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Received 20 December 2022; Received in revised form 15 April 2023; Accepted 17 April 2023; Available online 20 April 2022
https://doi.org/10.1016/j.jhep.2023.04.015

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Financial support

This work was supported by the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2021-I2M-C&T-B-018), National High-Level Hospital Clinical Research Funding (2022-PUMCH-A-018, 2022-PUMCH-C-043).

Conflict of interest

The authors declare that there is no conflict of interest.
Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Hang Yi and Qihao Leng were involved in conceptualizing drafting, and literature review of the letter, and Jie Zhou, Shifang Peng and Yousheng Mao revised the letter for final submission. All authors approved the final version for submission and publication of the content. Hang Yi and Qihao Leng contributed equally as co-first authors.

Data availability statement

The present study used publicly available data from the Journal Citation Reports on Web of Science (https://jcr.clarivate.com/).

Ethics approval statement

The publicly available data were anonymous and ethical approval and patient consent statement can be waived.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.04.015.

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Author names in bold designate shared co-first authorship

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Aetiology of liver disease and response to immune checkpoint inhibitors: An updated meta-analysis confirms benefit in those with non-viral liver disease

To the Editor:
Clinical outcomes for advanced hepatocellular carcinoma (HCC) have significantly improved with the introduction of immune checkpoint inhibitors (ICIs), but results from initial trials have suggested that the aetiology of liver disease may be a predictive marker of clinical benefit, and stratification based on aetiology has been recommended. The differential response has been supported by preclinical models and reinforced in the recent review.[1,2] But as more clinical data emerge, the association between liver disease aetiology and response to ICI-based therapy has become less clear.

The possibility that aetiology was an important factor for response to ICI-based therapy was raised by the subgroup analysis of the IMbrave 150 trial.[3] The trial met its endpoint demonstrating an overall survival advantage for atezolizumab+bevacizumab compared with sorafenib (hazard ratio [HR] 0.58; 95% CI 0.42 to 0.79; p <0.001), but in the non-viral sub-group, the HR was only 0.91 (0.52-

1.60), comparing unfavourably with the hepatitis B and C cohort with HRs of 0.51 and 0.43, respectively. But what is also striking in the subgroup analysis is that the median overall survival for the 53 non-viral, sorafenib-treated patients was 18 months, considerably better than the 12.4 and 12.6 months for the hepatitis B and C cohort.[4] Initial studies have not suggested that patients with non-viral HCC have a better prognosis with sorafenib than those with viral aetiology; in fact, if anything, the data indicates that those with HCV do better.[5] Hence, the overperformance of the control group in

