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Diagnostic performance of platelet count/spleen diameter ratio to detect esophageal varices in patients with cirrhosis

Rendimiento diagnóstico del índice de recuento de plaquetas/diámetro del bazo para detectar várices esofágicas en pacientes con cirrosis

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Abstract

Introduction: The platelet count/spleen diameter (PC/SD) ratio is a noninvasive method for the diagnosis of esophageal varices (EV) used as an alternative to endoscopy in patients with cirrhosis.

Objective: To evaluate the diagnostic performance of the PC/SD ratio (cut-off point <909) to detect EV in patients with cirrhosis treated at a tertiary referral hospital in Bogotá D.C., Colombia.

Materials and methods: A prospective diagnostic test accuracy study was conducted in 66 patients with cirrhosis treated at the Hospital Universitario de La Samaritana between July and December 2018. A descriptive analysis of the data was performed. In addition, the diagnostic performance of the PC/SD ratio (cut-off point <909) for the detection of EV was compared with the findings reported in the esophagogastroduodenoscopy (gold standard), calculating its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-). A significance level of p<0.05 was considered.

Results: The mean age of the participants was 65.5 years, 53.03% were female, and the most common causes of cirrhosis were alcohol consumption (40.90%) and autoimmune hepatitis (22.72%). EV was diagnosed in 48 patients (72.72%). The PC/SC ratio showed sensitivity of 60%, specificity of 78%, PPV of 0.88, NPV of 0.42, LR+ of 2.73, and LR- of 0.51.

Conclusion: The low sensitivity, specificity, and NPV found in the present study suggest that the PC/SD ratio (cut-off point <909) may not be a useful diagnostic test for detecting EV in patients with cirrhosis.

Keywords: Platelet Count; Esophageal Varices; Liver Cirrhosis (MeSH).

Resumen

Introducción. El índice de recuento de plaquetas/diámetro del bazo (RP/DB) es un método no invasivo para el diagnóstico de varices esofágicas (VE) que se usa como alternativa a la endoscopia en pacientes con cirrosis.

Objetivo. Evaluar el rendimiento diagnóstico del índice RP/DM (punto de corte <909) para detectar VE en pacientes cirróticos atendidos en un hospital de tercer nivel de Bogotá D.C., Colombia.

Materiales y métodos. Estudio prospectivo de validez de prueba diagnóstica realizado en 66 pacientes cirróticos atendidos en el Hospital Universitario de La Samaritana entre julio y diciembre de 2018. Se realizó un análisis descriptivo de los datos. Además, el rendimiento diagnóstico del índice RP/DM (punto de corte <909) para la detección de VE se comparó con los hallazgos de la esofagogastroduodenoscopia (prueba de oro), calculándose su sensibilidad, especificidad, valor predictivo positivo (VPP), valor predictivo negativo (VPN), razón de probabilidad positiva (LR+) y razón de probabilidad negativa (LR-). Se consideró un nivel de significancia de p<0.05.

Resultados. La edad promedio de los participantes fue 65.5 años, 53.03% eran mujeres y las causas más comunes de cirrosis fueron consumo de alcohol (40.90%) y hepatitis autoinmune (22.72%). Las VE fueron diagnosticadas en 48 pacientes (72.72%). El índice RP/DM tuvo una sensibilidad de 60%, una especificidad de 78%, un VPP de 0.88, un VPN de 0.42, una LR+ de 2.73 y una LR- de 0.51.

Conclusión. La baja sensibilidad, especificidad y VPN encontrados en el presente estudio sugieren que el índice RP/DM (punto de corte <909) podría no ser una prueba diagnóstica útil para detectar VE en pacientes cirróticos.

Palabras clave: Recuento de plaquetas; Varices esofágicas; Cirrosis hepática (DeCS).

