The Association Between Hepatic Venous Pressure Gradient Baseline and the Response Rate of Carvedilol on Portal Hypertension

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Abstract

Objective: To assess the association between hepatic venous pressure gradient (HVPG) baseline and the response rate of cirrhotic in patients who received carvedilol treatment.

Methods: In total 48 cirrhotic patients with a basic HVPG value greater than 12 mmHg were included (from July 2011 to October 2014). All patients received carvedilol treatment and underwent the second HVPG measurement 7 days later. In the following, all participants received an endoscopic variceal ligation (EVL) treatment.

Results: HVPG was significantly reduced from 16.04 ± 3.10 to 12.76 ± 5.26 mmHg following carvedilol treatment. The response rate was about 58.33% (28/48). The response rate of the HVPG < 16 mmHg group (71.4%) was significantly higher than that of the HVPG ≥ 16 mmHg group (40%) (P < 0.05). Patients were followed up for a median of 26 months, ranged from 6 to 33 months. During the follow-up period (two years), the rebleeding rate was 9.97% and 49.56% in HVPG < 16 and HVPG ≥ 16 mmHg groups, respectively, with a statistically significant difference (P = 0.004). Also, the mortality rate (at 2 years) was 5.26% and 21.05%, respectively, which was significant (P = 0.035).

Conclusions: This study demonstrated that the response rate of carvedilol on portal hypertension may be affected by the HVPG baseline, and the carvedilol was effective in reducing HVPG, especially for those with a HVPG < 16 mmHg.

Keywords: Portal Hypertension, Hepatic Venous Pressure Gradient, Nonselective β-Blocker, Carvedilol, Response Rate

1. Background

Portal hypertension is a major complication of cirrhosis (1, 2). Esophageal varices is one of the most serious complications of portal hypertension. There is a high risk of esophageal varices bleeding, which a serious threat to the health of patients.

Hepatic venous pressure gradient (HVPG) is the international golden standard for evaluating portal vein pressure (3). In addition, it has been used as a prognostic marker of portal hypertension, particularly for the occurrence of bleeding from gastroesophageal varices (4-6). The risk of variceal bleeding depends on the degree of portal pressure. Patients with an HVPG below 10 - 12 mmHg rarely experience bleeding (7). Some studies reported that reducing the HVPG to below 12 mmHg or by ≥ 20% from baseline after treatment with the nonselective β-blocker (NSBB) is associated with declined risk of both bleeding and mortality (8, 9).

NSBB can decrease portal pressure, and a number of diagnoses and therapeutic guidelines recommended this technique as the first-line therapy for the prevention of gastroesophageal varices hemorrhage in cirrhosis (3). However, in up to 60% of patients, propranolol treatment does not result in reduced HVPG, which increases the risk of rebleeding (4, 10, 11). As a result, providers prefer other pharmacological treatments. Carvedilol is a nonselective β-blocker with intrinsic anti-α1-adrenergic activity. The effect of carvedilol on lowering portal pressure is influenced by β1, β2, and α1-blockade. β1-blockade reduces cardiac output, β2-blockade elicits splanchnic vasoconstriction, and α1-blockade reduces intrahepatic resistance (12). Banares et al. (13) reported that chronic carvedilol administration resulted in a hemodynamic response rate of 58% (number of responders to the total patients who receive drug treatment) compared to a 23% response rate in the propranolol group. Our literature review revealed that no study has evaluated the impact of the HVPG baseline on the response rate of carvedilol treatment.
2. Objectives

Hence, the present study intended to assess the association between HVPG baseline and the response rate of cirrhotic patients who received carvedilol treatment.

3. Methods

3.1. Selection of Patients

In this retrospective follow-up study, conducted from July 2011 to October 2014, 48 patients with cirrhotic portal hypertension who had an episode of esophageal and gastric varices bleeding were studied. All participants received at least 2 HVPG measurements. Esophageal and gastric varices bleeding was confirmed by endoscopy. Endoscopy showed signs of recent bleeding such as white nipple coating or blood clots on gastric varices in 29 (out of 48) patients. Besides, the presence of distinct and large esophageal gastric varices, as the source of the bleeding, was confirmed in 19 patients.

