**in vivo** *38*: 2968-2972 (2024)
doi:10.21873/invivo.13779

# Long-term Effect of the HCV Elimination With Direct-acting Antivirals on the Progression of Gastroesophageal Varices

YUKIHISA YURI, TAKASHI NISHIMURA, NAOTO IKEDA, TOMOYUKI TAKASHIMA, NOBUHIRO AIZAWA, TARO KIMURA, KOHEI YOSHIHARA, RYOTA YOSHIOKA, SHOKI KAWATA, YUTA KAWASE, RYOTA NAKANO, HIDEYUKI SHIOMI, SHINYA FUKUNISHI, SHINICHIRO SHINZAKI and HIRAYUKI ENOMOTO

*Department of Gastroenterology, Hyogo Medical University, Nishinomiya, Japan*

**Abstract.** *Background/Aim: Gastroesophageal varices (GEV) hemorrhage is a serious complication that can lead to unfavorable outcomes in cirrhotic patients. However, the clinical impact of HCV elimination [sustained viral response (SVR)] by direct-acting antivirals (DAAs), particularly on the long-term effects on the endoscopic findings of GEV have not been sufficiently evaluated. This study aimed to investigate whether HCV elimination with DAA treatment suppresses the progression of GEV. Patients and Methods: The clinical courses of the endoscopic findings of GEV were retrospectively compared between patients without an SVR (non-SVR group: n=71) and those who achieved an SVR with DAAs (DAA-SVR group: n=38). Results: At 1, 3, 5, and 7 years, the cumulative GEV progression rates were 8.7%, 32.8%, 45.6%, and 66.2%, respectively. At 3 years, the cumulative GEV progression rate in the DAA-SVR group was similar to that in the non-SVR group. Beyond 3 years, cases with GEV progression were found in the non-SVR group, but not in the DAA-SVR group. At 7 years, the cumulative GEV progression rate in the DAA-SVR group was significantly lower than that in the non-SVR group ($p<0.05$, log-rank test). Variceal hemorrhage occurred in eight patients in the non-SVR group, while no bleeding events were observed in the DAA-SVR group during the observational period [8/71 (11.3%) vs. 0/38 (0.0%), $p<0.05$]. Conclusion: DAA treatment suppresses the progression of GEV over the long term.*

*Correspondence to:* Hirayuki Enomoto, Department of Gastroenterology, Hyogo Medical University, Mukogawa-cho 1-1, Nishinomiya, 663-8501 Hyogo, Japan. Tel: +81 798456472, Fax: +81 798456474, e-mail: enomoto@hyo-med.ac.jp

*Key Words:* Hepatitis C virus, sustained viral response, liver cirrhosis, direct-acting antivirals, gastroesophageal varices.



Hemorrhage of gastroesophageal varices (GEV) is a serious complication that can lead to unfavorable outcomes in cirrhotic patients, and the management of GEV is thus clinically important (1-6). Infection with hepatitis viruses, including hepatitis B virus (HBV) and hepatitis C virus (HCV), is a major cause of chronic liver diseases (CLDs) worldwide (7-10). However, recent advances in antiviral drugs have made it possible to control viral replication in most patients with chronic hepatitis viral infection. In particular, current treatments with direct-acting antivirals (DAAs) can cause a high rate of HCV elimination (sustained virological response: SVR), and various positive effects, including improvement of the hepatic function and the inhibition of carcinogenesis (11-14). However, the clinical impact of HCV-SVR by DAAs, particularly the long-term effects on the endoscopic findings of GEV, has not been sufficiently evaluated.

We previously compared the clinical courses of the endoscopic findings of GEV in HCV-related cirrhotic patients who did not achieve an SVR (non-SVR group), those who achieved an SVR with interferon (IFN) treatment (IFN-SVR group), and those who achieved an SVR with DAA treatment (DAA-SVR group). In the IFN-SVR group, the incidence of GEV exacerbations was low, while the clinical course of the DAA-SVR group was comparable to that of the non-SVR group (15). However, in comparison to the IFN-SVR group, the DAA group included elderly patients with a poorer hepatic function. In addition, the use of DAA became available in our country in 2014, and the long-term effect of DAA-SVR on endoscopic findings has not been sufficiently evaluated. We herein show the results of longer-term observations of Japanese patients who achieved an SVR with DAAs.

