

LETTER TO THE EDITOR

Open Access



Risk of confounding variables in multivariate analysis

Bruno Gagnon^{1,2,3,4*} and Andrew M. R. Hanna⁵

Dear Editor,

We too read with interest the article “The Role of Opioids in Cancer Response to Immunotherapy” by Botticelli et al., which suggests that opioids impair the immune response to cancer in patients receiving immunotherapy [1].

First, we are in complete agreement with the concerns raised by Maltoni et Rossi [2] in the first letter you published in response to this article.

Second, while it has been some months since the original article was published, we would like to bring to your attention a new point to consider:

In the Results section, the authors state: “...opioids use was significantly higher in patients affected by NSCLC [Non-Small Cell Lung Cancer] ($p < 0.0001$), in patients with a worse ECOG PS [Eastern Cooperative Oncology Group Performance Status] ($p < 0.0001$), in second-line setting subgroup ($p = 0.009$), in patients taking corticosteroids ($p < 0.0001$), and in patients with a high tumor burden ($p = 0.006$)” [1].

Of those five listed variables, the only one that was not included in the multivariate analysis (MA) was NSCLC. Given that the opioid and non-opioid cohorts consisted of 62% and 22% NSCLC patients, respectively [1], which is an approximately threefold (2.82) difference in proportion, we think that this would have been an important

variable to include in the MA. Furthermore, melanoma was overrepresented in the non-opioid group by more than three-fold (3.59; 17% vs. 61% in opioid and non-opioid cohorts, respectively) [1].

The 5-year survival rate of NSCLC, when treated with nivolumab (one of the four immunotherapy drugs included in the study) is 15.6%, compared to 34.2% for melanoma [3]. Tracheal, bronchus, and lung cancers (such as NSCLC) have an age-standardized global mortality rate of 23.74 per 100,000, whereas malignant skin melanoma has a considerably lower rate of 0.78 per 100,000 [4]. Considering these facts, we think that the type of cancer could be a confounding variable that should have been considered in the MA.

If the authors are willing to reanalyze their results, we would be curious to know if and how their conclusions may change if the MA includes the type of cancer. Had the type of cancer been included in the published MA, we suspect that the observed effect of opioids on progression-free survival and overall survival would disappear.

Acknowledgements

Not applicable.

Authors' contributions

AMRH was a major contributor in writing the manuscript. Both authors read and approved the final manuscript.

Funding

No funding.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable (this is a letter to the Editor without original data).

This comment refers to the article available online at <https://doi.org/10.1186/s12967-021-02784-8>.

*Correspondence: gagnon.bruno@crchudequebec.ulaval.ca
¹ Department of Family and Emergency Medicine, Faculty of Medicine, Université Laval, Quebec City, QC, Canada
Full list of author information is available at the end of the article



Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Family and Emergency Medicine, Faculty of Medicine, Université Laval, Quebec City, QC, Canada. ²Cancer Research Centre, Université Laval, Quebec City, QC, Canada. ³Réseau Québécois de recherche en soins palliatifs et de fin de vie du FRQS (RQSPAL), Quebec City, QC, Canada. ⁴Équipe de recherche Michel-Sarrazin en oncologie psychosociale et soins palliatifs, Université Laval, Quebec City, QC, Canada. ⁵Division of Palliative Care, Bruyère Research Institute, Ottawa, ON, Canada.

Received: 7 March 2022 Accepted: 10 March 2022

Published online: 09 April 2022

References

1. Botticelli A, Cirillo A, Pomati G, Cerbelli B, Scagnoli S, Roberto M, Gelibter A, Mammone G, Calandrella ML, Cerbelli E, Di Pietro FR, De Galitiis F, Lanzetta G, Cortesi E, Mezi S, Marchetti P. The role of opioids in cancer response to immunotherapy. *J Transl Med.* 2021;19(1):119. <https://doi.org/10.1186/s12967-021-02784-8>.
2. Maltoni M, Rossi R. Risk of detrimental recommendations for cancer pain management. *J Transl Med.* 2021;19(1):160. <https://doi.org/10.1186/s12967-021-02831-4>.
3. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Drilon A, Wolchok JD, Carvajal RD, McHenry MB, Hosein F, Harbison CT, Grosso JF, Sznol M. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non-small cell lung cancer treated with nivolumab. *JAMA Oncol.* 2019;5(10):1411–20. <https://doi.org/10.1001/jamaoncol.2019.2187>.
4. Lin L, Yan L, Liu Y, Yuan F, Li H, Ni J. Incidence and death in 29 cancer groups in 2017 and trend analysis from 1990 to 2017 from the global burden of disease study. *J Hematol Oncol.* 2019;12(1):96. <https://doi.org/10.1186/s13045-019-0783-9>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

