ANSWERING REVIEWERS

August 8, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12034-review.doc).

Title: Impact of fecal occult blood on obscure gastrointestinal bleeding; observational study

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12034

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 00185965

Paper by Kobayashi et.al is technically well done paper without major concerns. Minor concerns are regarding:

1. **Retrospective design this type of trial can easily conduct as prospective.**

Thank you for the reviewer's comment. The authors also recognize that a prospective study is needed to draw a final conclusion with respect to the impact of FOBT on OGIB and is not difficult to be conducted.

We added the following sentences in page 14 in discussion.
"Second, the study was retrospective. A prospective study is needed to draw a final conclusion with respect to the impact of FOBT on OGIB"

2. **Some result has been shown as percentage and some of them as Odds ratio. I think that Odds ratios are more appropriate.**

The authors appreciate the reviewer's important suggestion. We added odds ratios in results as follows.
"The prevalence of SBDs was significantly higher in patients with a positive FOBT than in those with a negative FOBT (46 vs. 25%; odds ratio [OR] 2.5; 95% confidence interval [CI] 1.4-4.5; P = 0.002). In the disease-specific analysis, the prevalences of ulcers and active bleeding were higher in patients with a positive FOBT. The prevalence of ulcers in the small bowel was significantly higher in the positive FOBT group than the negative FOBT group (11 vs. 2%; OR 6.2; 95% CI 1.3–28.6; P = 0.009). Similarly, the prevalence of active bleeding was significantly higher in the positive FOBT group than the negative

FOBT group (15 vs. 4%; OR 4.3; 95% CI 1.4–13.5; P = 0.007)." (line 5-13 in page 10)
"Among patients with occult OGIB, the prevalence of SBDs was higher in the positive FOBT group than the negative FOBT group (45 vs. 18%; OR 3.9; 95% CI 1.6–9.5; P = 0.002)."(line 18-21 in page 10)
"In contrast, among patients with previous overt OGIB, there was no significant difference in the prevalence of SBDs between the positive and negative FOBT groups (47 vs. 33%; OR 1.8; 95% CI 0.8–4.0; P = 0.18)." (page 10-11)

3. Key words should be in alphabetical order.

Thank you for the reviewer's comment. The authors collated key words in alphabetical order.

4. Introduction Page 5 Line 7 :...balloon ASSISTED enteroscopy

We appreciate the reviewer's kind suggestion. The authors revised the sentence as the reviewer suggested.

5. Materials and methods Page 6 line third from the bottom the sentence is unclear: CE was performed 8 h after ingestion, and sensor array and recording devices were removed." CE has been removed after 8 hours.

Thank you for the reviewer's comment. We revised the following sentence.
"Sensor array and recording devices were removed 8 h after CE ingestion."

6. Page 7 line 8 from above threshold of 100ng/ml for or

Thank you for the reviewer's comment. We revised the following sentence.
"A positive test was accepted at a threshold of 100 ng/ml for the higher reading of the two tubes."

7. General concern Angioectasia should be replaced with Angiectasia without o.

We appreciate the reviewer's kind suggestion. We standardized to "angiectasia".

Reviewer 02537831

1. The time discrepancy between the FOBT and CE should be listed in Table 1.

Thank you for the reviewer's comment. We added the time discrepancy between the FOBT and CE in Table 1.

2. In the analysis of predictive factors of SBDs in patients with OGIB, Overt OGIB and a hemoglobin level ≤ 10.6 g/dL had P values < 0.3 in univariate analysis, why they can be used in multivariate analysis?

We appreciate the reviewer's important comment. We performed a multivariate analysis by using the

logistic regression model in order to explore independent risk factors. When we developed the final model, we investigated all possible combinations of candidate variables for which the p values were less than 0.3 in univariate analysis to avoid losing important variables. Because the number of patients included was small, it is possible that some true risk factors were not identified.

3. The great limitation of this retrospective study is that the time discrepancy between the FOBT and CE is too long. But this is not referred in the part of discussion.

Thank you for the reviewer's comment. Since the study patients didn't have ongoing bleeding and medical urgency for them was low, the time discrepancy between the FOBT and CE was likely to be created.

We added the following sentences in page 14 in discussion.
"Third, the time discrepancy between the FOBT and CE was long (8.5 days). Since the study patients didn't have ongoing bleeding and medical urgency for them was low, the time discrepancy between the FOBT and CE was likely to be created."

Reviewed by 00050420

The author reported 'The impact of fecal occult blood on obscure gastrointestinal bleeding; observational study'. Sometimes it is very difficult to find the cause of bleeding in obscure gastrointestinal bleeding. Therefore these findings are important to those with closely related research interests. But there are some problems in this manuscript.
Review could not understand the table 4. What does the '(n=55) and (n=51)' means? Sometime the readers could not fully understand due to structure of tables.

Thank you for the reviewer's comment. We revised Table 4.

	Positive FOBT patients with occult OGIB (n = 55)	Negative FOBT patients with occult OGIB (n = 51)	P value
Ulcer	7% (n = 4)	0% (n = 0)	0.049
Erosion	20% (n =11)	14% (n = 7)	0.39
Angiectasia	16% (n = 9)	8% (n = 4)	0.18
Tumor	7% (n = 4)	0% (n = 0)	0.049
Active bleeding	13% (n = 7)	0% (n = 0)	0.008

If the numbers of patients was filled up, it is easier to grasp the point of tables (Table 3 & 4).