## Patients and Methods

*Patients.* In our previous study (15), we retrospectively assessed HCV-related cirrhotic patients with GEV and whose follow-up endoscopic findings were available. All patients were instructed to abstain from alcohol intake. Patients whose HCV RNA levels were undetectable at 24 weeks after the end of the antiviral treatment

Table I. *Basic characteristics of the overall population (n=109).*

| | |
|---|---|
| Age (years) | 66 (62-71) |
| Sex (Male/Female) | 57/52 |
| Child-Pugh grade (A/B/C) | 68/40/1 |
| AST (U/l) | 62 (43-89) |
| ALT (U/l) | 49 (30.5-81) |
| Total bilirubin (mg/dl) | 1.0 (0.8-1.4) |
| Albumin (g/dl) | 3.7 (3.3-3.95) |
| Platelet count ($\times 10^3$/μl) | 73 (57.5-93) |
| Prothrombin time (%) | 75.7 (68.75-83.35) |
| Form of esophageal varices (F3/2/1/ND) | 0/13/92/4 |
| Form of gastric varices (F3/2/1/ND) | 1/7/27/74 |

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; ND: not detected.

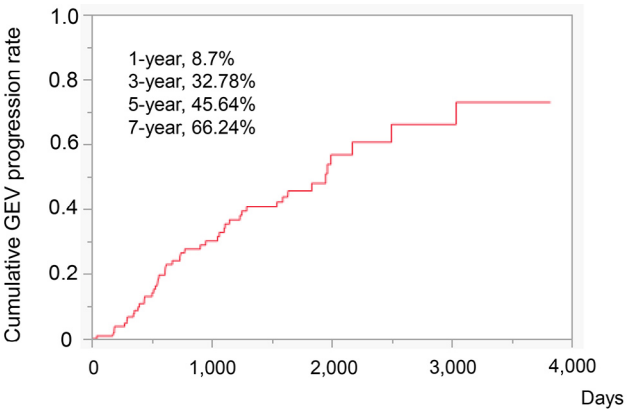


Figure 1. *The rate of gastroesophageal varices (GEV) progression in the overall population. The GEV progression rates at 1 year, 3 year, 5 year, and 7 years are 8.7%, 32.8%, 45.6%, and 66.2%, respectively.*

were defined as those who attained a sustained viral response (SVR). In this study, we focused on investigating whether the progression of GEV was suppressed in the DAA-SVR group (patients with an SVR with DAA therapies) in comparison to the non-SVR group (patients without an SVR during the follow-up period). The follow-up data in the non-SVR group were mainly obtained prior to the development of the DAA therapy, and no new patients with GEV were found for the non-SVR group. In addition to the patients in the previous study (15), we included 1 patient with GEV who achieved an SVR with DAA therapy. Thus, 109 patients (non-SVR group, N=71; DAA-SVR group, N=38) were analyzed in the present study.

*Endoscopic findings of GEV.* Endoscopic findings of GEV and therapeutic indications have been described in our previous report (15). In brief, the forms of GEV were categorized into 3 grades (F1, F2, or F3). F2 varices with red color sign(s) and F3 varices were considered as indications for endoscopic treatment. GEV were observed by esophagogastroduodenoscopy (EGD) every 6-12 months. Progression of GEV was defined by an upgrade of the type, development of therapeutic indications, or bleeding events. In the present study, we compared the rate of GEV progression between the non-SVR and DAA-SVR groups.

*Follow-up observation of the endoscopic findings of GEV.* In the non-SVR group, the follow-up period was calculated as the time interval between the day on which GEV were first detected and the day on which the last follow-up EGD was conducted or when progression of GEV was observed without antiviral treatment. In the DAA-SVR group, the follow-up period was calculated as the time interval between the last day on which EGD was conducted before the initiation of the antiviral therapy and the day on which the last follow-up EGD was conducted or the day on which the progression of GEV was observed after achieving an SVR. This study was conducted with the approval of our institutional ethics committee (No. 3431).

*Statistical analyses.* For quantitative variables, the patient data are shown as the median value [interquartile range (IQR)], and statistical differences between the groups were assessed using the Mann-Whitney *U*-test. For categorical data, the statistical differences were evaluated using Pearson's chi-squared test. Using the Kaplan-Meier method, we generated curves for cumulative GEV progression, and the clinical courses of the groups were compared using the log-rank test. *p* Values of $<0.05$ were considered to indicate statistical significance. All statistical analyses were conducted using JMP Pro 17 (SAS Institute Inc., Cary, NC, USA).

