Peer Review File

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Reviewer A

Comment 1: This manuscript is well written and informative. Please cite references as shown below.

1. Sumida Y, Yoneda M, Yoneda M, Okanoue T, Nakajima A; Japan Study Group of NAFLD (JSG-NAFLD). Current and new pharmacotherapy options for non-alcoholic steatohepatitis. Expert Opinion On Pharmacotherapy, in press.
2. Sumida Y, Yoneda M, Tokushige K, Kawanaka M, Fujii H, Yoneda M, Imajo K, Takahashi H, Eguchi Y, Ono M, Nozaki Y, Hyogo H, Koseki M, Yoshida Y, Kawaguchi T, Kamada Y, Okanoue T, Nakajima A, Atsushi Nakajima; Japan Study Group of NAFLD (JSG-NAFLD). Antidiabetic therapy in the treatment of nonalcoholic steatohepatitis. Inter J Mol Sci 2020;21 (6),1907.
3. Sumida Y, Okanoue T, Nakajima A; Japan Study Group of NAFLD (JSG-NAFLD). Phase 3 drug pipelines in the treatment of non-alcoholic steatohepatitis. Hepatol Res. 2019 Nov;49(11):1256-1262.
4. Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol. 2018 Mar;53(3):362-376.

Response 1: The reviewer is thanked for the rating, comments, and the valuable hints. The new references mentioned above were considered and cited accordingly in the revised manuscript.

The following sentences were added in the section 4:
“Furthermore, the combination of compounds that adress various targets of the metabolic pathways involved in NASH progression, e.g. GLP-RA/glucagon receptor agonist and GLP-RA/gastrointestinal peptide agonist, are promising future options (53, 53a).”

The following sentences were added in the section “Which pharmacological therapies are permitted?”:
“An overview of NAFLD agents currently under development and their pharmacologic targets is provided by Sumida et al. (59a). There are 5 candidates who have been successful in studies, but which will be launched in 2021 at the earliest (obeticholic acid, elafibranor, selonsertib, cenicriviroc, and resmetirom) (59b). “

Reviewer B

Comment 1: This is an interesting and well written paper. However, several reviews

have been written on this general topic and it is not clear what it is added in the literature by this review.
Response 1: Thank you for the excellent remark. This point was addressed more specifically in the revised version and the following passus has been included into the abstract:
“This review aims to identify risk factors, management strategies, and open questions concerning NAFLD patients.”

Comment 2: In addition several interesting topics are missing such as NALFD in lean.
Response 2: I agree with the reviewer and revised the manuscript accordingly. The following passus and references were included into section 2 of the review:
“Lean NAFLD is drawing considerable attention. Leung et al. prospectively followed up 72 lean (BMI <25 kg/m2) and 235 overweight (BMI ≥25 kg/m2) patients with biopsy-proven NAFLD. Lean patients had a lower grade of steatosis and lower stage of fibrosis than overweight patients. In addition, the event-free survival was better in lean patients (44a,44b).
44a.Tobari M, Hashimoto E, Taniai M, Ikarashi Y, Kodama K, Kogiso T, et al. Characteristics of non-alcoholic steatohepatitis among lean patients in Japan: Not uncommon and not always benign. J Gastroenterol Hepatol. 2019; 34: 1404-1410.
44b.Leung JC, Loong TC, Wei JL, Wong GL, Chan awAW, Choi PC, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology. 2017; 65: 54-64.

Comment 3: SGLT2 studies on NAFLD patients,
Response 3: A short paragraph dealing with SGLT2 and antidiabetic therapy has been included in the revised manuscript within chapter 4 treatment:
“SGLT2 inhibitors as well as GLP-1 RAs might have a positive effect on the treatment of NAFLD in T2DM patients. A systematic review was published recently (53b).”

Comment 4: a proposed diagnostic algorithm etc.
Response 4: Within chapter 3 a diagnostic algorithms is proposed: “Diagnostic algorithms for differentiating NAFLD by non-invasive tools are presented by Roeb et al. in (51, 15)”. Since this algorithm has already been published, a new illustration has been omitted here.

