

FIB-4 VALUE BEFORE DAA THERAPY AS A PREDICTOR OF ESOPHAGEAL VARICES PROGRESSION AFTER SVR12 WITH DAA THERAPY

Attique Abou Bakr,¹ Amtiaz Ahmad,² Tayyab Shahzad,³ Madeeha Akram,⁴
Fawad Iqbal Janjua⁵

Abstract

Background and Objective: The objectives of this study were to assess the effect that direct-acting antivirals (DAAs) have on portal hypertension once a sustained viral response (SVR) has been achieved. Therefore, it is important to look at economical and noninvasive predictors. We looked into the factors that contributed to the emergence of EVs in hepatitis C infected patients after SVR with DAAs.

Methods: It was an Open-Label Single-Arm clinical trial conducted at department of Gastroenterology, AIMC/ Jinnah Hospital, Lahore during the period of 3 years and 4 months (from June 2017 to October 2020). Total of 99 patients who attained SVR post DAA therapy were enrolled in this study and their pre- and post-treatment esophagogastroduodenoscopy (EGD) findings were compared. EV progression and non-progression were assessed. Additionally, EV cumulative advancement rates were examined.

Results: Before DAA treatment, the fibrosis-4 index (FIB-4) was the only substantial predictor of EVs progression after SVR (95% confidence intervals: 1.25-1.54, odds ratios: 1.45, $p = 0.02$). Based on ROC curve analysis, patients with a FIB-4 of 8.5 or higher had a higher risk of EVs (sensitivity = 0.69, specificity = 0.91, positive predictive value = 0.36, negative predictive value = 0.98).

Conclusion: EV development is possible in patients with $FIB-4 \geq 8.5$, so EGD surveillance should continue after SVR.

Keywords: Hepatitis C, EV, Esophageal varices, Direct acting antivirals, Sustained viral response, FIB-4, .

How to cite: Abou Bakr A, Ahmad A, Shahzad T, Akram M, Janjua FI. FIB-4 value before DAA Therapy as a Predictor of Esophageal Varices Progression after SVR12 with DAA Therapy. JAIMC 2023 21(3): 134-139

Patients with chronic hepatitis C are now given direct-acting antivirals (DAAs) as their first line of treatment all over the world. Sofosbuvir/daclatasvir (SOF/DAC) and sofosbuvir/velpatasvir (SOF/VEL) are the most commonly prescribed drugs for hepatitis C infection in Pakistan, with eradication rate exceeding 90%. Additionally, SOF/VEL is thought to be extremely successful in the treatment of decompensated cirrhosis. SOF/VEL therapy with ribavirin was efficacious even

in patients previously treated with DAAs but had encountered virological failure.¹⁻⁴ Hepatic venous pressure gradient (HVPG) is a standard method of determining portal hypertension. After achieving SVR, HVPG of these patients decreased significantly over time.

Nevertheless, it was also demonstrated that most patients still had clinically significant portal hypertension (CSPH) even after achieving SVR and this fact poses a lingering risk of decompensation and death.⁵⁻⁸ Because of the high risk of internal bleeding, presence of esophageal varices (EVs) is among the major causes of mortality in these individuals.⁹ The Baveno VI guidelines endorse eluding endoscopic surveillance of EVs in patients with platelet counts of $>150 \times 10^9/L$ and liver stiffness values of 20 kPa, while the expanded-Baveno VI guidelines suggest the same for patients with platelet counts of $110 \times 10^9/L$ and liver stiffness

1-4. Department of Gastroenterology, Allama Iqbal Medical College Lahore

5. Department of Gastroenterology Gujranwala Medical College

Correspondence:

Dr. Attique Abou Bakr ; Assistant Professor of Gastroenterology;
Allama Iqbal Medical College Lahore.
Email: doctorattique07@yahoo.com

Submission Date: 16-01-2023

1st Revision Date: 04-06-2023

Acceptance Date: 08-07-2023

values 25 kPa.^{10,11} However, there are not many facilities that offer transient elastography. While DAAs have successfully brought about SVR, what is driving EV advancement remains a mystery. In order to pinpoint the variables that influenced the development as well as regression of EVs following an SVR, the endoscopic findings, pre and post DAAs administration were compared.

