Dear Editor,

We are very grateful to the reviewers for their interesting comments on our case series. We have answered any questions to the best of our abilities and taken into account their suggestions while making revisions to our manuscript. Below is a detailed response to each of the reviewer's comments:

Reviewer 1:

The authors present an interesting case series of four patients with jejunal Dieulafoy lesions(DL), who were diagnosed with chronic liver disease. But, the diagnosis of liver cirrhosis is not definite in case 1, 2, and 3, whose diagnosis was made only by cross sectional imaging or medical history. Moreover, patient 1 and 2 had multiple comorbidities including congestive cardiac failure which is well known to induce intestinal bleeding, such as angiodysplasia. Thus, the authors should present more firm and high-level evidences of liver cirrhosis, Otherwise, the cases of patient 1 and 2, at least, should be omitted.

Although the gold standard diagnostic tool for cirrhosis is liver biopsy, this is not an absolute requirement in our institution or in International guidelines as long as imaging criteria, laboratory indices and clinical examination support the diagnosis. Although we have not presented in detail these findings they were all supportive of a clinical diagnosis of cirrhosis in all 4 patients following the radiology report of cirrhosis. It is possible that the clinical features may have been overlooked initially as none of the patients had a history of any of the more common causes of chronic liver disease, any gross abnormalities in their liver function tests, or any features of acutely decompensated cirrhosis. In addition, because of the severe form of recurrent bleeding, the clinical priority and focus were to diagnose a cause of their bleeding. In addition, although we recognise that cardiac failure can be associated with other causes of obscure bleeding; these patients were diagnosed with DLs and no other cause such as angiodysplasias were found on extensive testing including capsule endoscopy.

Additionally, if they speculate an association between the shift in angiogenic factors in their patients and DLs, they need to present abnormal expression of some angiogenic factors in their patients.

We agree with this point which is the rationale for this case series, and have already began to prospectively collect serum from affected patients for future assessment of angiogenic factors, however at present this association is purely speculative based on our experience with abnormalities in angiogenic factors in patients with small intestinal angiodysplasias, which share some clinical features with small bowel DLs.

Minor 1) The authors should make a clear statement whether their patients had varices or not, although they stated they ruled out varices as a cause of bleeding.

None of the patients had oesophageal varices evident at endoscopy, however 2 of the 4 patients had evidence of intraabdominal varices on cross sectional imaging.

2) Do the authors think the possibility that their patient had isolated spider naevi, rather than DLs in case of patient 2, although spider naevi seems to be different from DLs in endoscopic features ?

Did they press the red spot directly with biopsy forceps to make sure it turned to be blanched ? Please explain your idea or give suggestion more about the relationship and /or difference between DLs and spider naevi.

This case series was written retrospectively after noticing a trend of jejunal DLs in patients with cirrhosis. The idea of a similarity between these lesions and spider naevi came from reviewing other case reports in the literature and so the lesions were not examined directly at endoscopy for specific features of spider naevi.

Reviewer 2:

The manuscript presents a case series of patients with small bowel Dieulafoy lesions producing obscure overt GI bleeding, who were also all anticoagulated, and also were diagnosed with liver cirrhosis of uncertain etiology. The manuscript is fairly well written, and addresses the topic in a proper way. I would consider it suited for publication in WJGE, after correction of minor issues. Below I have provided some comments on the authors' work.

ABSTRACT Accounting for 2% of what? Please specify.

This refers to DLs accounting for 2% of all causes of obscure gastrointestinal bleeding. We agree that this is difficult to follow and have amended the sentence in the revised manuscript.

Also modify in the introduction. Please modify "or a shift in angiogenic factors as a consequence of portal hypertension" to "or a shift in angiogenic factors as a consequence of portal hypertension or liver cirrhosis".

We agree with this suggestion and have amended the sentence in the revised manuscript.

INTRODUCTION The authors do not specify if the case series of patients presented represent consecutive cases, or are selected retrospectively from the center's database. Please specify that. Over what period of time were these cases encountered?

These for patients presented consecutively to our institution over approximately a 2 year period. As a tertiary referral centre for obscure gastrointestinal bleeding we keep a database of interesting cases which we encounter. However the case series was written retrospectively when we noticed a trend between small intestinal DLs and chronic liver disease.