After initial HVPG measurement, all patients received carvedilol treatment. Initially, 12.5 mg oral carvedilol was administered daily. A second hemodynamic study was conducted 7 days later to assess response. Patients whose HVPG was reduced by more than 20% (or to less than 12 mmHg) were defined as responders. For all patients, bleeding was well controlled after drug therapy. Since our patients had a history of bleeding, all of them received EVL treatment following the secondary HVPG measurement. Demographic and clinical information of participants were collected. This study was approved by the local ethics committee, and informed written consent was obtained from all patients.

Patients with clinical and endoscopic signs of portal hypertension were evaluated for inclusion. Inclusion criteria were as follows: (1) Being aged 18 to 75 years; (2) A baseline HVPG of $\geq 12$ mmHg; (3) Having a history of esophageal and gastric varices bleeding during the past 6 months; (4) Signing the HVPG consent and NSBB clinical trial informed consent.

Exclusion criteria were (1) Being younger than 18 years or older than 75 years; (2) Child-Pugh score of $>12$; (3) Hepatorenal syndrome or serum-creatinine of $>2.26$ g/dL; (4) Receiving splenectomy, PSE, or EVL; (5) History of NSBB treatment; (6) NSBB contraindications; (7) treatment with blood transfusion or vasoactive drugs during the week before inclusion; (8) Suffering from major portal vein thrombosis; and (9) Malignancy or life expectancy less than 3 months.

3.2. Hemodynamic Investigations

Hemodynamic examinations were performed after an overnight fast. HVPG was measured by the methodology described by Groszmann and Wong Charatrawee (14) and Bosch et al. (15). A catheter was inserted percutaneously into the right hepatic vein through the femoral or jugular veins, and the pressure in both free and wedged positions was recorded with a 5-F balloon-tipped catheter. Standard criteria were applied to confirm an adequate wedging of the portal vein (14, 15). The HVPG was determined by subtracting the free hepatic venous pressure (FHVP) from the wedged hepatic venous pressure (WHVP). All measurements were repeated in triplicate, and their mean value was considered in each case. If the difference between the readings was greater than 1 mm Hg, a new reading was recorded.

3.3. Follow Up

After performing procedures, all participants were followed up at regular intervals of 1, 3, and 6 months, and then every 6-12 months. For each patient, a brief physical examination and medical history recording were performed, including estimation of ascites and HE.

3.4. Statistical Analysis

Continuous variables were reported as means $\pm$ SD or percentages. For variables that were normally distributed, the t-test was used for comparing groups. Nonparametric tests were used for variables that did not follow a normal distribution. Categorical data were compared using the $\chi^2$ test. The rebleeding rate and survival rate were examined by Kaplan-Meier estimation. The log-rank test was used to compare the differences between each curve. Cox analysis was employed to identify independent prognostic indicators for rebleeding and death. A two-sided P-value of $<0.05$ was considered statistically significant. Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

4. Results

4.1. The Predictive Value of Baseline HVPG for Drug Response

The ROC curve was used for predicting carvedilol drug response, and the area under the ROC curve (AUROC) of the HVPG baseline was 0.715 (95% CI: 0.571 - 0.859, $P = 0.012$) (Figure 1), which suggests that HVPG baseline can predict the responsiveness of carvedilol treatment, and the relatively optimized cut-off value of the HVPG baseline ranged from 15.75 to 16.50 mmHg.

4.2. Baseline Characteristics of Patients

As mentioned before, 48 patients were investigated in the present study, which their characteristics are provided in Table 1. Since the cut-off value ranged from 15.75 to 16.50
mmHg, we choose 16 mmHg as the cut-off value. We divided the patients into two groups according to their HVPG baseline [HVPG < 16 mmHg group (n = 28) and HVPG ≥ 16 mmHg group (n = 20)]. There were no significant differences between the two groups concerning baseline characteristics.

