VOLUME 32 NUMBER 1 January 2026
pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases

Bacteroides eggerthii for MASLD

Infiltrative HCC as an immunotherapy-resistant subtype
SGLT2 inhibitors and liver fibrosis progression
Aspirin and HCC risk in MASLD
Hypothyroidism and liver-related events

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2025.0235
Clinical and Molecular Hepatology 2026;32:e68-e71

Correspondence

Emerging evidence supports direct-acting antiviral therapy for HCC patients beyond the early stage: Correspondence to editorial on "Direct-acting antiviral therapy for patients with HCV-related hepatocellular carcinoma: A nationwide cohort study"

Teng-Yu Lee[1,2], Pei-Chien Tsai[3], Shou-Wu Lee[1,2,4], and Ming-Lung Yu[3,5]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung; [2]School of Medicine, Chung Shan Medical University, Taichung; [3]Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung; [4]Department of Post-Baccalaureate Medicine, College of Medicine, Chung Hsing University, Taichung; [5]Hepatitis Research Center, College of Medicine and Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan

Keywords: Chronic hepatitis C; Antivirals; Hepatocellular carcinoma; Liver cancer; Survival

Dear Editor,

We sincerely appreciate the editorial by Dr. Ong and his colleagues[1] for their valuable comments and perspectives on our recent study.[2] In their editorial, they critically highlighted the uncertainty surrounding the survival benefits of direct-acting antiviral (DAA) therapy for patients with hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC), particularly those beyond the early stage. Although a sustained virological response (SVR) can be achieved in more than 90% of patients in Barcelona Clinic Liver Cancer (BCLC) stages B or C,[3,4] concerns remain regarding whether DAA therapy truly improves overall survival. Investigating this issue is particularly challenging due to the difficulty of controlling one of the most critical prognostic factors, i.e., HCC itself, given the diversity in tumor characteristics and treatment modalities.[5] Nevertheless, our recent study may help clarify the role of DAA therapy in the management of HCC patients in several key aspects. Our responses to the editorial are as follows:

Firstly, DAA therapy should be considered for all HCC patients without a short life expectancy.[6] As noted by Ong et al.[1], the survival benefits of achieving SVR become more evident over time, particularly beyond one year following HCV eradication in our study.[2] While numerous studies have demonstrated that HCV eradication not only improves liver function and reduces liver fibrosis but also lowers the risks of liver decompensation, HCC recurrence, and liver-related mortality,[7-9] these improvements may take time to manifest. Consequently, although DAA therapy has the po-

Corresponding author : **Ming-Lung Yu**
Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, 100 Tzyou1st Road, Kaohsiung 807, Taiwan
Tel: +886-7-311-7820, Fax: +886-7-321-2062, E-mail: fish6069@gmail.com
https://orcid.org/0000-0001-8145-1900

Editor: Han Ah Lee, Chung-Ang University College of Medicine, Korea

Received: Feb. 28, 2025 / **Accepted:** Mar. 1, 2025

Copyright © 2026 by Korean Association for the Study of the Liver
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

tential to extend survival in HCC patients, it may not provide timely benefits for those with a very limited life expectancy, such as individuals in the terminal stage of HCC. Encouragingly, advancements in HCC treatment in recent years have significantly improved patient outcomes, with an expected survival exceeding two years for those in BCLC stage B or C.[10,11] These developments further support our recommendation that DAA therapy should be strongly considered for all HCC patients who do not have a short life expectancy.

Secondly, the potential confounding effect of varying HCC treatment options was minimalized in our study. While we acknowledge that a stratified analysis of patients receiving different HCC treatment modalities would be valuable, one limitation of our database is the absence of detailed clinical course data for HCC patients. However, during the study period (December 2013 to December 2020), the reimbursed treatment options for HCC in Taiwan remained relatively uniform.[12] Specifically, curative treatments were administered for early-stage HCC, locoregional treatments for intermediate-stage HCC, and tyrosine kinase inhibitors for advanced-stage HCC. Notably, immunotherapy for HCC was not reimbursed by the Taiwan National Health Insurance during this timeframe.[2] Therefore, we believe that the potential confounding effect of treatment variability was minimized. While our study demonstrates that the survival benefit of SVR remained significant across BCLC stages 0-A and B-C,[2,13] further research focusing on patients receiving specific treatments, particularly immunotherapy, is highly warranted.