Comment 5: More recent Refs are needed
Response 5: According to the reviewer´s advice several recent references from 2019 and 2020 were added:

- 1b.Younossi ZM, Tacke F, Arrese M, Sharma BC, Mostafa I, Bugianesi E, et al. Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Hepatology. 2019; 69: 2672-2682.
- 44a.Tobari M, Hashimoto E, Taniai M, et al. Characteristics of non-alcoholic steatohepatitis among lean patients in Japan: Not uncommon and not always benign. J Gastroenterol Hepatol 2019;34:1404-10.
- 53a. Sumida Y, Yoneda M, Ogawa Y, et al. Current and new pharmacotherapy options for non-alcoholic steatohepatitis. Expert Opin Pharmacother. 2020;21(8):953-967
- 53b.Dougherty JA, Guirguis E, Thornby KA. A Systematic Review of Newer Antidiabetic Agents in the Treatment of Nonalcoholic Fatty Liver Disease [published online ahead of print, 2020 Jun 22]. Ann Pharmacother. 2020;1060028020935105
- 59b.Sumida Y, Okanoue T, Nakajima A; Japan Study Group of NAFLD (JSG-NAFLD). Phase 3 drug pipelines in the treatment of non-alcoholic steatohepatitis. Hepatol Res 2019;49:1256-1262.

Reviewer C:

Comment 1: This is an excellent review about NAFLD/HASH. I would recommend the "unification" and "simplification". Many information are given without critical evaluation and practical outcome.

For example, some statements are not clear:
In paragraph 1. "Definition of NAFLD" the information that moderate alcohol consumption is associated with the reduced risk of fatty liver is given; in the same paragraph the information that studies showing the positive role of alcohol suffer from significant limitations. Hence the reader must be confused.

Response 1: I apologize for the initial presentation of confusing information. The following sentences and the consequent recommendation have been included into paragraph 1:

"This evidence (from retrospective data) is still inconclusive because some recently published studies showed that modest alcohol consumption increases hepatic fat without increasing the risk of advanced fibrosis. Prospective data suggest that NAFLD patients with regular alcohol intake, although within the safe thresholds, are at higher risk of liver disease progression, including hepatocellular carcinoma (27a).

…..

Taken together, counseling NAFLD patients for alcohol abstinence should be maintained."

27a. Petroni ML, Brodosi L, Marchignoli F, Musio A, Marchesini G. Moderate Alcohol Intake in Non-Alcoholic Fatty Liver Disease: To Drink or Not to Drink?. Nutrients. 2019;11(12):3048

Comment 2: In the same paragraph the information that coffee consumption was calculated to increase the risk for fatty liver. In the other paragraph the information about the positive role of coffee consumption is given, what again leads to the confusion of a reader.
Response 2: In paragraph 1 the incorrectly inserted sentence dealing with coffee consumption was eliminated as well as the corresponding citation.

Comment 3: The paragraph about the screening is too excessive and non-conclusive. For example, the information about the leptin, adiponectin, resistin…. has no relevance to the screening.
Response 3: The paragraph was shortened in the revised manuscript and the passage about leptin, resistin etc. was deleted.

Comment 4: The authors should also clearly differentiate between screening for benign NAFL and for liver fibrosis and eventually for NASH (what is impossible without liver biopsy).
Response 4: This is a very good point, that was implemented in the revised manuscript:
“Up to now liver biopsy is the only diagnostic that can clearly differentiate between NAFL, NAFL with low inflammation and NASH (steatosis with lobular and portal inflammation and hepatocellular ballooning), and defining the presence or absence of even low fibrosis (20). For clinical purposes, a simple but robust algorithm for categorizing liver lesions in NAFLD patients was introduced by Bedossa et al. (49a).”