4.3. The Difference of HVPG Decreasing Effect and Response Rate Between Different HVPG Baseline Groups

At the end of the treatment period, the mean HVPG for the total population of 16.04 ± 3.10mmHg decreased to 12.76 ± 5.26 mmHg (decreased by 21.47 ± 25.02%), which was statistically significant (P < 0.001). The response rate was about 58.33% (28/48). In the HVPG < 16 mmHg group, the HVPG decreased significantly from 13.98 ± 1.22 to 10.31 ± 3.50 mmHg (decreased by 26.21 ± 24.37%; P < 0.001), the response rate was about 71.4% (20/28). In the HVPG ≥ 16 mmHg group, the HVPG also decreased significantly from 18.93 ± 2.58 to 16.18 ± 5.46 mmHg (decreased by 14.82 ± 25.00%; P < 0.001), the response rate was about 40.0% (8/20). The findings reveal that HVPG decreased more significantly in the HVPG < 16 mmHg group than in the HVPG ≥ 16 mmHg group (P = 0.029), the response rate of the HVPG < 16 mmHg group was significantly higher than that of the HVPG ≥ 16 mmHg group (P = 0.030) (Figures 2 and 3).

4.4. The Difference of HVPG Baseline Between Responders and Non-responders

In the present study, all 48 patients were categorized into two groups according to their responsiveness (named as responders group and non-responders group). We compared the HVPG baseline of the two groups. We found that the HVPG baseline of the responders group was lower than that of the non-responders group (14.88 ± 2.98 mmHg vs. 16.92 ± 2.15 mmHg, respectively), with statistical significance (P = 0.042).

4.5. The Effect of Other Relevant Factors on Responsiveness

The clinical characteristics of participants, separated by their group, are provided in Table 2. There was no significant difference between the two groups concerning the following factors.

4.6. Follow-Up Outcomes

All patients were followed up for a median of 26 months, ranging from 6 to 33 months. Among them, six were excluded, including two who were lost to follow-up, two who were due to drug intolerance, and two with poor compliance. Finally, 42 cases completed the clinical follow-up, that 10 (23.81%) experienced rebleeding, 7 (16.67%) died of gastrointestinal tract bleeding, and one (2.38%) died of hepatic failure. The outcomes of all participants, separated by HVPG baseline and hemodynamic response grouping, are provided in Table 3.

Figure 4 shows the rates of rebleeding and death in HVPG < 16 and HVPG ≥ 16mmHg groups, calculated using...
Table 1. Baseline Characteristics of all Patients

|                      | Overall (N = 48) | HVPG Baseline < 16 mmHg | HVPG Baseline ≥ 16 mmHg |
|----------------------|------------------|-------------------------|-------------------------|
| **Age (y)**          | 51.02 ± 10.84    | 50.57 ± 10.33           | 51.65 ± 11.76           |
| **Gender**           |                  |                         |                         |
| Male                 | 37 (77.1)        | 21 (75.0)               | 16 (80.0)               |
| Female               | 11 (22.9)        | 7 (25.0)                | 4 (20)                  |
| **Etiology**         |                  |                         |                         |
| HBV                  | 38 (79.2)        | 21 (75.0)               | 17 (85.0)               |
| Alcohol              | 4 (8.3)          | 3 (10.7)                | 1 (5.0)                 |
| Others               | 6 (12.5)         | 4 (14.3)                | 2 (10.0)                |
| **TBIL (mg/L)**      | 32.51 ± 25.24    | 29.71 ± 27.18           | 36.42 ± 23.70           |
| **ALT (IU/L)**       | 60.35 ± 100.82   | 55.89 ± 93.82           | 66.60 ± 112.10          |
| **AST (IU/L)**       | 54.72 ± 61.85    | 43.29 ± 22.20           | 49.40 ± 91.34           |
| **ALB (g/L)**        | 33.21 ± 10.85    | 33.11 ± 12.15           | 33.35 ± 9.02            |
| **Child-Pugh classification** |          |                         |                         |
| A                    | 24 (50.0)        | 14 (50.0)               | 10 (50.0)               |
| B                    | 17 (35.4)        | 10 (35.7)               | 7 (35.0)                |
| C                    | 7 (14.6)         | 4 (14.3)                | 3 (15.0)                |
| **Time interval between bleeding episode to 1st HVPG measurement (weeks)** | 13.54 ± 5.58 | 14.43 ± 5.42 | 12.30 ± 5.71 |
| **Ascites**          |                  |                         |                         |
| Yes                  | 24 (50.0)        | 12 (42.9)               | 12 (60.0)               |
| No                   | 24 (50.0)        | 16 (57.1)               | 8 (40.0)                |