Thirdly, distinguishing liver failure-related death from HCC-related death in HCC patients may be neither feasible nor necessary. Even in prospective clinical trials, determining the exact cause of death can be challenging; for instance, variceal bleeding may result from either underlying cirrhosis or advanced HCC, making attribution difficult. In contrast, overall survival serves as a comprehensive and reliable indicator of the survival benefit conferred by a given treatment, which is arguably the most crucial outcome for HCC patients.[14]

Fourthly, while prospectively establishing a DAA-untreated control group is theoretically a sound study design, it may not be ethically justifiable. Current clinical guidelines for the management of hepatitis C recommend initiating DAA therapy for HCC patients either after curative treatment or immediately upon diagnosis of incurable HCC, regardless of the HCC treatment strategy.[6,15,16] Given the accumulating evidence supporting the survival benefits of DAA therapy, withholding treatment from patients may be considered unethical. Conversely, establishing a DAA-untreated control group in a retrospective study could introduce significant selection bias, as patients with a short life expectancy may be less likely to receive DAA therapy. Although our study lacked a traditional DAA-untreated control group, we were able to use patients who did not achieve SVR as a comparator in this large-scale study. Since all patients in both study groups received DAA therapy from specialists in Taiwan, the potential selection bias associated with preferentially treating patients with inherently better liver function or greater access to specialized care was effectively minimized.

Lastly, while liver decompensation, i.e., Child-Turcotte-Pugh (CTP) class B in this study, is a prognostic factor in HCC patients, our data indicated that it was not associated with a decreased SVR rate (Table 1). As discussed in our manuscript,[2] the high SVR rate observed in this study may be attributed to patients receiving either pangenotypic or genotype-specific DAA therapies, with the probability of achieving SVR remaining largely unaffected by liver dysfunction (CTP score 5–6 vs. ≥7: 96.2% vs. 95.4%). Furthermore, our findings demonstrated that SVR was an independent predictor of improved overall survival after adjusting for other prognostic factors, including CTP class. Therefore, concerns that the improved overall survival in the SVR group may be attributable to better baseline liver function can likely be dismissed.

In summary, we thank Dr. Ong and his colleagues[1] for the opportunity to address important issues raised in their editorial. While our study adds to the growing body of evidence suggesting that achieving SVR through DAA therapy

Abbreviations:

ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CTP, Child-Turcotte-Pugh; CVA, cerebral vascular accident; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTN, hypertension; N, numbers; OR, adds ratio; SVR, sustained virological response

Table 1. Logistic regression model for risk factors of SVR in HCC patients receiving a DAA therapy

Variable		Number	SVR, number (%)	Crude		Adjusted	
				OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	≤65	612	590 (96.4)	1			
	>65	1,593	1,539 (96.6)	1.06 (0.64–1.76)	0.813		
Gender	Male	1,097	1,053 (96.0)	1			
	Female	1,108	1,076 (97.1)	1.41 (0.88–2.23)	0.15		
BMI (kg/m^2)	≤27	1,768	1,706 (96.5)	1			
	>27	437	423 (96.8)	1.10 (0.61–1.98)	0.756		
DM	No	1,581	1,532 (96.9)	1			
	Yes	624	597 (95.7)	0.71 (0.44–1.14)	0.156		
HTN	No	1,229	1,182 (96.2)	1			
	Yes	976	947 (97.0)	1.30 (0.81–2.08)	0.277		
CVA	No	2,133	2,059 (96.5)	1			
	Yes	72	70 (97.2)	1.26 (0.30–5.23)	0.753		
CAD	No	1,935	1,874 (96.8)	1		1	
	Yes	270	255 (94.4)	0.55 (0.31–0.99)	0.046	0.63 (0.34–1.15)	0.193
CKD	No	1,711	1,651 (96.5)	1			
	Yes	494	478 (96.8)	1.14 (0.80–1.63)	0.458		
ALT (IU/L)	≤80	1,410	1,368 (97.0)	1			
	>80	795	761 (95.7)	0.69 (0.43–1.09)	0.110		
HCV viral loads (IU/ml)	≤8×10^5	1,992	1,924 (96.6)	1	0.795		
	>8×10^5	213	205 (96.2)	0.91 (0.43–1.91)			
HCV genotype	Non-1	787	740 (94.0)	1	<0.001	1	<0.001
	1	1,414	1,386 (98.0)	3.14 (1.95–5.06)		4.85 (2.88–8.17)	
DAA regimen	Non-pangenotypic	1,782	1,713 (96.1)	1	0.029	1	<0.001
	Pangenotypic*	423	416 (98.4)	2.39 (1.09–5.24)		4.23 (1.86–9.64)	
DAA adherence	≤80%	25	16 (64.0)			1	
	>80%	2,180	2,113 (96.9)	17.74 (7.57–41.59)	<0.001	31.10 (12.28–78.74)	<0.001
Liver decompensation	CTP score 5-6	1,275	1,227 (96.2)	0.72 (0.43–1.21)	0.215		
	CTP score ³ 7	130	124 (95.4)	0.58 (0.23–1.47)	0.254		
BCLC stage	0	432	420 (97.2)	1			
	A	1,017	985 (96.9)	0.88 (0.45–1.72)	0.708		
	B	322	305 (94.7)	0.51 (0.24–1.09)	0.082		
	C	175	166 (94.9)	0.53 (0.22–1.27)	0.155		

ALT, alanine aminotransferase; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CTP, Child-Turcotte-Pugh; CVA, cerebral vascular accident; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HTN, hypertension; OR, adds ratio; SVR, sustained virological response.
*Pangenotypic DAA included glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

may improve survival in HCC patients across various disease stages, further research is needed to overcome its limitations.