METHODS

The duration of study was 3 years and 4 months (from June 2017 to October 2020). 99 of the 119 patients who received DAAs by October 2020 from June 2017 and fulfilled the criteria of this trial were enrolled (Figure 1). Twenty participants were excluded from the research as their endoscopic findings following DAAs had been studied prior to achieving SVR. No patient ever had treatment for varices prior to starting DAAs. They didn't have any co-morbid conditions including hemochromatosis, NASH, alcohol liver disease, portal vein thrombosis, PBC, Wilson's disease, PSC, HIV, or HBV. EVs were morphologically categorized into four classes in accordance with Japanese guidelines (none, F1, F2, and F3).¹² In general, EVs were evaluated by EGD every 6 months. New varices, growth of existing varices, emergence of red colour sign, and EV rupture were indicators of EV progression. Also, a decrease in the number of EVs was assumed as an improvement of EVs. The time between the final day of DAA administration and the initial EGD confirmation of EV progression or the final follow-up EGD was referred to as the observation period.

The baseline information included demographics like age, gender, the time between the most recent EGD and the start of DAA treatment, the kind of DAAs used, and laboratory values including platelet count, LFT and HCV-RNA levels. A measure of liver fibrosis called the fibrosis-4 index (FIB-4) is based on age, platelet count, AST, platelet and ALT^{1/2}. SVR12 was defined as the absence of detectable serum HCV-RNA by PCR at 12 weeks after the end of DAA therapy. The institutional review board gave approval. The Mann-Whitney U test was utilized to analyze

nonparametric, unpaired quantitative variables expressed as the median. Categorical variables were evaluated using Fisher's exact test. The receiver operating characteristic analysis was utilized to define the cut-off of the continuous variable. After constructing a cumulative incidence curve, Gray's test was used to determine whether or not there were significant differences between the two groups. Multivariate logistic regression analysis was done. SPSS 22 analyzed all data.^{13,14}

RESULTS

The time between the latest EGD and the commencement of DAA administration was 112 (45–189) Days. (Table 1). The study's sample size composed of 51 males and 48 females. The median age was 52 years. (34–70). Liver cirrhosis was detected in 46 individuals (46.46%). Among them, two patients of decompensated cirrhosis were treated with SOF/VEL. Prior to the commencement of DAAs, patients had undergone endoscopy: 66 patients (66.66%) had no EVs, 28 patients (28.28%) had F1 and 4 patients (4.04%) F2 EVs. One patient had F3 EV. Five patients (5.05%) had progression of varices from none to F1 (Table 2) (Figure 2), whereas three patients (3.03%) had progression from F1 to F2 and one patient (1.01%) had progression from none to F2 during the observation period, leaving 90 patients (90.9%) with no change in varices (Figure 3). There was no documented variceal rupture. Between the patients with and without EV advancement, there were no discernible variations in the age, sex, observation time, ALT, AST, Platelet counts, HCV-RNA levels, severity of liver cirrhosis, grade of EVs, or the DAA regimens. Only the FIB-4 was found to be a considerable predictor of the evolution of EVs in a univariate study ($p = 0.02$) as well as in multivariate analysis (odds ratios: 1.45, 95% confidence intervals: 1.25–1.54, $p = 0.02$). The FIB-4 cut-off for the progression of EVs in the ROC analysis was 8.5. (Sensitivity: 0.69, specificity: 0.91). It has a positive predictive value: 0.36, negative predictive value: 0.98, and diagnostic accuracy was 0.85. AUC was 0.77 (95% confidence

interval: 0.60-0.94). (Figure 3).

Table 1: Patient characteristics prior to receiving direct-acting antiviral therapy in the current study (DAAs).