Thank you for the reviewer's comment. We added the numbers of patients in Table 3 and 4.

Table 3. The prevalence of SBDs detected by CE in patients with positive and negative FOBTs

	Positive FOBT (n = 100)	Negative FOBT (n = 102)	P value
Any small bowel lesions (n = 72)	46% (n = 46)	25% (n = 25)	0.002
Ulcer (n = 13)	11% (n = 11)	2% (n = 2)	0.009
Erosion (n = 37)	21% (n = 46)	16% (n = 16)	0.33
Angiectasia (n = 22)	14% (n = 14)	8% (n = 8)	0.16
Tumor (n = 8)	5% (n = 5)	3% (n = 3)	0.45
Active bleeding (n = 19)	15% (n = 15)	4% (n = 4)	0.007

Table 4. The prevalence of each SBD detected by CE in patients with occult OGIB

	Positive FOBT patients with occult OGIB (n = 55)	Negative FOBT patients with occult OGIB (n = 51)	P value
Ulcer	7% (n = 4)	0% (n = 0)	0.049
Erosion	20% (n =11)	14% (n = 7)	0.39
Angiectasia	16% (n = 9)	8% (n = 4)	0.18
Tumor	7% (n = 4)	0% (n = 0)	0.049
Active bleeding	13% (n = 7)	0% (n = 0)	0.008

In "result of Abstract", "only positive FOBT was a predictive factors of SBDs in patients…" ? "only positive FOBT was a predictive factor of SBDs in patients…" The quality of language in the manuscript is relatively suitable for publication unless edited. Reviewer is unable to decide on acceptance or rejection until the authors have responded to the minor compulsory revisions.

We appreciate the reviewer's important comment. We revised the following sentence in result of abstract. Our English was checked again by a professional English language editing service (http://www.textcheck.com/certificate/KnxusG).
"In multivariate analysis, positive FOBT was only a predictive factors of SBDs in patients with OGIB (odds ratio 2.5, 95% CI 1.4-4.6, P = 0.003)."

Reviewed by 00052899

In this study, the authors analyzed 202 patients with OGIB who performed both CE and FOBT to identify the association between small bowel diseases and positive FOBT. They concluded that positive FOBT may be useful for predicting SBDs in patients with occult OGIB. Positive FOBT indicates higher likelihood of ulcers or tumors in patients with occult OGIB. Undergoing CE within a day after FOBT achieved a higher diagnostic yield for patients with occult OGIB. Overall, this manuscript is well prepared with good writing and large novelty. However, there are also several problems.

Comments: 1. In the abstract section, the full name of the abbreviation "CE" should be given when appeared at the first time.

We appreciate the reviewer's kind comment. We added the full name of the abbreviation "CE" in methods of abstract.
"202 patients with OGIB who performed both capsule endoscopy (CE) and FOBT were enrolled…"

2. The authors declared that three experienced endoscopists independently reviewed CE videos. The degree of disagreement between the endoscopists should be added.

Thank you for the reviewer's comment. We added the following sentence in page 9 in results.
"The mean of the three kappa values (reviewer A vs. B, A vs. C, B vs. C) was 0.9."

3. The authors concluded that positive FOBT may be useful for predicting SBDs in patients with occult OGIB. Therefore, the diagnostic value and accuracy might be presented.

We appreciate the reviewer's kind comment. We added the following sentence in page 10 in results.
"In other words, the mean sensitivity and specificity of FOBT for SBDs in the occult OGIB group were 74% and 42%, respectively, while the accuracy of FOBT for SBDs in the occult OGIB group was 63%."

4. In the result section of the manuscript, the authors declared that CE revealed significant lesions of the small bowel in 72 patients (36%), which is contradict with the following statement" identified as ulcers in 13 (6%), erosions in 37 (18%), angioectasias in 22 (11%), tumors in 8 (4%) and active bleeding in 19 (9%) patients.

We appreciate the reviewer's comment. Since some patients had more than 2 different kinds of small bowel diseases, total number of each disease was not equal to 72. We added the following sentence in page 9 in results.
"CE revealed significant lesions of the small bowel in 72 patients (36%), identified as ulcers in 13 (6%), erosions in 37 (18%), angiectasias in 22 (11%), tumors in 8 (4%) and active bleeding in 19 (9%) patients. There were some patients that had several types of SBD simultaneously."

5. After univariate analysis, the authors only selected 3 variables with $p<0.3$ for multivariate analysis. Why did you select 0.3 as a threshold?

We appreciate the reviewer's comment. We performed a multivariate analysis by using the logistic regression model in order to explore independent risk factors. When we developed the final model, we investigated all possible combinations of candidate variables for which the p values were less than 0.3 in univariate analysis to avoid losing important variables. Because the number of patients included was small, it is possible that some true risk factors were not identified.

6. There are several typographical errors.

We checked the manuscript again carefully. Our English was also checked again by a professional English language editing service. Thank you very much.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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