Authors' contribution

Study conception and design: T.Y.L., M.L.Y. Data acquisition, analysis and interpretation: T.Y.L., P.C.T., S.W.L., M.L.Y. Manuscript drafting: T.Y.L., P.C.T., M.L.Y. Critical revision for important intellectual content: T.Y.L., P.C.T.,

https://doi.org/10.3350/cmh.2025.0235

S.W.L., M.L.Y. All authors contributed to the revision of the final manuscript.

Conflicts of Interest

TY Lee: research support from Gilead, Merck and Roche diagnostics; consultant of BMS, Gilead, and AstraZeneca and speaker of Abbvie, BMS, Eisai, Gilead, Roche and AstraZeneca.

ML Yu: research support from Abbvie, Abbott Diagnostic, BMS, Gilead, Merck and Roche diagnostics; consultant of Abbvie, Abbott Diagnostic, BMS, Gilead, Roche and Roche diagnostics and speaker of Abbvie, BMS, Eisai, Gilead, Roche and Roche diagnostics. Other authors declare no conflicts of interest.

REFERENCES

1. Ong YL, Kaewdech A, Huang DQ, Wong YJ. Editorial on "Direct-acting antiviral therapy for patients with HCV-related hepatocellular carcinoma: A nationwide cohort study". Clin Mol Hepatol 2026;32:407-409.
2. Lee SW, Yang SS, Tsai PC, Huang CF, Chen CY, Hung CH, et al. Direct-acting antiviral therapy for patients with hepatitis C virus-related hepatocellular carcinoma: A nationwide cohort study. Clin Mol Hepatol 2025;31:899-913.
3. Chen LS, Lee SW, Yang SS, Tsai HJ, Lee TY. Advances in the era of direct-acting antivirals for hepatitis C in patients with unresectable hepatocellular carcinoma. Dig Dis 2022;40:616-624.
4. Lee SW, Chen LS, Yang SS, Huang YH, Lee TY. Direct-acting antiviral therapy for hepatitis C virus in patients with BCLC stage B/C hepatocellular carcinoma. Viruses 2022;14:2316.
5. Kim DY, Toan BN, Tan CK, Hasan I, Setiawan L, Yu ML, et al. Utility of combining PIVKA-II and AFP in the surveillance and monitoring of hepatocellular carcinoma in the Asia-Pacific region. Clin Mol Hepatol 2023;29:277-292.
6. Yu ML, Chen PJ, Dai CY, Hu TH, Huang CF, Huang YH, et al. 2020 Taiwan consensus statement on the management of hepatitis C: part (II) special populations. J Formos Med Assoc 2020;119:1135-1157.
7. D'Ambrosio R, Aghemo A. Treatment of patients with HCV related cirrhosis: many rewards with very few risks. Hepat Mon 2012;12:361-368.
8. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153:996-1005.e1.
9. Cabibbo G, Celsa C, Calvaruso V, Petta S, Cacciola I, Cannavò MR, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol 2019;71:265-273.
10. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681-693.
11. Hwang SY, Danpanichkul P, Agopian V, Mehta N, Parikh ND, Abou-Alfa GK, et al. Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment. Clin Mol Hepatol 2025;31(Suppl):S228-S254.
12. Su TH, Wu CH, Liu TH, Ho CM, Liu CJ. Clinical practice guidelines and real-life practice in hepatocellular carcinoma: a Taiwan perspective. Clin Mol Hepatol 2023;29:230-241.
13. Yeh ML, Liang PC, Tsai PC, Wang SC, Leong J, Ogawa E, et al. Characteristics and survival outcomes of hepatocellular carcinoma developed after HCV SVR. Cancers (Basel) 2021;13:3455.
14. Sankar K, Gong J, Osipov A, Miles SA, Kosari K, Nissen NN, et al. Recent advances in the management of hepatocellular carcinoma. Clin Mol Hepatol 2024;30:1-15.
15. Chen CY, Huang CF, Cheng PN, Tseng KC, Lo CC, Kuo HT, et al. Factors associated with treatment failure of direct-acting antivirals for chronic hepatitis C: a real-world nationwide hepatitis C virus registry programme in Taiwan. Liver Int 2021;41:1265-1277.
16. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of hepatocellular carcinoma. J Hepatol 2025;82:315-374.