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To
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World Journal of Gastroenterology

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World Journal of Gastroenterology

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Reviewer 1:
The manuscript by Werner et al. presents a large retrospective cohort of HCV patients treated with DAAs. Thanks for inviting me to review this paper, I enjoyed reading it. However, there are some minor points that should be clarified.
1) The values for creatinin in (0.6-0.8mg/dl) bilirubin (0.5-1mg/dl) and INR (1-1) were surprisingly low (table 1). In Table 2 Patient 3 has a MELD score of 24.... this is high..... surprisingly high for a patient with an initial INR, bilirubin and creatinin value below 1..... In Table 2 you can see that 25 patients had a MELD score above 10..... this is not possible if creatinin, bilirubin and INR are below 1..... Please check table 1! Surely the values present a typo. ...

Answer: The parameters in Table 1 are given as median, 25th, and 75th quartiles. We decided to use median and quartiles, because these parameters are not of Gaussian distribution. If we had used mean, SD, minimum, and maximum i. e. we would have had for creatinin: Mean 0.8 +/- 0.39 (0.4-5.9) mg/dl, and for bilirubin: 1.4 +/- 5.2 (0.2-80) mg/dl.

2) The relevance of the mutations in table 3 is really interesting.... this should be discussed in more detail.
We added a paragraph in the discussion:

"All patients in our cohort, who suffered from virological relapse showed RAVs at time-point of relapse." … "While for some RAVs (like NS5A L31M, Y93H) clear associations between existence of RAV and virological failure exist, for others (like NS5A A30S) this association is not well established [35]. This may lead to confusion in case of a future re-treatment, if minor RAVs have been detected, and even more in case of a baseline test in treatment naïve patients. However, as the population of patients with relapse after DAA treatment grows, the need for controlled trials with new DAA-combinations (e. g. pangenotypic protease inhibitor) for those patients to address this problem is obvious. Therefore, after virological relapse we recommend resistance testing for individualized adjustment of future DAA therapies."

3) Do the authors suggest to test each patient before initiating of DAA-treatment for mutations and susceptibility of the treatment?

Except for testing of Q80K in patients to be treated with simeprevir, we would not recommend baseline resistance testing, according to guidelines.

Reviewer 2
1) Authors should necessarily point out the severity of cirrhotic patients reffering to a modern classification of Child -Pugh that is evidenced in both articles, i.e., What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? BMC Gastroenterol. 2009 Nov 24;9:89. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol. 2009 Mar 17;9:21
Answer:

There are diverse scoring systems to assess severity of liver disease, like CTP score, MELD score, measurement of hepatic venous pressure gradient, assessment of spontaneous spleno-renal shunt, or measurement of Ammonia-blood levels.
However, we did not analyze our cohort for spontaneous spleno-renal shunt, and are not able to do so ex post due to lack of data. The same with the CTP score, which we could not calculate due to lack of data, especially concerning hepatic encephalopathy.

We tried to stage liver cirrhosis by assessing the MELD score, and tried to indirectly identify signs of portal hypertension by measurement of platelet count.
In response to your query, we added a paragraph:

"Diagnosis of liver cirrhosis was based upon liver histology, Fibroscan (>12.5 kPa), or clinical diagnosis (e.g. esophageal varices, ascites, distinct ultrasound signs of portal hypertension or liver cirrhosis). For assessment of severity of liver disease, we calculated the MELD score. In

this retrospective analysis, Child Turcotte Pugh score or other assessment scores for severity of liver disease could not be calculated due to lack of data (1, 2). For retrospective identification of patients with possible portal hypertension, a threshold of 100 platelets/nl was assumed."

1. Tarantino G, Citro V, Esposito P, Giaquinto S, de Leone A, Milan G, et al. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC gastroenterology. 2009;9:21. Epub 2009/03/19.
2. Tarantino G, Citro V, Conca P, Riccio A, Tarantino M, Capone D, et al. What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? BMC gastroenterology. 2009;9:89. Epub 2009/11/26.