## Results

*Basic characteristics of the studied cases and overall rate of GEV progression.* As described in the 'Patients and Methods' section, we added one patient with a DAA-SVR to the cases in the previous report and conducted long-term observation of the clinical courses. Basic data of the analyzed 109 cases are shown in Table I, and the characteristics of the non-SVR group (n=71) and the DAA-SVR group (n=38) are shown in Table II. The prothrombin time (%) was different between the two groups. The rates of GEV progression at 1, 3, 5, and 7 years were 8.7%, 32.8%, 45.6%, and 66.2%, respectively (Figure 1).

*Progression of GEV in the DAA-SVR and Non-SVR groups.* At 3 years, the rates of GEV progression in the DAA-SVR and non-SVR groups were similar (cumulative GEV progression rate: 31.39% *vs.* 33.76%, $p=0.7978$). However, beyond 3 years, cases with GEV progression were found in the non-SVR group, but not in the DAA-SVR group, and the rate of GEV progression in the DAA-SVR group was lower than that in the non-SVR group at 7 years (Figure 2).

Variceal hemorrhage, which is the most important clinical event in relation to the progression of GEV, occurred in eight patients in the non-SVR group, while no bleeding events were observed in the DAA-SVR group during the observational period [8/71 (11.3%) *vs.* 0/38 (0.0%), $p<0.05$] (Figure 3).

Table II. *Characteristics of the patients in the direct-acting antivirals (DAA)- sustained viral response (SVR) and Non-SVR groups.*

| | DAA-SVR (n=38) | Non-SVR (n=71) | *p*-Value |
|---|---|---|---|
| Age (years) | 68.5 (63.5-70.5) | 66 (62-71) | 0.3558 |
| Sex (Male/Female) | 16/22 | 41/30 | 0.1192 |
| Child-Pugh grade (A/B/C) | 22/16/0 | 46/24/1 | 0.5519 |
| AST (U/l) | 56.5 (42.25-79.25) | 63 (43-93) | 0.1956 |
| ALT (U/l) | 41 (28.75-75.5) | 54 (32-85) | 0.1384 |
| Total bilirubin (mg/dl) | 1.1 (0.8-1.4) | 1.0 (0.7-1.5) | 0.455 |
| Albumin (g/dl) | 3.5 (3.3-3.9) | 3.8 (3.3-4.0) | 0.2359 |
| Platelet count ($\times 10^3/\mu l$) | 75.0 (54.3-104.5) | 72.0 (58-92) | 0.5606 |
| Prothrombin time (%) | 71.25 (65.3-76.2) | 78.8 (71.2-87.0) | 0.0002 |
| Esophageal varices (F3/2/1/ND) | 0/4/33/1 | 0/9/59/3 | 0.8571 |
| Gastric varices (F3/2/1/ND) | 0/2/11/25 | 1/5/16/49 | 0.7756 |

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; ND: not determined.

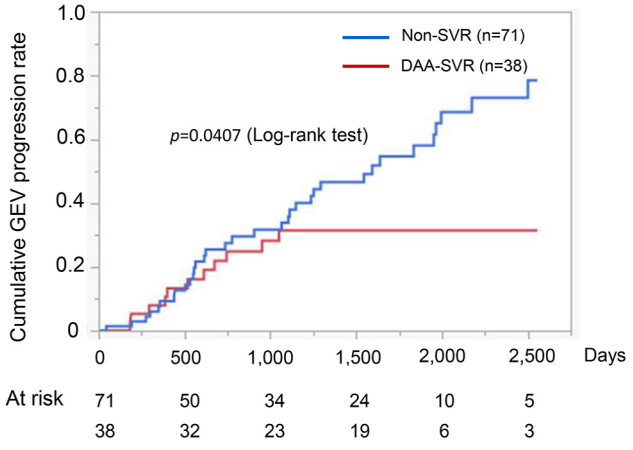


Figure 2. *The rate of gastroesophageal varices (GEV) progression at 7 years in the non-SVR and DAA-SVR groups. The rate of GEV progression in the DAA-SVR group is lower than that in the non-SVR group (log-rank test, p=0.0407).*