4 Abbreviations: TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin.

5. Discussion

This study demonstrated that the mean HVPG for the total population decreased significantly following carvedilol treatment, which confirms the effectiveness of carvedilol in reducing portal vein pressure. This finding is consistent with previous studies. Our study was focused on patients with bleeding histories, which also provided information for carvedilol’s usage in secondary prophylaxis of gastroesophageal varices hemorrhage.

The impact of the HVPG baseline on the responsiveness of carvedilol treatment was not reported. The findings revealed that HVPG decreased more significantly in the HVPG < 16 mmHg group, while the response rate was also significantly higher. These findings suggest that carvedilol is more effective in mild and moderate portal hypertension patients (HVPG baseline < 16 mmHg) for lowering portal pressure. The results are consistent with the Baveno V consensus, which proposed that patients with small varices with red wale marks or Child C class should be treated with nonselective beta-blockers (NSBB) (5). While for severe portal hypertension patients, the response rate was
rather lower, which suggests the necessity of using NSBB in combination with other drugs or with endoscopic or interventional therapy.

NSBB, such as propranolol and nadolol, which are the mainstay of pharmacologic therapy (16-18), can achieve this goal in 20–30% of patients. However, it causes an increase in portocollateral and intrahepatic resistance, which may hinder the reduction in portal pressure induced by the decreased inflow of portal venous (19, 20). Carvedilol is a nonselective β-blocker with intrinsic anti-α1-adrenergic properties, as such, its effect mimics those of the combination therapy using propranolol and prazosin. It’s now generally considered as a promising alternative that needs further investigation (5). In our study, we used a dose of 12.5 mg/day carvedilol in accordance with the studies by Tripathi D (21), our results also support the hypothesis that the dose is effective.

As we all know, the only way to determine the efficacy of NSBB is HVPG measurement, and there is no noninvasive way to replace it still (22-24), and the poor feasibility has been used as a reason against HVPG monitoring. Nevertheless, HVPG has been convincingly shown as a strong predictor of variceal bleeding and survival. Our study showed that the response rate is deeply influenced by the HVPG baseline, which may provide a theoretical base for guiding clinical medication.

In summary, patients with a HVPG baseline below 16 mmHg are more likely to be responders than those with a HVPG baseline above 16 mmHg. Carvedilol is effective in reducing HVPG, patients with portal hypertension may benefit from treatment with carvedilol as add-on therapy with EVL, especially for those whose HVPG < 16 mmHg.

**Figure 3.** Response rate of carvedilol treatment according to different HVPG baseline groups (*P < 0.05).
Table 2. Comparison of Baseline Characteristics and Hemodynamic Features between Initial Hemodynamic Responders and Nonresponders to Drug Therapy

| Variable     | Responder Group (N = 28) | Non-Responder Group (N = 20) | P Value |
|--------------|--------------------------|-----------------------------|---------|
| Age (y)      | 51.79 ± 10.35            | 49.95 ± 11.69               | 0.441a  |
| Gender       |                          |                             |         |
| Male         | 23                       | 14                          |         |
| Female       | 5                        | 6                           |         |
| Etiology     |                          |                             | 0.241d  |
| Virus        | 21                       | 17                          |         |
| Alcohol      | 4                        | 0                           |         |
| Others       | 3                        | 3                           |         |
| TBIL (mg/dL) | 34.21 ± 29.11            | 30.12 ± 20.61               | 0.834b  |
| ALT (IU/L)   | 64.18 ± 94.97            | 55.00 ± 110.80              | 0.267b  |
| AST (IU/L)   | 50.93 ± 29.52            | 58.70 ± 90.49               | 0.579b  |
| ALB (g/L)    | 34.03 ± 9.87             | 32.05 ± 12.26               | 0.508a  |
| BUN (mmol/L) | 5.33 ± 2.21              | 5.64 ± 2.36                 | 0.741a  |
| SCr (µmol/L)| 77.38 ± 21.48            | 75.24 ± 18.22               | 0.304a  |
| Child-Pugh classification |          |                             | 0.232c  |
| A            | 12                       | 12                          |         |
| B            | 11                       | 6                           |         |
| C            | 5                        | 2                           |         |
| Ascites      |                          |                             | 1.000c  |
| Yes          | 14                       | 10                          |         |
| No           | 14                       | 10                          |         |

