To the Editor,

We read with interest the systematic review and meta-analysis by Zhu et al reporting on the efficacy and safety of semaglutide in patients with nonalcoholic fatty liver disease (NAFLD)[1]. Analyzing three randomized control trials involving 458 patients, they found that semaglutide was effective at improving histologic and radiologic markers of nonalcoholic steatohepatitis (NASH) activity but not histologic fibrosis. The risk of serious adverse events was similar compared to placebo, and importantly, no cases of hepatic decompensation occurred.

We herein present a case of liver decompensation in a patient with NASH cirrhosis after the use of semaglutide. A 68-year-old female with compensated NASH cirrhosis (Model for Endstage Liver Disease-Na (MELD-Na) score 11) was prescribed semaglutide 2.4mg once weekly to manage her diabetes and obesity. Her other medications at the time included salbutamol for asthma. The semaglutide led to 10kg weight loss (11% body weight) within 8 weeks of treatment before it was stopped. After approximately 8% body weight loss she developed new onset hepatic encephalopathy (HE) requiring the use of lactulose and rifaximin. She also developed ascites requiring diuretic therapy (spironolactone 100mg and frusemide 40mg; further increases limited by postural hypotension) and two large-volume paracenteses. Patient adherence to prescribed medications was confirmed by her family during this time. Due to her rapid weight loss, her semaglutide was stopped. Despite stabilization of her weight, she continued to decompensate and her MELD-Na continued to rise (Figure 1). On referral to our service her MELD-Na was 22 (bilirubin 40µmol/L, creatinine 44, INR 1.6, Na 128). Investigations for alternate causes of decompensation including infection, alcohol consumption, hepatocellular carcinoma and portal vein thrombosis were negative. We concluded her liver decompensation was most likely secondary to semaglutide-induced rapid weight loss and malnutrition. She was commenced on high energy and high protein supplementation consisting of 60g Sustagen twice-daily and micronutrient replacement with thiamine. She also underwent assessment for liver transplantation. Over the following 3 months, she was reviewed each month by a transplant hepatologist and dietitian to assess her clinical progress, nutritional intake and adherence to treatment. Over this period, she managed to regain 5kg (6%) of her ideal body weight, and this was associated with an improvement in her ascites and HE and a reduction in MELD-Na to 19 (Figure 1). By 6 months her weight had returned to baseline, she no longer required abdominal paracentesis and her MELD-Na was 13. She was de-listed from the transplant waitlist and remains compensated at last follow-up.

Our case highlights the potential risk of rapid weight loss with semaglutide in the vulnerable NASH cirrhosis population. In our case, the rapidity of weight loss was significantly greater compared to the studies included in Zhu et al's meta-analysis (10kg after 8 weeks versus 6.5kg after 48-72 weeks). Loomba et al's study, included within the meta-analysis, involved patients with NASH cirrhosis and did not report any cases of hepatic decompensation[2]. Of note, our patients pre-semaglutide MELD-Na score was higher (11 for our patient vs. 7.6 in the study group), potentially conferring a greater predisposition to decompensation. It is interesting to note that despite stabilization of her weight after stopping semaglutide, our patient continued to decompensate until she was reviewed at our tertiary centre, as illustrated in Figure 1. Rapid weight loss is an established precipitant of hepatic

decompensation in the post bariatric surgery population[3], with pathophysiological mechanisms thought to involve endogenous free-fatty acid oxidative damage, mitochondrial dysfunction and gut dysbiosis leading to hepatic inflammation and fibrosis[4-6]. However, it should be noted that decompensation has generally occurred later (up to 5 years post-surgery) and degree of excess weight loss (i.e. the amount of weight above the ideal body weight) was up to 110%[7]. Furthermore, the use of glucagon-like peptide 1 agonists such a semaglutide causes delayed gastric emptying, which may impact the absorption of concomitantly administered oral medications and therefore their efficacy. This may have contributed to our patients' diuretic-refractory ascites. In patients with liver cirrhosis, it is therefore important to consider inadequate absorption of medical therapies as a contributor to failure to respond to standard treatment.