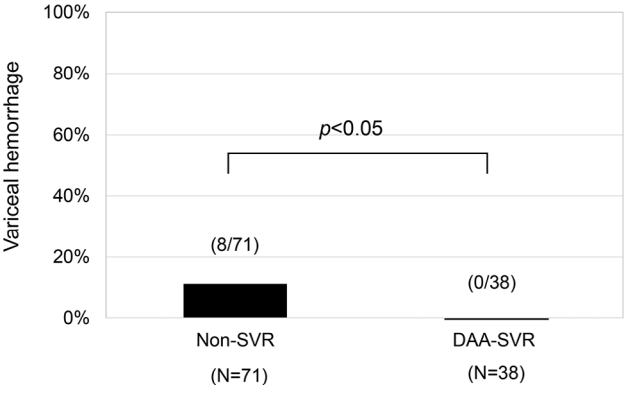


Figure 3. *Gastroesophageal varices (GEV) bleeding at 7 years. Bleeding was observed in eight patients in the non-SVR group, while none of the patients in the DAA-SVR group developed variceal hemorrhage.*

## Discussion

The development of GEV is a clinically important complication in patients with cirrhosis. HCV elimination with IFN treatment has been reported to reduce liver-related complications, including the progression of GEV (16-19). Currently, DAA is the mainstay of anti-HCV therapy (20), and HCV elimination with DAA therapy has been shown to reduce liver-related events (21). However, there are few reports on the clinical course of GEV after an SVR with DAAs. In particular, the long-term effect of an SVR with DAAs on the course of GEV is not clear, as DAA treatments have been available since the mid-2010s. In the present study, we report the long-term effects of an SVR with DAAs on GEV in Japanese patients.

We previously investigated the impact of eliminating HCV in patients with GEV and found that those who achieved an SVR through IFN treatment had a lower likelihood of GEV progression (15). It is known that portal hypertension does not improve (or even progresses) in some patients after HCV-elimination, and some previous studies have explored factors that predict the worsening of portal hypertension (14, 22-26). In the present study, no exacerbation beyond 3 years was observed in the DAA-SVR group, whereas exacerbation beyond 3 years was observed in the non-SVR group. Our results suggest that the rate of GEV exacerbation could be suppressed over a long-term clinical course by the achievement of an SVR with DAA therapy.

Moon *et al*. (27) investigated a large number of HCV-infected patients and reported that hemorrhage of GEV was suppressed after an SVR with DAA therapy. Recently, Hsieh *et al*. (28) reported that the exacerbation of GEV could be suppressed after an SVR with DAA therapy, even during a

relatively short observational period. Our study did not show a favorable short-term effect; however, a difference was observed with long-term observation. This difference may have depended on the characteristics of the studied cases. Their study included patients with F0 or F1 GEV. In contrast, our DAA group included patients with F2 or F3 GEV. Some studies suggest that clinically significant portal hypertension is present after an SVR (29-31), and the timing at which the effect of DAA therapy becomes apparent would vary depending on the patient's characteristics. Careful attention should be paid to interpreting the results of the changes in portal hypertension, including the endoscopic findings of GEV, after a patient achieves an SVR.

The present study is associated with several limitations. First, this was a retrospective, single-center analysis. Second, the number of patients is limited. Third, we did not determine the factors that could predict progression of GEV.

In summary, our results suggest that DAA treatment suppresses the progression of GEV up to seven years after HCV treatment using DAAs. A future study with a larger number of patients to confirm our long-term observations.

## Funding

This research received no external funding.

## Conflicts of Interest

The Authors have no conflicts of interest in relation to the present study.

## Authors' Contributions

Study design: Y.Y. and H.E. Data acquisition: Y.Y., T.N., N.I., T. T., N.A, T.K., K.Y., R.Y., S.K., Y. K., R.N., H.S. and H.E. Data analyses: Y.Y., T. N., S.S. and H.E. Writing and editing the first draft of the manuscript: Y.Y., S.S and H.E. The final version of the manuscript was approved by all the Authors.

## Acknowledgements

The Authors thank Kanazawa N, Kiriyama H, Fujii S, Nagumo E, Mega Y, Kido H, and Shimoji Y (Hyogo Medical University) for technical and secretarial assistance.