* Independent-samples t test
* Mann–Whitney test
* Chi-square test
* Fisher’s exact test

Table 3. Overall Rebleeding and Mortality During the Whole Follow-Up Period

| HVPG Baseline | Hemodynamic Response |
|---------------|----------------------|
| All Patient Completed Follow up (N = 42) | < 16 mmHg (N = 23) | ≥ 16 mmHg (N = 19) | Responders (N = 23) | Non-responders (N = 19) |
| Rebleeding    | 10                   | 2                    | 8                   | 3                  | 7                  |
| Mortality     | 8                    | 2                    | 6                   | 3                  | 5                  |

* Data are presented as number.

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Footnotes

Authors’ Contribution: L.F.W. and Q.D. contributed equally to work, dual first authorship. Study concept and design: C.Q. Z.; Analysis, and interpretation of data: L.F.W., Q.D., and X.Y. W.; Drafting of the manuscript: L.F.W., and Q.D.; Critical revision of the manuscript for important intellectual content: C.Q. Z.; Statistical analysis: L.F.W., and Q.D.; Acquisition of data: X.Y. W., X.G. T. and G.C. W.

Conflict of Interests: The authors declare no conflict of interest regarding this article.

Ethical Approval: This study was approved by the local ethics committee, and informed written consent was obtained from each patient.
Figure 4. Cumulative non-rebleeding rate and survival rate in HVPG < 16 mmHg group and HVPG ≥ 16 mmHg group during the follow-up. A, Graph shows that cumulative non-rebleeding rate is significantly higher in HVPG < 16 mmHg group (solid line) than in HVPG ≥ 16 mmHg group (dotted line) (P = 0.004, log-rank test). B, Graph shows that cumulative survival rate is significantly higher in HVPG < 16 mmHg group (solid line) than in HVPG ≥ 16 mmHg group (dotted line) (P = 0.035, log-rank test).

Figure 5. Cumulative non-rebleeding rate and survival rate in responders group and non-responders group during the follow-up. A, Graph shows the cumulative non-rebleeding rate in responders group (solid line) and in non-responders group (dotted line) with no significant difference (P = 0.050, log-rank test). B, Graph shows the cumulative survival rate in the responders group (solid line) and in the non-rebleeding group (dotted line) with no significant difference (P = 0.195, log-rank test).

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References
1. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding-unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. Hepatology. 2008;47(5):1764-72. doi: 10.1002/hep.22271. [PubMed: 18435460].
2. Kim MY, Baik SK, Lee SS. Hemodynamic alterations in cirrhosis and portal hypertension. Korean J Hepatol. 2010;16(4):347-52. doi: 10.3350/kjhep.2010.16.4.347. [PubMed: 21415576]. [PubMed Central: PMC3104610].
3. Burroughs AK, Thalheimer U. Hepatic venous pressure gradient in 2010: optimal measurement is key. Hepatology. 2010;51(6):1894-6. doi: 10.1002/hep.23710. [PubMed: 20512984].
4. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology. 2010;51(4):1445-9. doi: 10.1002/hep.23478. [PubMed: 20077563]. [PubMed Central: PMC2882065].
5. de Franchis R, Baveno V. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagn...
6. Ripoll C. Hepatic venous pressure gradient and outcomes in cirrhosis. J Clin Gastroenterol. 2007;41 Suppl 1:S330-5. doi: 10.1097/MCG.0b013e31815d0d54. [PubMed: 17975485].