Variables	Total cases (n = 99)
Age (years)	52 (34-70)
Gender, n (%)	Male 51 (51.5%), Female 48 (48.5%)
Platelet count ($\times 10^9$ /L)	122 (86-159)
ALT (IU/L)	48 (39-71)
AST (IU/L)	39 (32-64)
FIB-4	4.81 (3.14-7.22)
Liver cirrhosis, n (%)	46 (46.46%)
HCV-RNA (log IU/ml)	6.2 (5.1-7.8)
EVs,	
none	66(66.6%)
F1	28(28.28%)
F2	4(4.04%)
F3	1(1.01%)
The interval from the latest EGD before DAAs to the start of DAAs (days)	112 (45-189)
DAAs regimen, n (%)	
Sofosbuvir/Daclatasvir	52 (52.52)
Sofosbuvir/Ribavirin	16 (16.16)
Sofosbuvir/Velpatasvir	31 (31.32)

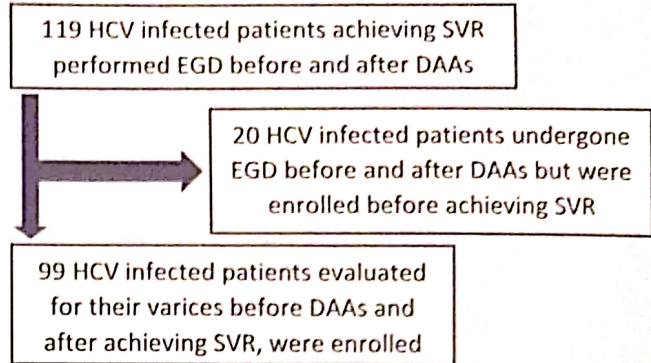


Figure 1: The flow-Chart of Participants

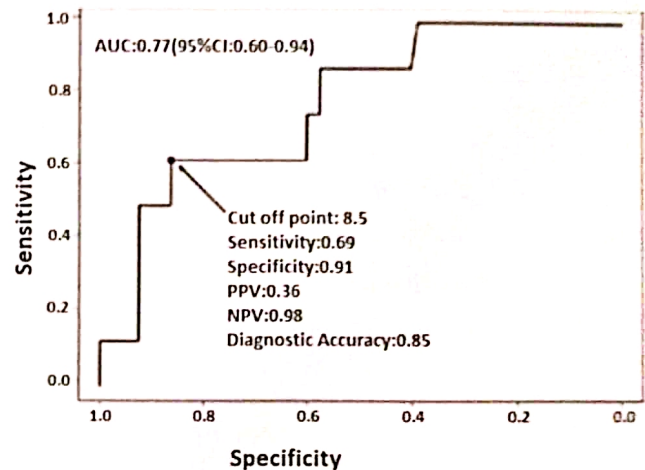


Figure 2: A Cutoff of FIB-4 for the Development of Esophageal Varices after a SVR was Determined using ROC. FIB-4's Optimal Cutoff was 8.5%

Table 2: The factors related with progression of Esophageal Varices (EV) after SVR (n=99)

Variable	EVs progression (-) (n = 90)	EVs progression(+) (n = 90)	Univariate analysis p value	Multivariate analysis Odds ratio P value	
Age (years)	52 (36-70)	72(31-68)	0.40		
Male, n (%)	46 (46.46%)	5 (55.5)	0.90		
Platelet count ($\times 10^9$ /L)	126 (92-157)	94 (61-125)	0.08		
ALT (IU/L)	47 (35-66)	49(41-69)	0.08		
AST (IU/L)	37 (28-52)	47 (41-68)	0.13		
FIB-4	4.49(3.24-6.68)	9.93 (5.1-11.8)	0.02	1.45	0.02
Liver cirrhosis	40 (44.4%)	6.3 (5.9-6.4)	0.40		
HCV-RNA (log IU/ml)	6.2 (5.5-6.3)	6.5 (5.1-6.9)	0.46		
EVs					
none	61 (67.77%)	5 (55.5)			
F1	25 (27.7%)	3 (33.3)			
F2	3(3.3)	1(11.1)	0.78		
F3	1(1.1%)	0(0%)			
Observation period (days)	288 (207-690)	409.5 (223.8-573)	0.78		
DAAs					
Sofosbuvir/Daclatasvir	47(52.22%)	5 (5.55%)			
Sofosbuvir/Ribavirin	15 (16.66%)	1(11.1)	0.78		
Sofosbuvir/Velpatasvir	28 (31.11%)	3 (33.3)			