Clinicians should consider the use of semaglutide cautiously in patients with underlying NASH cirrhosis and should strictly adhere to the prescribing information and dose escalation protocols as recommended and consider using a lower dose of the drug. Failure to follow strict dose escalation protocol may lead to significant gastrointestinal side effects including nausea and vomiting, which may precipitate weight loss and decompensation. Furthermore, clinicians must exercise a low threshold for cessation should weight loss occur rapidly (≥1% of body weight/week) or signs of liver decompensation develop.

Responses to reviewers comment are in *italics*

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: Dear colleagues! I read with interest your Letter to the Editor, that refers recently published in WJG systematic review by K. Zhu et al on the efficacy and safety of semaglutide in non-alcoholic fatty liver disease. The letter may bring new to the field and could be interesting to the readers. The manuscript requires appropriate revision according to the Journal's recommendations on research methods and reporting. I have a few comments.

1. Please, check the initial MELD-Na score - my calculation lead to the number of points 23, in contrast to provided in the Letter (22). *Thank you for your insightful comments and suggestions for our paper. We have double checked the MELD-Na score and can confirm it was 22. We believe the peer reviewer may have accidentally swapped the values for creatinine and bilirubin around to get the 23 result.*
2. There is a need for better description of the treatment before decompensation occured (whether all recommendation were followed by the patient) and after it. *Added extra information as suggested with thanks.*
3. Please, list the concomitant medications. *Salbutamol listed. This was her only other medication prior to semaglutide use.*

4. What is an "alcohol misuse"? Is it an "alcohol abuse"? Please, add the certain information on the use of the alcohol by the patient, as alcohol intake may lead to Moderate Drug Interaction with semaglutide. *Thank you for your suggestion. The patient did not consume alcohol and we have updated the text to reflect this.*
5. Please, explain the misuse of semaglutide - per international prescribing information initial dose should be 0.25 milligrams (mg) injected under the skin (SC) once a week for 4 weeks and 0.5 mg SC once a week on weeks 5 through 8. *The patient was incorrectly prescribed the 2.4mg dose from the start of her treatment. This occurred before she was referred to our transplant service. We have added text at the end of the discussions emphasising that clinicians need to strictly adhere to dose escalation protocols.*
6. Please, describe the weight change before the decompensation event. *We have specified that she began to decompensate after approximately 8% weight loss.*
7. As GLP-1 agonists may delay gastric emptying, which may impact the absorption of concomitantly administered oral medications, this should be mentioned in the discussion as standard treatment prescribed for liver cirrhosis could be of lower efficacy in this case. *Thank you for this important insight. We have modified our discussion to include the concerns about delayed gastric emptying from GLP-1 agonists contributing to failure to respond to standard treatment.*
8. The last phrase is not enough clear. Namely, what is a "rapid weight loss" (in kg/month)? *Please see edit, we have approximated it at 1% per week, but as there is obviously a lack of evidence and other cases of this occurring in the literature, this definition of 'rapid' is an estimate.*
9. Should the maximal dose of the medication be lower in case of liver cirrhosis? *It is hard to make a clear recommendation given the paucity of cases, but we have suggested in our discussion that clinicians should consider using a lower dose.*
   Please, add that strict following of the prescribing information and the initial dose escalation schedule are the must, especially in such a vulnerable group of patients as subjects with liver cirrhosis.
   Thank you, that is an important suggestion and we have added it to the manuscript.

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)
Specific Comments to Authors: The manuscript of Peverelle et al. is clear and organized and the data presented are relevant for clinical practice. The language and grammar are accurate and appropriate, with a title that reflects the main subject of the manuscript. The abstract summarizes the work described in the manuscript, and the keywords are appropriate. The findings are new and relevant for clinical practice. References are appropriate and the figure is of good quality with correct and explicative labeling. In the discussion, I would suggest adding a comment on the fact that despite the patient's weight substantially not changing after the interruption of semaglutide, liver function continued to deteriorate in the successive 6

months. Moreover, in the parallelism with bariatric surgery regarding liver decompensation, it should be underlined that in these patients decompensation occurred later and their weight loss reached 110%.
Thank you for your insightful comments and suggestions. We have amended the manuscript to reflect the differences noted in the bariatric surgery population.

