

Response letter

Dear reviewers,

Thank you for your valuable comments and my answers are described below;

Answer to Reviewer 1: 03474689

1: Why the percentage of elderly patients are higher in late group than in early group.

Answer: Discussion p.12 line 13-18: In Japan, aging tendency in general population is remarkable. And use of oral ATDs and NSAIDs is increasing also with the aged of population (p.7 line7-9). Therefore, the incidence of LGIB is higher in elderly patient (p.12 line 15). As thinking about time course, it is natural LGIB increases in late group.

2: The incidence of colonic DH is as low as 5.9% in early group than late group 23.0% , because of higher incidence of more elderly patients in the late group, was there any relation with the severity of the disease, and location of the Diverticulae.

Answer: About the severity of the DH, and location of the diverticulae, it is not the aim in this study but excluded because we have to examine clinical course such as repetition of the disease. In another article we will analyze them.

3: The number of patients with DH started to increase rapidly in 2003, and peaked in 2008, why it is so.

Answer: Discussion: p.13 line 5-21. Low dose aspirin 100mg sales have decreased since 2008, is the fact that it is relevant whether or not isn't clear.

4: what is the reason for gender difference, DH higher in male than female.

Answer: Discussion p.15 line 10-13: These findings suggest ethnic differences, but the exact factors involved are not yet well understood. DH in Japan is more common in men, because it may be one of the reasons the men listed as the risk of arteriosclerosis in the Japan Atherosclerosis Society Guidelines.

Answer to Reviewer 2

Reviewer's code: 03026970

Major comments: 1. The causes of LGIB and the risk factors for DH had already been reported, however this study shows changes in the causes of LGIB over time between patient in early group and late group in Japan.

2. The title "Increase in colonic diverticular hemorrhage in comparison with non-diverticular hemorrhage" does not cover the content that some changes took place in the causes of LGIB, which is one of the highlights of the research.

Answer: Thank you for very good comment on the title of the manuscript. I would like to change the title to "Increase in colonic diverticular hemorrhage and confounding factors" according to your suggestion.

3. Several former large-scale studies have demonstrated that obesity is a consistent risk factor for diverticular bleeding. This factor was not included in the article.

Answer: Thank you for useful comment. This one analysis was added concerning the Body mass index. And there is a significant meaning as is shown in Result section (p.12 line 7) and Table 1.

4. Discuss: The incidence of colonic DH is increasing in aging people, as well as the prevalence of diverticulosis. Is there an association?

Answer: Discussion p.12 line 13-18: In Japan, aging is remarkable. And use of oral ATDs and NSAIDs and arteriosclerosis disease is increasing with the aging of population (p.7 line7-9). As much as it is aged, it is thought that the prevalence of diverticulosis increases (p13 line 12-17). For these two reasons, it is natural to think that the incidence of DH increases in aged population. However, we do not have enough data on the prevalence of diverticulosis.

Minor comments:

1. Table 2: The cause "others" includes 8 elements, and it occupies a large proportion (13.9%). How about list them out, as some may take bigger proportion than those causes list above?

Answer: Rectal ulcers, stercoral ulcers, rectal mucosal prolapse, pneumatosis cystoides intestinalis, enteric endometriosis, submucosal tumors, radiation enteritis, and nonspecific inflammation did not show any significantly differences between in EG and in LG. And frequency of nonspecific inflammation was 91 patients (5.1%) and rectal ulcer 54 patients (3.0%) in 1995-2013, but other diseases were as less as 1%.

2. Patients were divided into two groups. The cut-off point was set at the year 2006 without explaining. Is it a random choice?

Answer: Materials and methods: p.10 line 11-12: The 1803 patients who underwent colonoscopy for overt LGIB were divided into two groups by time period, with each consisting of about half of the patients as is added p.15 line 21-26 reason. If we divide time period at 2000, number of patients is not balanced enough for analysis in each period. Thus, the 1803 patients were divided into two groups by time period, with each consisting of about half of the patients.