7. Garcia-Tsao G, Groszmann RJ, Fisher RI, Conin HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology. 1985;3(3):419-24. doi: 10.1002/hep.1840030313. [PubMed: 3873388].

8. D’Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: A systematic review. Gastroenterology. 2006;131(5):1611-24. doi: 10.1053/j.gastro.2006.09.013. [PubMed: 1710332].

9. Bosch J, Garcia-Pagan JC. Prevention of variceal rebleeding. Lancet. 2003;361(9365):952-4. doi: 10.1016/S0140-6736(03)13631-5. [PubMed: 12648985].

10. Albillos A, Banares R, Gonzalez M, Ripoll C, Gonzalez R, Catalina MV, et al. Value of the hepatic venous pressure gradient to monitor drug therapy for portal hypertension: a meta-analysis. Am J Gastroenterol. 2007;102(5):1116-26. doi: 10.1111/j.1572-0241.2007.00911.x. [PubMed: 1739137].

11. Feu F, Garcia-Pagan JC, Bosch J, Luca A, Escorsell A, Rodés J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet. 1995;346(8982):1056-9. doi: 10.1016/s0140-6736(95)91740-3. [PubMed: 7806173].

12. Pedersen ME, Cockcroft JR. The vasodilatory beta-blockers. Curr Hypertens Rep. 2007;9(4):269-77. doi: 10.1007/s11906-007-0050-2. [PubMed: 17686376].

13. Banares R, Moitinho E, Matilla A, Garcia-Pagan JC, Lampreave JL, Piera C, et al. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatology. 2002;36(6):S367-73. doi: 10.1053/hep.2002.36947. [PubMed: 12447861].

14. Groszmann RJ, Wangcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology. 2004;39(2):280-2. doi: 10.1002/hep.20062. [PubMed: 14767976].

15. Bosch J, Garcia-Pagan JC, Berzigotti A, Abraldes JG. Measurement of portal pressure and its role in the management of chronic liver diseases. Semin Liver Dis. 2006;26(4):348-62. doi: 10.1055/s-2006-951063. [PubMed: 17051449].

16. Poynard T, Cales P, Pasta L, Ideo G, Pascal JP, Pagliaro L, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian Multicenter Study Group. N Engl J Med. 1999;341(22):1532-8. doi: 10.1056/NEJM199910053422202. [PubMed: 1674004].

17. D’Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology. 1995;22(1):332-54. doi: 10.1002/hep.1840220145. [PubMed: 7604247].

18. Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T. Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. Hepatology. 1997;25(1):63-70. doi: 10.1053/hep.1997.v25.pmo008985266. [PubMed: 8985268].

19. Groszmann RJ. Beta-adrenergic blockers and nitrovasodilators for the treatment of portal hypertension: The good, the bad, the ugly. Gastroenterology. 1997;113(5):1794-2. doi: 10.1053/gast.1997.v113.agast971131794. [PubMed: 9352888].

20. Gupta TK, Toruner M, Chung MK, Groszmann RJ. Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. Hepatology. 1998;28(4):926-31. doi: 10.1002/hep.510280405. [PubMed: 9755227].

21. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology. 2009;50(1):825-33. doi: 10.1002/hep.23045. [PubMed: 19610055].

22. Bosch J, Garcia-Pagan JC. Complications of cirrhosis. I. Portal hypertension. Hepatology. 2000;32:141-56. doi: 10.1053/hep.2000.08422-5.

23. Luca A, Garcia-Pagan JC, Feu F, Lopez-Talavera JC, Fernandez M, Bru C, et al. Noninvasive measurement of femoral blood flow and portal pressure response to propranolol in patients with cirrhosis. Hepatology. 1995;22(1):33-8. [PubMed: 7806671].

24. Merkel C, Sacerdoti D, Bolognesi M, Bombanato G, Gatta A. Doppler sonography and hepatic vein catheterization in portal hypertension: assessment of agreement in evaluating severity and response to treatment. Hepatology. 1998;28(4):622-30. doi: 10.1053/hep.1998-827889810285-9.