## References

1 Shung DL, Laine L: Review article: Upper gastrointestinal bleeding - review of current evidence and implications for management. Aliment Pharmacol Ther 59(9): 1062-1081, 2024. DOI: 10.1111/apt.17949

2 Tapper EB, Parikh ND: Diagnosis and management of cirrhosis and its complications: a review. JAMA 329(18): 1589-1602, 2023. DOI: 10.1001/jama.2023.5997

3 Garcia-Tsao G, Abraldes JG, Rich NE, Wong VW: AGA clinical practice update on the use of vasoactive drugs and intravenous albumin in cirrhosis: expert review. Gastroenterology 166(1): 202-210, 2024. DOI: 10.1053/j.gastro.2023.10.016

4 Yoshiji H, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, Kawaguchi T, Kurosaki M, Sakaida I, Shimizu M, Taniai M, Terai S, Nishikawa H, Hiasa Y, Hidaka H, Miwa H, Chayama K, Enomoto N, Shimosegawa T, Takehara T, Koike K: Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. J Gastroenterol 56(7): 593-619, 2021. DOI: 10.1007/s00535-021-01788-x

5 Inoue-Yuri M, Enomoto H, Wakabayashi I, Yuri Y, Aizawa N, Ikeda N, Takashima T, Fujiwara A, Yoshioka R, Kawata S, Yoshihara K, Ota S, Nakano R, Shiomi H, Nishimura T, Nishiguchi S, Iijima H: Modification of the ALBI-PLT score for the prediction of high-risk varices. In Vivo 36(3): 1360-1366, 2022. DOI: 10.21873/invivo.12839

6 Luo X, Hernández-Gea V: Update on the management of gastric varices. Liver Int 42(6): 1250-1258, 2022. DOI: 10.1111/liv.15181

7 Enomoto H, Akuta N, Hikita H, Suda G, Inoue J, Tamaki N, Ito K, Akahane T, Kawaoka T, Morishita A, Ogawa E, Tateishi R, Yoshiji H: Etiological changes of liver cirrhosis and hepatocellular carcinoma-complicated liver cirrhosis in Japan: Updated nationwide survey from 2018 to 2021. Hepatol Res 54(8): 763-772, 2024. DOI: 10.1111/hepr.14047

8 Droc G, Istrate M, Mercan-Stanciu A, Dodot M, Isac T, Toma L, Zgura A, Trifan A, Serbanica AN, Iliescu L, Micu L: Safety and efficacy of direct-acting antiviral therapies for chronic HCV infection in hemodialysis patients. In Vivo 36(6): 2918-2922, 2022. DOI: 10.21873/invivo.13033

9 Harimoto N, Itoh S, Yamanaka T, Hagiwara K, Ishii N, Tsukagoshi M, Watanabe A, Araki K, Yoshizumi T, Shirabe K: Mac-2 binding protein glycosylation isomer as a prognostic marker for hepatocellular carcinoma with sustained virological response. Anticancer Res 42(1): 245-251, 2022. DOI: 10.21873/anticanres.15479

10 Cooke GS, Flower B, Cunningham E, Marshall AD, Lazarus JV, Palayew A, Jia J, Aggarwal R, Al-Mahtab M, Tanaka Y, Jeong SH, Poovorawan K, Waked I, Hiebert L, Khue PM, Grebely J, Alcantara-Payawal D, Sanchez-Avila JF, Mbendi C, Muljono DH, Lesi O, Desalegn H, Hamid S, de Araujo A, Cheinquer H, Onyekwere CA, Malyuta R, Ivanchuk I, Thomas DL, Pimenov N, Chulanov V, Dirac MA, Han H, Ward JW: Progress towards elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission update. Lancet Gastroenterol Hepatol 9(4): 346-365, 2024. DOI: 10.1016/S2468-1253(23)00321-7

11 D'Ambrosio R, Degasperi E, Anolli MP, Fanetti I, Borghi M, Soffredini R, Iavarone M, Tosetti G, Perbellini R, Sangiovanni A, Sypsa V, Lampertico P: Incidence of liver- and non-liver-related outcomes in patients with HCV-cirrhosis after SVR. J Hepatol 76(2): 302-310, 2022. DOI: 10.1016/j.jhep.2021.09.013

12 Enomoto H, Takashima T, Nishimura T, Aizawa N, Ikeda N, Yuri Y, Okamoto M, Yoshihara K, Yoshioka R, Kawata S, Ota S, Nakano R, Shiomi H, Iijima H: Liver cirrhosis in Japan: Future global trends in the era of progressive antiviral therapy. Port Hypertens Cirrhos 1(3): 178-183, 2022. DOI: 10.1002/poh2.30