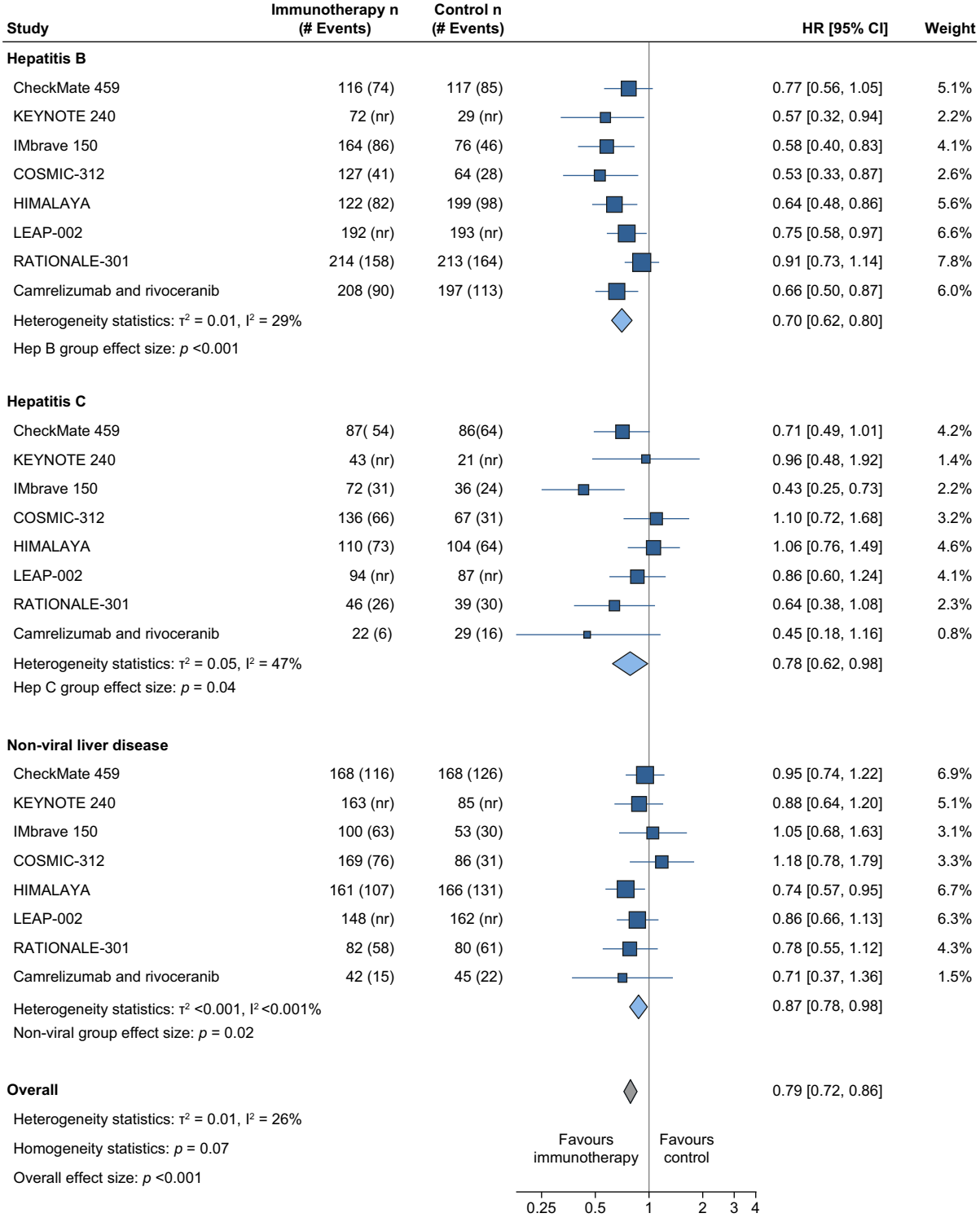

Fig. 1. Meta-analysis of eight randomised trials of ICI-based systemic therapy for advanced HCC separated into subgroups according to disease aetiology. A restricted maximum likelihood random effects model was used. HCC, hepatocellular carcinoma; HR, hazard ratio; ICI, immune checkpoint inhibitor.

the subgroup analysis of IMbrave 150 trial may explain, at least in part, the apparent lack of benefit of atezolizumab+bevacizumab in non-viral patients. Additionally, the response rate of 27% in the non-viral cohort was similar to that reported for non-viral cohorts in the initial studies of single-agent PD-1 inhibitors.[6,7] However, a subsequent meta-analysis, including data from IMbrave 150, CheckMate 459 and KEYNOTE-240, concluded that immunotherapy was superior to control in those with viral aetiology but provided no survival advantage in those of non-viral aetiology.[1]

Since then a further six randomised-controlled trials have been reported; COSMIC-312[8], HIMALAYA[9], LEAP-002[10], RATIONALE-301[11], Camrelizumab and rivoceranib[12] and ORIENT-32[13]. We have performed an updated meta-analysis to explore the relationship between liver disease aetiology and clinical outcome for patients treated with ICI-based therapy (Fig. 1). We excluded the ORIENT-32 trial since it was conducted exclusively in China in a population in which 94% had hepatitis B infection.

The meta-analysis used a restricted maximum likelihood random effects model. A low degree of heterogeneity in the HRs is indicated by $I^2 = 26\%$ and $T^2 = 0.01$. The findings reveal a significant survival advantage across both non-viral and viral aetiologies (HR 0.79, 95% CI 0.72 to 0.86, p <0.001), with the largest estimated benefit for those with hepatitis B (hepatitis B: HR 0.70, p <0.001; hepatitis C: HR 0.78, $p = 0.04$; non-viral: HR 0.87, $p = 0.02$). For the non-viral subgroup, the HIMALAYA trial reported the most significant benefit with ICIs, indicating the potential importance of CTLA-4 inhibition in this subpopulation. In this respect, publication of the CheckMate 9DW trial comparing nivolumab and ipilimumab with sorafenib, is eagerly awaited.

Based on this analysis, it is premature to conclude that patients with non-viral liver disease do not benefit from ICI-based therapy.

In addition to all the potential pitfalls of *post hoc* analysis, it has to be acknowledged that in the majority of cases, HCC development is multifactorial and includes demographic factors, severity and activity of the underlying disease, metabolic factors (diabetes, obesity), and lifestyle factors (alcohol intake, smoking). Specifically, the distinction of NASH/NAFLD and ASH can be challenging in light of recent data indicating that harmful drinking can be observed in up to 30% of obese patients.[14] Overall, these issues complicate the (*post hoc*) evaluation of how "one" underlying liver disease might influence the effectiveness of a specific therapy. In this context, preclinical models can be very helpful not only to understand the molecular mechanisms that may underlie differential efficacies, but also to develop hypothesis-based strategies to improve the efficacy of therapy in a specific sup-group such as patients with fatty liver.