Comment 5: Liver biopsy in not a method for choice to determine the stage of fibrosis currently. Fibroscan (or other elastography method) in now generally accepted for fibrosis staging (liver biopsy is method of choice for NASH diagnosis).
Response 5: The following paragraph explaining the basics of detecting fibrosis by elastography has been included into the revised manuscript:
“Ultrasound-based transient hepatic elastography has been the first true bedside technique to reproducible screen for liver fibrosis. In comparison to other techniques TE has an excellent interobserver variability, small sampling error, and good reproducibility. If liver fibrosis is suspected, TE should be performed directly after the

abdominal ultrasound and routine blood tests. In cases of severe obesity (BMI >30) or ascites, the XL probe should be used (49b)."

Comment 6: In the paragraph 3 "Diagnostic tool" the authors must clearly differentiate between the diagnosis of NAFL, NASH and fibrosis.
Response 6: All paragraphs have now been revised with special regard to the differentiation of NAFLD, NAFL, NASH and fibrosis.

Comment 7: While NAFL is diagnosed by ultrasound, quantified by CAP in daily routine and by MR in studies, fibrosis is diagnosed by liver elastography. NASH could be diagnosed by biopsy or probably by some serum tests (the authors did not mention for example the metabolonomic diagnostic tool).
Response 7: The reviewer is thanked for this valuable suggestion. The condensed rating was taken into account and the following paragraph has been included in the manuscript:
"A recently published noninvasive lipidomic serum tests assessed by two panels of triglycerides distinguished between NAFLD and NAFL and between NASH and NAFL with high accuracy (50a). Thus, metabolomics provides a new technology for noninvasive biomarkers to improve NAFLD diagnosis."

Comment 8: In table 2 the sensitivity and specificity of different tests should be mentioned and the authors should not confuse the reader by mixing serum tests and imaging methods.
Response 8: We thank the reviewer for the suggestion and replaced the table accordingly. Serum test are now separated from imaging methods and liver function tests.
The sensitivity and specificity of all tests mentioned in table 2 are discussed in the references listed in the right column of table 2. The references are given as examples. As sensitivities and specificities differ greatly between the individual studies, the specific mention in table 2 was omitted

Comment 9: In the Paragraph 4. "Treatment" the authors should point out why to treat the patients with NASH (not NAFL) and should mention the results of studies showing the regression of fibrosis.
Response 9: I thank the expert for this interesting addition. The following sentences have been added in paragraph 4:
"NAFL displays hepatic steatosis without evidence of inflammation and increased risk of developing liver-related complications. Patients with NASH, however, should be

treated to prevent NASH progression to advanced fibrosis, to prevent cirrhosis and to prevent the development of its hepatic complications."…..
"Hepatic fibrosis displays the main characteristic predicting liver related and all cause mortality in NAFLD. Cenicriviroc, a promising new antifibrotic agent, blocks the CCR5 and CCR2 receptor. The efficacy and safety of Cenicriviroc in patients with NASH and liver fibrosis were assessed in the CENTAUR study, a phase 2b, double-blind, randomized, placebo-controlled, multinational study with 289 NASH subjects (51a). In the Cenicriviroc group, the fibrosis score remained improved by at least one level, with patients with advanced fibrosis benefiting the most (51a)."

Friedman S, Sanyal A, Goodman Z, et al. Efficacy and safety study of cenicriviroc for the treatment of non-alcoholic steatohepatitis in adult subjects with liver fibrosis: CENTAUR Phase 2b study design. Contemp Clin Trials. 2016;47:356-365

Comment 10: The ultimate treatment option (liver transplantation) is not mentioned at all.
Response 10: I agree with the reviewer and implemented this treatment option in a short paragraph:
"NASH is a rapidly growing etiology of end-stage liver disease in the US and elsewhere with significantly higher post-transplant survival compared to HCV (53c). Currently NASH is the second leading cause for liver transplantation overall, even the leading cause in in females. Given the rate of increase, NASH will likely rise to become the leading indication for liver transplantation in males as well (53c, 53d). "