PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatment approach and survival from glioblastoma: results from a population-based retrospective cohort study from Western Norway
AUTHORS	Bjorland, Line; Fluge, Oystein; Gilje, Bjornar; Mahesparan, Rupavathana; Farbu, Elisabeth

VERSION 1 – REVIEW

REVIEWER	Amir R. Afshari (Pharm. D, Ph. D) Department of Physiology and Pharmacology, Faculty of Medicine, North Khorasan university of Medical Sciences, Bojnurd, Iran
REVIEW RETURNED	18-Aug-2020

GENERAL COMMENTS	The authors have examined the treatment and survival of glioblastoma in a real-world setting. However, there are several points and the authors should consider that the manuscript needs major paraphrasing. 1- The term 'glioblastoma' is a general word. what is the exact type of this tumor? GBM? Anaplastic? which one?? you should abbreviate the glioblastoma in the abstract to GBM. As below: Glioblastoma multiforme (GBM) 2- The references in paragraph 1 need more recent publications, such as: https://doi.org/10.2174/1389200221666200714101038 3- When you abbreviate a famous word like temozolomide you should use TMZ not Tmz. 4- There are many grammatical errors in the manuscript.Please, correct. 5- Actually, with respect, the manuscript is boring. lack of promising results, deficit in influential words in the abstract and discussion as well as conclusion sections may be the reasons. You should express the advantages of your manuscript better.

REVIEWER	Anna Snavely Wake Forest School of Medicine, Winston-Salem, NC, US
REVIEW RETURNED	A01-Dec-2020

GENERAL COMMENTS	Thank you for opportunity to review this interesting study. A few questions/comments. 1. Why did you choose a cut-off of 7 for the Charlson comorbidity index? Did you consider treating it as a continuous variable in the logistic regression models instead? 2. Table 1 highlights differences in characteristics between those patients with histologically confirmed GBM and those with MRI-

	based diagnosis. Is there a reason you didn't include the survival experience for these 2 groups? 3. Log-rank tests were used to compare survival between age and treatment groups. While interesting, these tests do not account for other patient characteristics. It would be useful to also use Cox proportional hazards models to compare treatments after adjusting for patient characteristics. Is there still a difference in treatment, or is the difference driven by patient characteristics? Hazard ratios would also be a helpful addition for comparing between groups. The addition of survival modeling would really strengthen this paper. 4. It would be helpful to report the number of deaths seen in the cohort (useful to know how much censoring is present).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1. The term 'glioblastoma' is a general word. What is the exact type of this tumour? GBM? Anaplastic? Which one? You should abbreviate the glioblastoma in the abstract to GBM. As below: Glioblastoma multiforme (GBM).
Reply: As the reviewer correctly points out, there are some confusion related to the nomenclature describing primary brain tumours. Glioblastoma is by definition histological grade IV, thus patients with anaplastic glioma (grade III) were not enrolled in this study. We have clarified this in the manuscript by adding the histological grade. Glioblastoma multiforme (abbreviated GBM) was previously the common term to describe glioblastoma WHO grade IV, with multiforme reflecting the heterogeneity and variability of the cells of these tumours. However, in the 2016 World health organization classification of tumours of the central nervous system, the nomenclature was changed and the former term glioblastoma multiforme was replaced by glioblastoma. To further clarify this, we have removed the abbreviation GBM from the manuscript, and replaced it with the written out up-to-date term glioblastoma.

2. The references in paragraph 1 need more recent publications, such as: https://doi.org/10.2174/1389200221666200714101038.
Reply: We appreciate the reviewers' suggestion of this reference, which we have added as a reference in the introduction of the manuscript.

3. When you abbreviate a famous word like Temozolomide, you should use TMZ not Tmz.
Reply: We agree, and have incorporated the abbreviation in the manuscript.

4. There are many grammatical errors in the manuscript. Please, correct.
Reply: We apologize for any grammatical errors. To improve the grammar, a native speaking researcher have proofread and edited the manuscript.

5. Actually, with respect, the manuscript is boring. Lack of promising results, deficit in influential words in the abstract and discussion as well as conclusion sections may be the reasons. You should express the advantages of your manuscript better.
Reply: We acknowledge that real-world studies are not necessarily providing promising results, as opposed to i.e. randomized controlled trials. However, we argue that real-life data provides important knowledge in contribution to the existing literature. This is of particular importance in a disease where many patients are not eligible to clinical trials. Due to the retrospective nature of this study, we cannot

prove causality, and have therefor avoided bold conclusions. However, in response to the reviewers' suggestion, we have now rephrased the conclusion of the abstract into "Our results point out a substantial risk of undertreating glioblastoma, especially in elderly patients".

Reviewer 2:
1. Why did you choose a cut-off of 7 for the Charlson comorbidity index? Did you consider treating it as a continuous variable in the logistic regression models instead?
Reply: This is an appropriate comment. There is to our knowledge no established consensus on cut-off value when defining severe comorbidity according to Charlson score. Studies on other cancer types have used a wide range of cut-off values. With a cut-off value of seven, approximately 10% of the patients met the criteria for severe comorbidity, which we considered clinical relevant. We tested the logistic regression model both with Charlson score as a continuous and as a categorical value, with nearly similar results, and with acceptable goodness of fit in both alternatives. However, as we acknowledge the uncertainty related to the cut-off value, we have no treated Charlson score as a continuous variable in the revised manuscript.

2. Table 1 highlights differences in characteristics between those patients with histologically confirmed glioblastoma and those with MRI-based diagnosis. Is there a reason you didn't include the survival experience for these 2 groups?
Reply: We prioritized to present survival experience for groups by treatment, instead of survival by diagnostic groups, as we considered this to be of higher clinical relevance. However, as the reviewer points out, it is also relevant to compare groups by diagnostic approach, and have this to the result section of the revised manuscript.

3. Log-rank tests were used to compare survival between age and treatment groups. While interesting, these tests do not account for other patient characteristics. It would be useful to also use Cox proportional hazards models to compare treatments after adjusting for patient characteristics. Is there still a difference in treatment, or is the difference driven by patient characteristics? Hazard ratios would also be a helpful addition for comparing between groups. The addition of survival modeling would really strengthen this paper.
Reply: We appreciate this comment, and we agree that Cox proportional hazards models may strengthen this paper. We have added univariate and multivariate Cox proportional hazards regressions models to analyse the effect of clinical covariates and treatment approach on outcome. These results are presented in the result section and in an additional table (table 3).

4. It would be helpful to report the number of deaths seen in the cohort (useful to know how much censoring is present).
Reply: We agree, and have reported the number of deaths in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Anna Snavely Wake Forest School of Medicine, USA
REVIEW RETURNED	12-Jan-2021

GENERAL COMMENTS	The authors have adequately responded to my previous concerns.