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Received 31 March 2023; Accepted 10 April 2023; Available online 21 April 2023
https://doi.org/10.1016/j.jhep.2023.04.012

Financial support

The authors received no financial support to produce this manuscript.

Conflicts of interest

TM Consultancy: Eisai, BMS, Adaptimmune. Ipsen, Roche, AstraZeneca, MSD, Beigene Funding: MSD. AV Consultancy/Speaker: AstraZeneca, Amgen, BeiGene, Böhringer Mannheim, BMS, BTG, Daichi-Sankyo, EISAI, Incyte, Ipsen, MSD, PierreFabre, Roche, Servier, Sirtex, Tahio, Terumo.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

TM: Concept and design, collection of data, interpretation of data, drafting and reviewing and approving final manuscript. SG: Analysis of data, interpretation of data, reviewing final manuscript. AL: Analysis of data, interpretation of data, reviewing final manuscript. AV: interpretation of data, drafting and reviewing and approving final manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.04.012.

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Effects of CFTR modulator therapies on liver stiffness and bile flow: A single-centre experience

To the Editor:

We found the review by Jérémy Dana, Dominique Debray *et al.*[1] published in the *Journal of Hepatology* in October 2021 very interesting. In this review, the authors suggest using liver stiffness rather than liver tests during cystic fibrosis transmembrane regulator (CFTR) modulator therapy to allow for early detection of treatment response or progression of cystic fibrosis-related liver disease (CFLD); however, to date, no data has been published.

Liver enzyme tests (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) are poorly sensitive markers of liver disease in CFLD and only persistently elevated gamma-glutamyltransferase (GGT)[2] is associated with the development of cirrhosis. Liver steatosis, a frequent and less aggressive liver disease in patients with cystic fibrosis (CF), may be a cofounding factor in determining GGT alterations.[3] Due to the focal nature of the fibrosis and the impossibility of obtaining multiple samples, liver biopsy is rarely performed in patients with CF. Liver stiffness (LS), which is generally evaluated by vibration-controlled transient elastography (VCTE) using Fibroscan,[4] could be useful, as it assesses a tissue volume that is about 100-fold larger than that of a standard biopsy specimen. Moreover, VCTE has not only been used for the assessment of classical hepatic damage, but also for biliary damage, such as in primary biliary cholangitis[5] and sclerosing cholangitis.[6] It has also recently been described as a predictor of clinical outcomes and a useful surrogate endpoint in therapeutic trials. However, VCTE may be influenced by vascular or lymphatic stasis.[7] CFTR modulator therapies are expected to either prevent or improve CFLD by correcting CFTR defects in cholangiocytes and enhancing $HCO3^-$ secretion, as the "bicarbonate umbrella" protects cholangiocytes against hydrophilic bile acids.[8] Moreover, increasing HCO_3^- coupled water in bile may stimulate bile flow and contribute to a reduction in viscosity and biliary obstruction. However, this mechanism has not yet been fully supported by the relatively rare findings of inspissated bile secretion, hence other mechanisms, *e.g.* involving intestinal inflammation or dysbiosis, are still under investigation.[1] Data regarding the efficacy of CFTR modulators on CFLD are scarce.[9] Moreover, liver enzyme alterations are often observed in treated patients with CFLD and, if consistent (5-10x), therapy must be discontinued.[10]

This prospective single-centre cohort study was carried out to evaluate liver function in patients treated with CFTR modulators over time. All patients with CF who were eligible to start ivacaftor/tezacaftor/elexacaftor in the Cystic Fibrosis *Centre of the Città della Salute e della Scienza della Città of Torino*, Italy were enrolled (Jan 2021-Aug 2022). All patients were evaluated before starting treatment and at 1, 3 and 6 months with haematological examinations and LS measurement obtained by VCTE. Fifty-five patients were enrolled: mean age 17.7 years (SD 4.9), 49% males. Pre-treatment, the mean VCTE was 5.1 kPa (SD 1.8). At baseline, mean AST/ALT/GGT levels were 24.4 (SD 9.8), 26 (SD 17) and 14.5 IU/L (SD 9.1), respectively. The patients were classified by VCTE into: normal (<5 kPa: n = 34, 62%), mild liver fibrosis (5-7 kPa: n = 10, 18%), or moderate-severe liver fibrosis (>7 kPa: n = 11, 20%).

Two patients (1 male, 1 female) (3.6%) discontinued treatment at 3 and 6 months. One had a worsening of spirometry (FEV1 reduction) and the other had a worsening of LS with a significant rise (>5x the upper limit of normal) in liver enzyme levels.

A significant mean LS reduction (mean difference [MD] -0.46, $p = 0.046$) was observed at month 6 (Fig. 1A). Patients