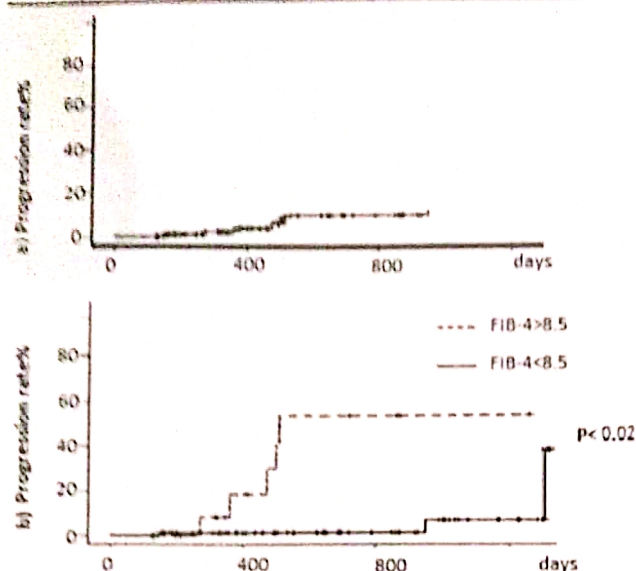


Figure 3: (a) The cumulative rates of progression of esophageal varices (EVs) in all patients following SVR. (b) The overall rates at which EVs have advanced since being classified using the FIB-4 cutoff value. The cumulative progression rates of EVs were 2.6%, 10.0%, and 14.5%, respectively, at 1, 2, and 3 years (a). Patients with FIB-4 ≥ 8.5 revealed a significant statistical difference in the cumulative EVs progression rates compared to those with FIB-4 < 8.5. ($p = 0.02$) (b)

The cumulative EVs progression rates in patients with FIB-4 < 8.5 were 2.6%, 10.0%, and 14.5%, respectively, at 1, 2, and 3 years at that time (Figure 5a). In patients with FIB-4 ≥ 8.5 , the cumulative progression rates of EVs at 1, 2, and 3 years were 8.2%, 51.4%, and 58.4%, respectively. Patients with a FIB-4 < 8.5 had significantly slower cumulative EV progression rates than those with FIB-4 ≥ 8.5 . ($P = 0.02$). In 33 individuals who had EVs before receiving DAAs, the factors associated with their advancement were investigated (Table 3). As previously indicated, six patients (18.18% of the 33 studied) shown an improvement in their EVs during the course of the observation period. Regarding age, sex, duration of observation, ALT, AST, platelet counts, HCV-RNA levels, FIB-4, DAAs regimen, or grade of EVs, the patients with and without EV improvement did not differ substantially from one another (Table 3). Of the six participants whose EVs improved throughout the course of the monitoring period, three had taken beta-blockers and one had taken an angio-

genic receptor blocker (ARB). However, just one patient had advanced EV and was given an ARB. Everyone here took these medicines to treat high blood pressure rather than high portal pressure.

