



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 35217

Title: Factors associated with carcinoid syndrome in patients with gastrointestinal neuroendocrine tumors

Reviewer's code: 03664977

Reviewer's country: Thailand

Science editor: Ya-Juan Ma

Date sent for review: 2017-06-30

Date reviewed: 2017-07-07

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

Re: Manuscript 35217

Name of Journal: World Journal of Gastroenterology

Manuscript Type: retrospective study

Title: Factors associated with carcinoid syndrome in patients with gastrointestinal neuroendocrine tumors

AIM: To discover unknown factors associated with carcinoid syndrome (CS) with the goal of earlier diagnosis of CS.

Reviewer comments:

1. The nature of retrospective study; case-control study using US administrative claims



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may cause several confounders and details eg. the database is not designed for research, and may had misclassification. Additionally, the CS cases with minor symptoms such as cutaneous flushing, diarrhea with few bowel movements/day may underdiagnosed¹.

2. The authors have to discuss why the number of 25% of both population of GI-NETS cases in development dataset and validation dataset had carcinoid syndrome (CS) which was higher than those previous reports of 3-21% of NET patients^{1, 2}

3. The number of new cases of NETs in 2012 is reported from 6.98 cases per 100,000 individuals thus this study included 2162 cases which should be derived from 30,974,212 population by calculation. Therefore this number is not equivalent to the the information in methods which mentioned that the newly diagnosed cases with GI NETs is included during the 1/1/2010 - 12/31/2014 and the PharMetrics Plus database is comprised of 150 million patients enrolled in US health insurance plans, with an annual capture of 40 million. Is it correct?

4. In addition, the key diagnosis of CS is still doubtful, for example the standard guideline recommends a 24-h urinary 5-HIAA analysis should be performed for all patients with a small intestinal primary NET, as well as those with symptoms suggestive of the carcinoid syndrome³ but it's not well noted in this study.

5. The predictive factor for CS were liver disorder [OR 3.38 (2.07 - 5.51)], enlargement of lymph nodes [OR 2.13 (1.10 - 4.11)], and abdominal mass [OR 3.79 (1.87 - 7.69)] were interesting and give some new information. However, the tumor burden and the behavior of aggressive tumor progression may be key important factors instead of the reported predictors³.

6. Finally, the strength of this study is the high number of sample size in both dataset compared to previous report⁴. In addition, the clinical presentation of this study is different from the large study from Japan⁵. The authors should add discussion in this aspect.

References:

1. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol* 2017;18:525-534.
2. Ducreux M. Carcinoid syndrome in neuroendocrine tumors: a prognostic effect? *Lancet Oncol* 2017;18:426-428.
3. Singh S, Asa SL, Dey C, et al. Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus. *Cancer Treat Rev* 2016;47:32-45.
4. Salyers WJ, Vega KJ, Munoz JC, et al. Neuroendocrine tumors of the gastrointestinal tract: Case reports and literature review. *World J Gastrointest Oncol* 2014;6:301-10.



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5. Ito T, Igarashi H, Nakamura K, et al. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. *J Gastroenterol* 2015;50:58-64.



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Name of journal: World Journal of Gastroenterology

Manuscript NO: 35217

Title: Factors associated with carcinoid syndrome in patients with gastrointestinal neuroendocrine tumors

Reviewer's code: 00058401

Reviewer's country: Brazil

Science editor: Ya-Juan Ma

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> [Y] Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> [Y] Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> [] High priority for publication
<input type="checkbox"/> [Y] Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> [] Rejection
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		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> [Y] No	

COMMENTS TO AUTHORS

The manuscript is of good quality and written in good English, Unfortunately the authors did not make a single reference to the transport system of serotonin that may represent a significant role on the metastasis of carcinoid tumors ,besides the tumors size .Serotonin Transport (Serotonin Transporter),PMAT,and others have been exhaustively studied.At present we don't know if these transporters are inactivated in the liver.The work deserves publication.