References

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3. Eilenberg M, Langer FB, Beer A et al. Significant Liver-Related Morbidity After Bariatric Surgery and Its Reversal-a Case Series. Obes Surg. 2018 Mar;28(3):812-819.
4. Verna EC, Berk PD. Role of fatty acids in the pathogenesis of obesity and fatty liver: impact of bariatric surgery. Semin Liver Dis 2014;34:98-107.
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6. Drenick EJ, Fisler J, Johnson D et al. Hepatic steatosis after intestinal bypass-prevention and reversal by metronidazole, irrespective of protein-calorie malnutrition. Gastroenterology 1982;82:535-548.
7. Moolenaar LR, de Waard NE, Heger M. Liver injury and acute liver failure after bariatric surgery an overview of potential injury mechanisms. Journal of Clinical Gastroenterology,56(4), 311-323.

Illustration
Figure 1.

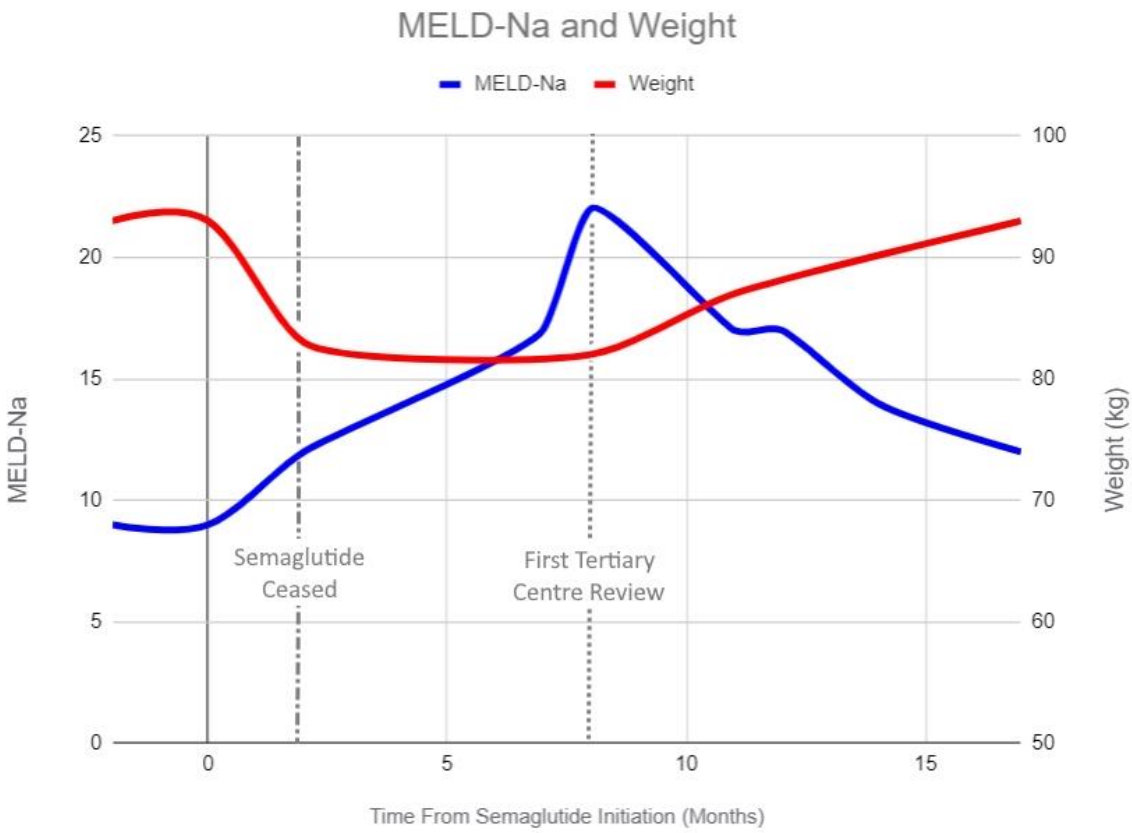

Figure 1. Patient's weight change with semaglutide use and MELD-Na score over time.