DISCUSSION

This study examined the evolution of esophageal varices following the attainment of SVR after DAAs therapy and found that the FIB-4 cutoff value before DAA treatment had an excellent NPV for EV evolution. If before starting DAAs, FIB-4 is < 8.5 the frequency of endoscopic surveillance for varices can be decreased. At 1 and 3 years after attaining SVR, the cumulative varices progression rates were 8.21% and 32.3%, respectively, according to one study¹⁵. Despite the fact that these values were greater than in our study, this may have been attributable to patient background variations. Prior to receiving DAAs, all 37 patients were cirrhotic in the earlier research with GEV, and 15 of them (40.5%) had decompensated cirrhosis. Contrarily, in our study, only 33 (33.33%) of the patients had EV diagnosed prior to receiving DAAs, despite the fact that 46 of the patients (46.46%) had liver cirrhosis. Furthermore, there were only two patients with advanced cirrhosis in our study. The data suggested that the lower values of cumulative progression rates of EVs in our study were due to the relatively limited number of individuals with advanced liver cirrhosis. In the previous study, the cumulative advancement rates of GEVs over 1 and 3 years in cases who had not achieved SVR were 9.2%, and 33.7% respectively.¹⁵ Their cumulative progression rates appeared to be much greater than those of our trial even after accounting for the participants' various backgrounds, demonstrating the efficiency of achieving SVR for inhibiting EVs progression.

Additionally, it was found that patients with low grade varices had much less variceal progression than individuals with high grade varices.¹⁵ In our analysis, the proportion of patients with F2 varices prior to DAA therapy was low, but five of 61 patients (8.2%) without EVs prior to DAA therapy had advanced EVs after establishing an SVR. F2 EVs before DAAs were

reduced in one patient (50%) after SVR. In this study, 12(24%) of 50 patients with small varices developed large varices after attaining SVR, while eight (12.5%) patients without baseline varices developed varices after achieving SVR.¹⁶ In light of these results, it is difficult to anticipate the progression of varices and CSPH after SVR, based solely on endoscopic judgments prior to the treatment of DAAs.

EVs may advance in cases with a FIB-4 ≥ 8.5 , which was the only significant predictor of their progression after obtaining SVR. In contrast, the opposite was found true in most of the people whose pre-treatment FIB-4 was <8.5 . The Baveno VI guidelines endorsed EGD surveillance and periodic testing for all cirrhotic patients at diagnosis.¹⁰ Routine Endoscopy survey, however, could be expensive considering that less than half of these patients had EVs.¹⁷ The existence of advance liver fibrosis was confirmed with a specificity $>95\%$ and a PPV of $>80\%$ for the FIB-4 > 3.25 .¹¹ Based on above, employing the FIB-4 for determining the frequency of endoscopy surveillance of EVs after SVR was fair in terms of reduced cost and decreased discomfort. Endoscopic inspections and medication reduce the bleeding-related mortality in these patients, hence EGD is performed more often than the required criteria. The FIB-4 is helpful at predicting EV occurrence but not EV rupture, according to Kraja et al.¹⁸ However, our findings demonstrate that in patients with a FIB-4 less than 8.5 before DAAs, EV evolution following the attainment of SVR is unusual. Thus, EGD surveillance may be reduced in these patients, particularly if no or low grade EVs present. Even after SVR, FIB-4 ≥ 8.5 individuals may develop CSPH, hence vigilant EGD surveillance is advised in such cases.

Six patients who had verified EVs before receiving DAA treatment showed regression in varices after SVR. However, none of the characteristics, including the FIB-4, were substantially correlated with the overall regression of varices. On the other hand, three patients whose EVs were improving and one patient whose EVs were progressing after SVR, respectively, had also been taking beta-blocker or ARB for some con-

current condition. Although the efficacy of these drugs for the treatment of high portal pressure is already proved,^{10,19} a large prospective randomized study would be required to test EVs in patients who got SVR. These drugs may be a suitable option for patients who had small EVs prior to DAAs therapy and these would help to limit EV progression after SVR.^{12,20}

In our study, the vast majority of participants had either no or very small EVs and had a good functional reserve of liver. Even in compensated cirrhosis with no EVs or small EVs, there may be "a point of no return" when HCV elimination no longer prevents CSPH development. This is due to the fact that in individuals with high FIB-4 levels, EVs had significantly progressed. Even after SVR, patients with decompensated cirrhosis can still have CSPH, hence vigilant endoscopic surveillance should be carried out in these situations as these patients would have little chance to have a reduction in HVP. The present study has some limitations, including the relatively small number of patients with high-grade EVs, its retrospective cohort design, no control groups, such as non-SVR cases, and the limited duration of monitoring. The comparatively prolonged interval between the most recent endoscopy and the DAAs treatment may have overrated EV development and underestimated EV healing. Therefore, a new comprehensive prospective trial will be necessary.

