with diagnostic pathways or pre-hospital health care, but it is influenced by stage at
diagnosis, tumor histology, administration of primary cytoreduction plus chemotherapy, and patient
age. This is important in the context of this study as Spain does not have early referral to cancer
pathways (as in the case in the UK TWW). I have reviewed this study and aside from from minor
spelling/grammatical issues I suggest this study should be accepted.
My only comment is whether you have been able to look at the differences in standard vs radical/ultraradical surgery in this cohort, if applicable?

Response to reviewer: Comparing primary surgery and interval surgery in patients with stage III and IV cancer is a hot topic due to the different starting point. In fact, we did perform this comparison, and it will be included in a future paper. In that regard, we observed significant differences in survival in favour of primary surgery.

Or if there are any differences in terms of surgical complexity scores, if recorded?

Response to reviewer: Unfortunately, due to the heterogeneity between centres, we did not have all the data needed to calculate the surgical complexity scores.

Reviewer: 2

Dr. James Zhang, University of Chicago

Comments to the Author:

This study aimed to assess the impact of pre-hospital factors (diagnostic pathways, first presentation to healthcare services, intervals, participation in primary care) on 1- and 5-year survival in people with epithelial ovarian cancer (EOC). The analysis has been carefully carried out with several important contributing factors evaluated. There are a few conceptual, methodological, and presentational issues that require clarification.

1. Cancer stage. The cancer stages have been combined into two groups with I and II, and III and IV, respectively, likely due to small sample size (Table 1). However, this variable was not presented in the results in univariate or multivariate analysis (Table 5). (It appeared in the Supplementary Table 1.) Given cancer stage is a key driving factor for survival (and it seemed to have some difference in Table 1), a more organized/streamlined discussion/presentation of the stage and its association with the diagnostic pathways may help readers to better understand the prognostic value of pre-hospital factors in addition to cancer stage in EOC.

Responding to reviewer comment: Cases were grouped into early or advanced stages due to the similarity in therapy and prognosis. We modified table 5, eliminating the column with the univariate analysis to present the results of the multivariate analysis at 1 year. In line with the reviewer’s comments and to be more consistent, in Table 5 we present the variables age, stage and treatment received. In the Results, we comment on the significantly higher HRs in each age stratum at 5 years’ follow-up and the significant increase in stage at 1 and 5 years. We also discuss the association with the type of treatment received both at 1 and 5 years, although the magnitude decreases.

Text added to the Results: Table 5 shows the variables included and the results of the multivariate Cox regression at one- and five-years’ follow-up. In the Cox survival models, advanced tumour stage at the time of surgery was a significant risk factor both at one year (hazard ratio [HR] 3.84, 95% confidence interval [CI] 1.23, 12.02) and at five years (HR 5.36, 95% CI 3.07, 9.36). The type of treatment received was also a significant risk factor, although the magnitude of the association decreased at five years’ follow-up. Regarding age, the magnitude of the HR for five-year survival increased with age.

Test added summary: In the Cox models, survival was influenced by advanced stage at one year (HR 3.84, 95% CI 1.23, 12.02) and five years (HR 5.36, 95% CI 3.07, 9.36), as was the type of treatment received, although this association was attenuated over follow-up.

2. Clinical outcomes. The study assessed both 1- and 5-year survivals (Abstract) but only results on 5-year survival were reported in the Abstract. What kind of difference these two measurements make in understanding the role of pre-hospital factors? A more thought-out discussion/presentation in this line will likely benefit the readers in understanding the conceptual framework of the impact of the pre-hospital factors.

Responding to reviewer comment: We added the results for survival at 1 year and 5 years in the Abstract and point out the differences in these measures in relation to age, stage, and types of treatment. Likewise, this information is reflected in the results and is consistent with the Conclusions.
Text added to the Abstract: In the Cox models, survival was influenced by advanced stage at one year (hazard ratio [HR] 3.84, 95% confidence interval [CI] 1.23, 12.02) and five years (HR 5.36, 95% CI 3.07, 9.36), as was the type of treatment received, although this association was attenuated over follow-up. Age became significant at five years of follow-up.  
3. Statistical analysis and results reporting. One major finding is that most of the variables were not statistically significant (Abstract). The wording may need to be modified to present clearly that this is the case, for example, “Patients whose first contact did not involve primary care had a slight disadvantage (HR 1.39, 95% CI 0.93, 2.09) compared to those who did go through this service. Diagnostic pathways involving referral to elective gynecological care from specialists other than family physicians (HR 0.80, 95% CI 0.51, 1.26) and self-presentation to emergency services (HR 0.82, 95% CI 0.52, 1.31) had a small advantage over patients referred from family physicians, although the difference was not statistically significant” (Abstract, Results). Perhaps using some wording more neutral than “had a small advantage” or “had a slight disadvantage”.

Responding to reviewer comment: We observed no association between survival and the starting point involving primary care, referral to elective gynecological care from specialists, or self-presentation to emergency services.

Modification to text in Abstract: Survival was not associated with a starting point involving primary care (HR 1.39, 95% CI 0.93, 2.09), diagnostic pathways involving referral to elective gynecological care from non-GPs (HR 0.80, 95% CI 0.51, 1.26), or self-presentation to emergency services (HR 0.82, 95% CI 0.52, 1.31).

4. Conclusion. “Survival in EOC is not associated with diagnostic pathways or pre-hospital health care, but it is influenced by stage at diagnosis, tumor histology, administration of primary cytoreduction plus chemotherapy, and patient age.” (Abstract, Conclusions). The effects of stage, age etc. were not reported in the Results in the Abstract hence should not appear here unless the authors add the information in the Results in the Abstract. It is not surprising that the diagnostic pathways or pre-hospital health care were not statistically significant given the complex fabric of interactions among those variables and possible measurement errors, but a more nuanced discussion in this line may help advance the research in the right direction.

Responding to reviewer comment: We agree with the reviewer’s comment, and although we already pointed out in the section on strengths and limitations that we cannot rule out the risk of information biases that could distort some estimates, we added that “given the different interactions between variables as well as possible measurement errors, it is unsurprising that survival is not statistically associated with pre-hospital health care.”

Text added to the discussion (Strengths and limitations): (given the different interactions between variables as well as possible measurement errors, it is unsurprising that survival is not statistically associated with pre-hospital health care).