13 Hamill V, Wong S, Benselin J, Krajden M, Hayes PC, Mutimer D, Yu A, Dillon JF, Gelson W, Velásquez García HA, Yeung A, Johnson P, Barclay ST, Alvarez M, Toyoda H, Agarwal K, Fraser A, Bartlett S, Aldersley M, Bathgate A, Binka M, Richardson P, Morling JR, Ryder SD, MacDonald D, Hutchinson S, Barnes E, Guha IN, Irving WL, Janjua NZ, Innes H: Mortality rates among patients successfully treated for hepatitis C in the era of interferon-free antivirals: population based cohort study. BMJ 382: e074001, 2023. DOI: 10.1136/bmj-2022-074001

14 Lynch EN, Russo FP: Outcomes and follow-up after Hepatitis C eradication with direct-acting antivirals. J Clin Med 12(6): 2195, 2023. DOI: 10.3390/jcm12062195
15 Yuri Y, Nishikawa H, Enomoto H, Yoh K, Iwata Y, Sakai Y, Kishino K, Ikeda N, Takashima T, Aizawa N, Takata R, Hasegawa K, Ishii N, Nishimura T, Iijima H, Nishiguchi S: Impact of sustained virological response for gastroesophageal varices in Hepatitis-C-virus-related liver cirrhosis. J Clin Med 9(1): 95, 2019. DOI: 10.3390/jcm9010095
16 Fernández-Rodríguez CM, Alonso S, Martinez SM, Forns X, Sanchez-Tapias JM, Rincón D, Rodriguez-Caravaca G, Bárcena R, Serra MA, Romero-Gómez M, Fernandez I, Garcia-Samaniego J, Fuente J, Solá R, Moreno-Otero R, Planas R, Group for the Assessment of Prevention of Cirrhosis Complications and Virological Response (APREVIR): Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: Outcomes and factors predicting response. Am J Gastroenterol 105(10): 2164-2172, 2010. DOI: 10.1038/ajg.2010.294
17 Kwok RM, Tran TT: Management of cirrhotic patients after successful HCV eradication. Curr Treat Options Gastroenterol 15(2): 305-315, 2017. DOI: 10.1007/s11938-017-0134-2
18 Di Marco V, Calvaruso V, Ferraro D, Bavetta MG, Cabibbo G, Conte E, Cammà C, Grimaudo S, Pipitone RM, Simone F, Peralta S, Arini A, Craxì A: Effects of eradicating Hepatitis C virus infection in patients with cirrhosis differ with stage of portal hypertension. Gastroenterology 151(1): 130-139.e2, 2016. DOI: 10.1053/j.gastro.2016.03.036
19 Smith-Palmer J, Cerri K, Valentine W: Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits. BMC Infect Dis 15: 19, 2015. DOI: 10.1186/s12879-015-0748-8
20 Vieira R, Caldas C, Carvalho JA, Costa E, Magalhaes TR, Queiroga FL: HCV core-antigen assay as an effective alternative to HCV RNA quantification in patients with Hepatitis C. In Vivo 37(4): 1498-1503, 2023. DOI: 10.21873/invivo.13234
21 Hanafy AS, Bassiony MA, Basha MAA: Management of HCV-related decompensated cirrhosis with direct-acting antiviral agents: who should be treated? Hepatol Int 13(2): 165-172, 2019. DOI: 10.1007/s12072-019-09933-8
22 Calvaruso V, Celsa C, D'Ambrosio R, Simone F, Petta S, Cacciola I, Enea M, Battaglia S, Pandolfo A, Licata M, Degasperi E, Cabibbo G, Di Marco L, Pennisi G, Borghi M, Di Martino V, Filomia R, Abdel-Hadi Y, Crapanzano L, Raimondo G, Lampertico P, Craxì A, Cammà C, Di Marco V: RESIST-HCV criteria to monitor progression of low-risk esophageal varices in patients with compensated cirrhosis after HCV eradication: The SIMPLE study. Am J Gastroenterol 117(11): 1816-1824, 2022. DOI: 10.14309/ajg.0000000000001878