In conclusion, the FIB-4 measurement was proven to be valuable as a non-invasive, low-cost predictor for development of EVs.

Funding sources:

None

Conflict of interest:

None

REFERENCES

1. Chayama K, Suzuki F, Karino Y, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 1 hepatitis C virus infection with and without cirrhosis. *J Gastroenterol* 2018; 53: 557–65.
2. Toyoda H, Chayama K, Suzuki F, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. *Hepatology* 2018; 67: 505–13.

3. Curry MP, O'leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med* 2015; 373: 2618–28.
4. Gane EJ, Shiffman ML, Etzkorn K, et al. Sofosbuvir-velpatasvir with ribavirin for 24 weeks in hepatitis C virus patients previously treated with a direct-acting antiviral regimen. *Hepatology* 2017; 66: 1083–9.
5. Maruyama H, Kobayashi K, Kiyono S, et al. Incidence and hemodynamic feature of risky esophageal varices with lower hepatic venous pressure gradient. *Int J Med Sci* 2019; 16: 1614–20.
6. Afdhal N, Everson GT, Calleja JL, et al. Effect of viral suppression on hepatic venous pressure gradient in hepatitis C with cirrhosis and portal hypertension. *J Viral Hepat* 2017; 24: 823–31.
7. Lens S, Alvarado-Tapias E, Mariño Z, et al. Effects of all-oral anti-viral therapy on HVPg and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. *Gastroenterology* 2017; 153: 1273–83.e1.
8. Grgurevic I, Bozin T, Madir A. Hepatitis C is now curable, but what happens with cirrhosis and portal hypertension afterwards? *Clin Exp Hepatol* 2017; 4: 181–6.
9. D'ambrosio R, Aghemo A, Rumi MG, et al. The course of esophageal varices in patients with hepatitis C cirrhosis responding to interferon/ribavirin therapy. *Antiviral Ther* 2011; 16: 677–84.
10. De Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; 63: 743–52.
11. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology* 2017; 66: 1980–8.
12. The Japan Society for Portal Hypertension. The General Rules for Study of Portal Hypertension. 3rd edn. Tokyo: Kanehara, 2013.
13. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology* 2007; 46: 32–6.
14. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; 48: 452–8.
15. Yuri Y, Nishikawa H, Enomoto H, et al. Impact of sustained virological response for gastroesophageal varices in hepatitis-C-virus-related liver cirrhosis. *J Clin Med* 2019; 9: 95.
16. Puigvehi M, Londoño M-C, Torras X, et al. Impact of sustained virological response with DAAs on gastroesophageal varices and Baveno criteria in HCV-cirrhotic patients. *J Gastroenterol* 2020; 55: 205–16.
17. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD. Practice Guidelines Committee of American Association for Study of Liver Diseases, Practice Parameters Committee of American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhaging in cirrhosis. *Am J Gastroenterol* 2007; 102: 2086–102.
18. Kraja B, Mone I, Akshija I, Koçollari A, Prifti S, Burazeri G. Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients. *World J Gastroenterol* 2017; 23: 4806–14.
19. Tandon P, Abraldes JG, Berzigotti A, Garcia-Pagan JC, Bosch J. Renin-angiotensin-aldosterone inhibitors in the reduction of portal pressure: A systematic review and meta-analysis. *J Hepatol* 2010; 53: 273–82.
20. Ishikawa T, Sasaki R, Nishimura T, et al. A novel therapeutic strategy for esophageal varices using endoscopic treatment combined with splenic artery embolization according to the Child-Pugh classification. *PLoS One* 2019; 14: e0223153.
21. Mandorfer M, Kozbial K, Schwabl P, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. *J Hepatol* 2016; 65: 692–9.