3. Table 3: According to the data above, there were some patients use both ATDs and NSAIDs. Readers may want to know how this part of patients been categorized, as it did not appear in the table 3 individually. 4. It would be better if the author provided the follow-up data.

Answer: We did not analyze the patients who is taking combination of NSAIDs and ATDs in the present study because they comprised as little as 1.4% as is shown in Table1.

Answer to Reviewer 4

Reviewer's code: 03252901

I read the manuscript with interest; however, if certain data can be added and clarified it would be more valuable to our readers. Can the authors inform us as to where the diverticular bleed was located? In the right, left or other parts of the Colon. Most recent data suggest that diverticular bleed more commonly originates from the left colon.

Answer: About location of the DH, we did not examine it precisely in this study because it will be analyzed in our successive article in combination with severity of the disease.

What percent of diverticular bleeds stopped spontaneously and in others what interventions were taken to stop the diverticular bleed (e.g. endoscopic, surgical)?

Answer: About rebleeding during hospitalization, vascular embolization, surgical treatment, endoscopic treatment and death in DH, it is non-examination in this study. However, it has analyzed them, and is expected to mention in another article.

Why was a cut off date of 2006 chosen for the early group? The authors state that ATD use increased after 2001 and they attribute the increase of LGIB to the use of these drugs. Can they clarify this?

Answer: Materials and methods: p.10 line 11-12: The 1803 patients who underwent colonoscopy for overt LGIB were divided into two groups by time period, with each consisting of about half of the patients as is added p.15 line 21-26 reason. If we divide time period at 2000, number of patients is not balanced enough for analysis in each period. Thus, the 1803 patients were divided into two groups by time period, with each consisting of about half of the patients.

They included past smokers as smokers. Was there a cut off time? Someone who has not smoked for over 10 years may not have the same risk as a current smoker.

Answer: We did not provide more information about smoking, because our study is retrospective study.

Answer to Reviewer 4

Reviewer's code: 03259763

Abstract: p.4 line 17 and 22: The authors include? ... and arteriosclerotic diseases...“ and ?... arteriosclerotic disease...“ as being more common in patients with colonic DC in the Results and Conclusions of the Abstract. But the extent of arteriosclerotic disease itself was not assessed in this study, rather risk factors for the development of arteriosclerotic disease, such as diabetes and hypertension. It would be helpful if the authors explain this in the manuscript.

Answer: We did not examine the arteriosclerosis itself. Added p.16 line 5-6 reason. “We had not evaluated by carotid artery ultrasonography for arteriosclerosis in this study.”

Introduction: p. 10, line 11: ... is showing an increase in diverticulosis due to an insufficient dietary intake of fiber..“ the prevalence of (asymptomatic) diverticulosis is increasing. A reason that is acknowledged due to the available data in the literature is the increasing age in our populations. Data on the role of fiber in the pathogenesis of diverticulosis is conflicting though, and thoughts on this should be addressed very carefully. I therefore suggest to rewrite this paragraph, as fiber currently should not be considered as a secured risk factor for the development of asymptomatic diverticulosis.

Answer: According to your suggestion the sentence of "due to insufficient dietary intake of fiber" deleted it.

Discussion: This study was conducted in a Japanese cohort. Diverticula in Asians are more common in the right colon, contrary to the western world, where they are more common in the left colon. It seems reasonable, to state the fact, that this data therefore can not necessarily be conferred to western countries. The authors demonstrate the spectrum and risk factors for LGIB and colonic DH between 1995-2013 at Fukuoka University Hospital, it could be of interest to compare and expand this data this with rural regions and other ethnicities, possibly the authors want to include this in the discussion. The incidence of colonic DH is increasing in our aging populations, as is the prevalence of diverticulosis. Is there an estimate how these two trends are connected?

Answer: Discussion p.12 line 13-18: In Japan, aging is remarkable. And use of oral ATDs and NSAIDs and arteriosclerosis disease is increasing with the aging of population (p.7 line7-9). As much as it is aged, it is natural to think that the prevalence of diverticulosis increases. For these two reasons, it is thought that the incidence of DH increases.