23 Iwai S, Akahane T, Takaya H, Kubo T, Tomooka F, Shibamoto A, Suzuki J, Tsuji Y, Fujinaga Y, Nishimura N, Kitagawa K, Kaji K, Kawaratani H, Namisaki T, Matsumoto M, Yoshiji H: Ratio of von Willebrand factor to ADAMTS13 is a useful predictor of esophagogastric varices progression after sustained virologic response in patients with hepatitis C virus-related liver cirrhosis. Hepatol Res, 2024. DOI: 10.1111/hepr.14077
24 Bauer D, Kozbial K, Schwabl P, Chromy D, Simbrunner B, Stättermayer AF, Pinter M, Steindl-Munda P, Trauner M, Ferenci P, Reiberger T, Mandorfer M: Angiopoietin 2 levels decrease after HCV-cure and reflect the evolution of portal hypertension. Dig Liver Dis 54(9): 1222-1229, 2022. DOI: 10.1016/j.dld.2022.02.013
25 Cerrito L, Ainora ME, Nicoletti A, Garcovich M, Riccardi L, Pompili M, Gasbarrini A, Zocco MA: Elastography as a predictor of liver cirrhosis complications after hepatitis C virus eradication in the era of direct-acting antivirals. World J Hepatol 13(11): 1663-1676, 2021. DOI: 10.4254/wjh.v13.i11.1663
26 Ibrahim ES, Abdel-Samiee M, Youssef MI, El-Shazly H, A El-Gendy AE, Sakr AA, Elwazzan D, Nassar MR, Aly Elshormilisy A, Madkour A, Kamal M, Amrousy YM, Elkhadry SW, Abdelsameea E: Variceal recurrence 4 years post endoscopic band ligation in hepatitis C patients who achieved sustained virological response with oral direct-acting antiviral therapy. J Viral Hepat 28(2): 279-287, 2021. DOI: 10.1111/jvh.13426
27 Moon AM, Green PK, Rockey DC, Berry K, Ioannou GN: Hepatitis C eradication with direct-acting anti-virals reduces the risk of variceal bleeding. Aliment Pharmacol Ther 51(3): 364-373, 2020. DOI: 10.1111/apt.15586
28 Hsieh YY, Chen WM, Chang KC, Chang TS, Hung CH, Yang YH, Tung SY, Wei KL, Shen CH, Wu CS, Ding YJ, Hu JH, Huang YT, Lin MH, Lu CK, Lin YH, Lin MS: Direct-acting antivirals reduce the *de novo* development of esophageal varices in patients with Hepatitis C virus related liver cirrhosis. Viruses 15(1): 252, 2023. DOI: 10.3390/v15010252
29 Uchida Y, Imai Y, Tsuji S, Uemura H, Kouyama JI, Naiki K, Ando S, Sugawara K, Nakao M, Nakayama N, Mizuno S, Tomiya T, Mochida S: Significance of portal venous blood flow as a factor to determine liver function in patients with decompensated cirrhosis due to hepatitis C virus infection following achievement of sustained viral response by sofosbuvir plus velpatasvir. Hepatol Res 53(9): 815-828, 2023. DOI: 10.1111/hepr.13926
30 Díez C, Berenguer J, Ibañez-Samaniego L, Llop E, Pérez-Latorre L, Catalina MV, Hontañón V, Jiménez-Sousa MA, Aldámiz-Echevarría T, Martínez J, Calleja JL, Albillos A, Bellón JM, Resino S, González-García J, Bañares R: Persistence of clinically significant portal hypertension after eradication of hepatitis c virus in patients with advanced cirrhosis. Clin Infect Dis 71(10): 2726-2729, 2020. DOI: 10.1093/cid/ciaa502
31 Semmler G, Lens S, Meyer EL, Baiges A, Alvardo-Tapias E, Llop E, Tellez L, Schwabl P, Mauro E, Escudé L, Díez C, Ibañez-Samaniego L, Puente Á, Fortea JI, Abadía M, Zanetto A, Conthe A, Hernandez-Évole H, Luzko Scheid IS, Jia J, Yoshiji H, Francque SM, Tsochatzis EA, Russo FP, Crespo G, Forns X, Bañares R, Villanueva C, Hernández-Gea V, Reiberger T, Bosch J, García Pagán JC, Mandorfer M, A study by the Baveno Cooperation: an EASL consortium: Non-invasive tests for clinically significant portal hypertension after HCV cure. J Hepatol 77(6): 1573-1585, 2022. DOI: 10.1016/j.jhep.2022.08.025

*Received August 15, 2024*
*Revised September 3, 2024*
*Accepted September 4, 2024*