



PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 76672

Title: Expression of Hepatocyte Nuclear Factor 4 alpha, Wingless-Related Integration Site, and β -Catenin in Clinical Gastric Cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00504362

Position: Editorial Board

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Chile

Author's Country/Territory: China

Manuscript submission date: 2022-03-25

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-03-25 13:40

Reviewer performed review: 2022-03-28 22:32

Review time: 3 Days and 8 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

This is an interesting and well-designed manuscript. However this reviewer has some minor concerns, 1. There are some grammars throughout the text. 2. Please provide all product codes in order to facilitate the reproducibility of these results, by other researchers. 3.-This reviewer missed a more detailed explanation about the significance in the context of the pathophysiology of gastric cancer of the results obtained.



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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00505755

Position: Editorial Board

Academic degree: PhD

Professional title: Senior Research Fellow

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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SPECIFIC COMMENTS TO AUTHORS

Scale bar for the figure picture may be added in Figures.



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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

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Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Comments to Authors: Authors explored the relationship between HNF4 α /WNT/ β -catenin signal and the development of gastric cancer in clinical patient specimens. Generally, it is an interesting study, however there are some comments and questions the authors should address all were detailed below: Major corrections:

- The introduction is too long and needs to be summarized.
- Provide the refence for the used scoring system for interpretation of immunohistochemistry
- What was the criteria for selecting specimens from patients?
- Which type of gastric cancers was the aim of the study?
- What was the size of explored specimens?

In results section: authors said" Gastric cancers are divided into tubular adenocarcinoma, signet ring cell carcinoma and mucinous adenocarcinoma according to the WHO histological classification. In Table 3, HNF4 α was strongly positive expressed in tubular and mucinous adenocarcinoma but was relatively weak in signet ring cell carcinoma" the total number of specimens presenting each type of these cancers wasn't mentioned in except in table 3??

- Discussion is too long and also needs to be summarized



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Reviewer's code: 00225291

Position: Editorial Board

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Spain

Author's Country/Territory: China

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

The manuscript shows differential expression of different markers (HTNF4 α , WNT5a, etc...) in cancerous lesions vs non-cancerous lesions in patients with gastric cancer. This is potentially interesting, but the manuscript shows several pitfalls and overstatements. In addition, the manuscript needs rewriting and there are some English usage errors. TITLE (Clinical correlation between HNF4 α , WNT5a and β -catenin in gastric cancer) does not match the results shown in the manuscript. True, the expression of the markers analyzed differ depending on the origin of the tissue studied (cancerous vs non cancerous) or the type of the gastric tumor (tubular, signet ring, mucinous) but it has nothing to do with the clinical evolution of patients, and I think this is major concern with the manuscript. The INTRODUCTION is too long and can be shortened. For instance, the sentence "The earliest understanding of HNF4 α is that HNF4 α mutation is related to several forms of maturity-onset diabetes of the young[8, 9]." can be left out with no detrimental effect on the content of the manuscript. The paragraph "Increasing evidence has shown that HTNF4 αprogression of gastric cancer are still unclear" needs to be shortened, if not deleted altogether. MATERIALS AND METHODS 1.- There is a discrepancy in the number of paired tissue sections "...158 gastric tumors and 164 matched para-tumor tissue sections...". How can it be paired with different numbers? It is later mentioned that "...6 slices were not included due to quality problems...". The number should match both groups. 2.- When explaining the statistical tests run, only the Chi squared is mentioned, but in the supplementary tables, regression analysis and Pearson correlation analysis are cited. 3.- The terms used all over the text to identify the origin of the tumoral vs non-tumoral blocks (gastric cancer and para cancerous,



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respectively) is confusing. Patients suffer from gastric cancer and I thus dare suggest the term "tumoral tissue" or "tumoral sections" for the samples with cancerous lesions, and "peritumoral" or "para-cancerous" for the paired samples with no cancerous lesions from a given patient. 4.- Percentages are expressed using two decimal places (91,72%), and one decimal place (91,7%) would be sufficient. 5.- Some P values given in the text do not match those given in tables. For instance, in the text it is stated "In Table 3, HNF4 α was strongly positive expressed in tubular and mucinous adenocarcinoma but was relatively weak in signet ring cell carcinoma (P < 0.001)." But in the footnote to table 3 the P value shown is "***P<0.000." Same in table 4 6.- In table 4, heading should read "...according to Lauren classification" 7.- When commenting on the results of table 5, it is said "Using the X² test of paired comparison analysis, we found that there was a positive correlation between HNF4 α and WNT5a expression in GC (X² = 1.5, P > 0.05) (Table 5)". This P value discards any correlation. 8.- Results given in tables 7 and 9 are scarcely significant and relevant. 9.- The first table should be one describing the characteristics of the population studied. 10.- In several parts of the RESULTS section the notion that HNF4 α /WNT5a are biomarkers of cancer with diagnostic capability is stressed ("HNF4 α /WNT5a axis can be a biomarker of gastric cancer" or "WNT5a has a high diagnostic accuracy rate of 85.71%"). This is an overstatement. Diagnosis can be readily achieved based on well standardized anatomopathological criteria. In CONCLUSIONS, it is stated that "...the HNF4 α /WNT5a axis could be used as a potential diagnostic tool for gastric cancer." This, in my opinion, is an overstatement. The diagnosis is made upon anatomopathological findings. In this aspect, the results herein shown do not add to already existing diagnostic criteria. English usage needs to be revised. I will show but a few samples 1.- "Recent studies have showed...." correct to "Recent studies have shown..." 2.- "These pathological blocks of gastric cancer patients were selected from Tongji Hospital, and immunohistochemical staining was

carried out on 158 gastric tumors and 164 matched para-tumor tissue sections from Tongji Hospital” change to “Pathological blocks of gastric cancer patients were selected from Tongji Hospital, and immunohistochemical staining was carried out on 158 gastric tumors and 164 matched para-tumor tissue sections” 3.- “The expression of HNF4 α and WNT5a might be used as early prediction biomarkers for prediction in the early stage of GC” correct to “The expression of HNF4 α and WNT5a might be used as early prediction biomarkers in GC” 4.- “Archival human gastric cancer tissues...” correct to “Archived human gastric cancer tissues...” 5.- “The co-expression of HNF4 α and WNT5a in gastric cancer and the correlations with the clinicopathological characteristics in GC” correct to “Co-expression of HNF4 α and WNT5a in gastric cancer and correlation with the clinicopathological characteristics”. Similar changes in other headings. 6.- “And it still suggests that the expression of the two factors in gastric cancer is positively correlated both at RNA and protein level[17, 29, 32]” Unclear sentence. 7. Legend to figure 1 “Figure 1. The expression of HNF4 α in gastric cancer (GC) and para-cancerous tissue (PC). A、 B: The representative figures of HNF4 α expressed at different grades of pathological scores in GC (A) and PC (B), which is nuclear staining. C: The numbers of samples expressing HNF4 α in GC and PC groups. Specimens were examined under a light microscope (200 \times).” correct to “Figure 1. Expression of HNF4 α in gastric cancer (GC) and para-cancerous tissue (PC). Representative figures of HNF4 α expression (nuclear staining) at different grades of pathological scores in GC (A) and PC (B). C: Numbers of samples expressing HNF4 α in GC and PC groups. Specimens were examined under a light microscope (200 \times)” Similar changes are required in other figure legends.