Please review the spelling of "under recognised" and "characterised". Please change "attachment to tiny mucosal defect" to "attachment to a tiny mucosal defect". Please change "similarity of the lesions to spider naevi" to "similarity of these lesions to spider naevi". CASE 3 Please change "represent" to "re-present". Please change ?was found in her fundus" to ?was found in her gastric fundus". CASE 4 Please describe what D1 stands for. Please change "were ligated and clipped" to "were ligated and/or clipped".

Some spelling suggestions have been amended in the revised manuscript, others are due to differences in the use of English dialect and the journal's editors are free to change to fit with their preferred grammatical dialect. D1 stands for the first part of the duodenum and this has been amended.

Reviewer 3:

The paper by Hollerann et al is a case series of 4 patients with intermittent overt gastrointestinal bleeding (GIB) with previously undiagnosed chronic liver disease who turn out to have proximal jejunal Dieulofoy lesions (DL). The paper is a useful addition to the literature concerning this difficult to treat lesion. A few comments are required:-

1. **The incidence of DL needs documenting in the introduction as readers will require this information to determine the risk in their own population. Is there a global geographic distribution in the incidence of this lesion?**

As inferred by the 2nd reviewer it may have been unclear from the introduction that DLs are the cause of bleeding in 2% of all patients with gastrointestinal bleeding. The wording of this sentence has been amended in the revised manuscript. In relation to a global geographic distribution of DLs, this is an interesting question as there have certainly been reports of geographical differences in other causes of obscure bleeding. However none of the literature that I have reviewed has reported on any geographical differences to date. This may be due to the rarity of the condition and the fact that most of the reports have been from single centres only. Any of the meta-analyses on the topic of DLs seem to focus on treatment outcomes rather than epidemiology.

2. **The availability of wireless capsule endoscopy (WCE) is widespread in most developed countries at the current time and I suspect that a few of these cases presented are historic when use of WCE was confined to regional/ tertiary centres.**

We acknowledge that WCE may be more widely available in most developed countries (although not currently in Ireland), however although this would likely have identified active bleeding at an earlier stage, diagnostic features of a DL were only present at WCE in one case. Due to the recurrent nature of bleeding from DLs, a number of diagnostic tools had to be employed in all cases for a definitive diagnosis.

3. **It would be helpful if the authors could present a suggested algorithm both for the diagnosis of DL and management of these lesions, including the need for liver imaging etc. This inclusion would make the paper much more appealing as DL are very troublesome and frequently treatment resistant and the development of a pathway for diagnosis and management could be used as a tool for improved patient outcomes. For example, When should interventional radiology be utilised? Rebleed after apparent successful endoscopic therapy? I would argue that as soon as the diagnosis of DL has been made then either radiological or surgical intervention is required as endoscopic therapy is rarely if ever successful alone. I would suggest publication of this case series subject to the suggestions above.**

We agree that DLs, particularly in the small intestine present a difficult challenge both in terms of diagnosis and treatment. As they are so infrequently encountered by most gastroenterologists and are known to have a poor outcome, it would be very valuable to have a standardised treatment guideline available. In terms of diagnosis, we feel that the current algorithms recommended by both the British and American societies of gastroenterology for the approach to obscure gastrointestinal bleeding are appropriate for the diagnosis of DLs. These guidelines recommend capsule endoscopy as the first second line investigation in stable patients with angiography used in unstable patients or

those in whom capsule endoscopy is negative for a bleeding source. Due to the intermittent nature of bleeding from DLs, as in all of our cases angiography is often unable to detect a bleeding source and interventional radiologists are understandably reluctant to perform embolization without evidence of a definite bleeding site. We are unable to provide a treatment algorithm from our limited anecdotal experience; however we agree that it would be of huge clinical advantage if available. The objective of this case series was to alert readers of the possibility of small bowel DLs in patients with obscure bleeding and cirrhosis with the hope that persistent investigation despite initially negative results may lead to an earlier diagnosis for patients. In addition our planned future research in the field of angiogenesis may yield targeted medical therapies for this condition.