

Dear Dr Yaun Qi, Scientific Editor,

July 7, 2016

Please find attached a revised version of our manuscript.

Name of journal: World Journal of Gastroenterology

Manuscript NO.: 27042

Column: Evidence-Based Medicine

Title: Cost-effectiveness of duodenal biopsies as a routine screening in iron deficiency anemia patients

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Reviewer code: 02941324 and 00047789

First decision: 2016-06-20 10:51

Scientific editor: Yuan Qi

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown using yellow highlight for additions.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in World Journal of Gastroenterology.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Reviewer (#1) comments:

Quality adjusted life-years (QALY) outcome seemly the major results but there are no detail how to calculate in the Method section

Response:

We thank the reviewer for this important comment.

The most common outcome unit used in cost-effectiveness analysis is Quality-Adjusted Life Year (QALY), which incorporates both the quality of life and life expectancy. The quality of each health state is measured on a scale of 0 to 1 and is based on patient's preferences over the health states. For example, the score of perfect health is 1 and the score of death is 0. States that are 'worse than dead' would have a negative score.

To calculate QALYs, various steps apply:

- 1. Develop a description of each health state (health condition)*
- 2. Choose the method for determining utilities of the health state on a scale of 0 to 1.*
- 3. Estimate the score for each health states by median (or mean) of a sample of healthy subjects*
- 4. Multiply utilities by the length of life for each option to obtain QALYs.*

The methods that are used for determining utilities of the health state are: (1) Standard Gamble (SG), (2) Time Tradeoff (TTO) and (3) Visual Analog Scale (VAS). The SG method is based on the rational decision making paradigm "Expected Utility Theory" (EUT). (For more information see: Karen L. Rascati. Essentials of Pharmacoeconomics. 2009. pages: 68-74).

We have added a sort clarification about the term QALY both in the Methods section, (first paragraph , highlighted), and in the Comments section. In case the reviewer believes that the explanation in the main text should be more detailed we will gladly do so.

Reviewer (#2) comments:

Dear Authors, I have read with interest your paper. It is well written, and the idea is interesting, as it shows a novel methodological approach to the management of celiac disease, with relevant saving of money. There is just one point I'd like to highlight to improve the discussion: beyond IDA, also the endoscopic appearance of duodenal villi may predict CD. Authors should at least discuss it in their discussion, mentioning briefly different tools for the evaluation of celiac disease, with proper references, including at least: - Water immersion technique in adults (please see Gasbarrini et al - Gastrointestinal Endoscopy 2003) and in children (Cammarota et al - J Pediatric Gastroenterol Nutr 2009) - Narrow Band Imaging (please see Singh et al - Endoscopy 2010) - I-scan technology (Cammarota et al - Dig Dis Sci 2013) Please also keep in mind a review article published in World J Gastroenterol in 2013 on the topic (Endoscopic tools for the diagnosis and evaluation of celiac disease- G Ianiro, A Gasbarrini, G Cammarota- World J Gastroenterol 19 (46), 8562-70) good work!

Response:

We thank the reviewer for his comment and suggestion. We therefore added a section in the discussion (highlighted) mentioning the different endoscopic tools used in aid of diagnosing celiac disease, and included the above references.

Editor comments:

1. First, could you give me the word version document about your article ? **so that I can edit them easily.**

Response:

Attached in a word version document (as a separate document)

2. Comments

The comments section aims to help readers avoid misunderstanding or over-interpretation of your study by summarizing the content of your article, including technical details, in a precise and simple manner. The comments section is broken down into the following subsections: background, research frontiers, innovations and breakthroughs, significance of the applications, terminology, and comments from peer reviewers. The specific requirements for each subsection are provided below.

Response:

We hereby attach the comments section

Comments:

Background:

Iron deficiency anemia (IDA) is a common presentation of celiac disease (CD) found in as many as 50% of the patients at the time of diagnosis. However, the need for routine duodenal biopsies in IDA patients, independent of their celiac serology results, is still debated.

The latest clinical guidelines for the diagnosis and management of CD published in 2013 recommend routine SBBs during upper endoscopy in when the probability for CD is 5% or more. As the prevalence of CD among patients with IDA is about 5%, duodenal biopsies and serology for tTG antibodies are therefore recommended.

Research frontiers:

According to recent studies, quality of life of celiac patients is inferior compared to healthy population. About 5% of IDA patients are diagnosed with CD. No studies were done to estimate the cost effectiveness of routine SBBs, regardless celiac serology status, in IDA patients in order to diagnose CD patients earlier and by that reduce morbidity and mortality. According to our knowledge, this is the first study which explore the cost effectiveness of performing routine SBBs to diagnose celiac in IDA patients. We measured, using a Markov

model, quality adjusted life years (QALY), average cost and the incremental cost effectiveness ratio (ICER).

Innovations and breakthroughs:

Our model shows that routine SBBs, regardless of serology status, yielded higher QALY, lower cost and higher ICER than performing SBBs only in patients with positive serology. These results were valid as long as cost of SBBs stayed less than 67\$. In addition, the ICER of strategy A was preferable, providing the cost of biopsy stays under 77\$

Applications:

Upper endoscopy with routine SBBs is a cost-effective approach with improved QALYs in patients with IDA when the prevalence of CD is 5% or greater. SBBs should be a routine screening tool for CD among patients with IDA, regardless of their celiac antibody status.

Terminology:

QALY: The most common outcome unit used in cost-effectiveness analysis is Quality-Adjusted Life Year (QALY), which incorporates both the quality of life and life expectancy. The quality of each health state is measured on a scale of 0 to 1 and is based on patient's preferences over the health states.

ICER: The incremental cost-effectiveness ratio is a statistic used in cost-effectiveness analysis to summarise the cost-effectiveness of a health care intervention, defined by the difference in cost between two possible interventions, divided by the difference in their effect

3. Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) DOI (<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.**)

For those references that have not been indexed by PubMed, a printed copy of the first page of the full reference should be submitted.

Response:

The references were changed according to the requirements.

Please note that some changes in the references were done in the revised manuscript (1 deleted and 5 added in the revised manuscript compared to the original manuscript)

4. Please provide the decomposable figure of Figures, whose parts are movable and can be edited. So please put the original picture as word or ppt or excel format so that I can edit them easily.

Response:

Attached in a powerpoint version (as a separate document)