Introduction

Portal hypertension, defined as a hepatic venous pressure gradient (HVPG) >5 mmHg, is the main complication of liver cirrhosis and a predisposing factor for the formation of esophageal varices (EV) when HVPG is >10 mmHg.[1]

Estimates are that the annual incidence of EV varies between 5% and 9% in people with cirrhosis, but it has also been established that about one third of patients with compensated cirrhosis and up to 60% of patients with portal hypertension ascites develop EV.[2-4] On the other hand, the incidence of gastrointestinal bleeding in patients with cirrhosis is 12% and has a mortality rate of up to 22%, which depends on the severity of the disease, the size of the varices, the magnitude of the bleeding, and the level of care of the health institution where the patient is being treated.[5]

Esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis of EV, and the implementation of measures (pharmacological and/or endoscopic) to prevent the development of gastrointestinal bleeding depends on the findings of this test.[6] However, it is essential to keep in mind that EGD should only be performed by highly trained physicians because it is an invasive, high-cost test that is not available in all care centers and during which complications may occur. Patients with compensated chronic liver disease do not need an EGD if they have a platelet count >150 000 a liver stiffness using transient elastography <20 kPa;[7] nonetheless, elastography is a diagnostic test that is not widely available in Colombia.

In this context, several mechanisms have been developed to diagnose EV in patients with cirrhosis, such as platelet count in peripheral blood smear, measurement of serum albumin levels, Child-Pugh classification, right liver lobe diameter/albumin ratio, and platelet count/spleen diameter ratio (PC/SD).[8-10]

The PC/SD ratio, which was proposed by Giannini *et al.*[11] in 2003 and evaluated by Giannini *et al.*[12] in 2005, is a non-invasive predictor of EV with a cut-off point <909, a positive predictive value (PPV) of 96% and a negative predictive value (NPV) of 100%. This index is easy to obtain in any secondary care center because it only requires an ultrasound equipment and a clinical laboratory where platelets can be measured. However, it has not been studied in Colombia to date, so the objective of this study was to evaluate the diagnostic performance of the PC/SD ratio (cut-off point <909) to detect EV in patients with cirrhosis treated a tertiary care university hospital in Bogotá, D.C., Colombia.

Materials and methods

Design and study population

Prospective diagnostic test accuracy study. The study population included all patients over 18 years of age diagnosed with cirrhosis of the liver, of any etiology and severity according to the Child-Pugh classification, treated at the Gastroenterology Unit of the Hospital Universitario de La Samaritana Empresa Social del Estado in Bogotá, D.C., between July and December 2018 and tested for platelet count, EGD and PC/SD ratio (N=80).

Patients admitted with active gastrointestinal bleeding or hypovolemic shock, as well as those who had already received pharmacological, endoscopic, or surgical treatment for EV or who had cancer of any type in any site were excluded (n=14). The final sample consisted of 66 patients.

Procedures

Cirrhosis was diagnosed based on the liver biopsy results (METAVIR scoring system) or imaging findings (resonance or tomography) of patients who underwent any of these tests; in the latter, liver surface nodularity, expanded gallbladder fossa, hypertrophy of the caudate lobe, enlargement of the hilar periportal space, and whether the caudate-right lobe ratio was >0.65 were taken into account. The severity of liver disease was classified according to the Child-Pugh score, considering laboratory results (albumin, prothrombin time, and bilirubin levels) and the presence or absence of complications such as hepatic encephalopathy and/or ascites.

Moreover, esophageal varices were diagnosed via EGD, and the criteria of the American Society for Gastrointestinal Endoscopy established in the BAVENO VI consensus were considered for classification purposes: small <5mm or large >5mm.[7]

Automated platelet count by peripheral blood smear was expressed in platelets/microliter. Abdominal ultrasound was performed by radiologists using a Toshiba Nemio XG system, while EGD was performed by gastroenterologists with more than 10 years of experience using Olympus GIF H180 and Q150 systems.

Statistical analysis

After being included in a database, the information collected was analyzed in the SPSS statistical software (IBM SPSS Statistics for Windows, Version 21.0., Armonk, NY: IBM Corp.). In the descriptive analysis, categorical variables were expressed as absolute frequencies and percentages, and continuous variables as measures of central tendency and dispersion (mean, standard deviation, and interquartile ranges).

Similarly, sensitivity, specificity, PPV, NPV, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) of the PC/SD ratio (cut-off <909) for detecting EV in the study population were calculated, and the results were compared with the findings of the gold standard test (EGD), considering a significance level of $p<0.05$.

Ethical considerations

The study took into account the ethical principles for medical research involving human subjects established in the Declaration of Helsinki,[13] the medical ethics standards established in Law 23 of 1981 of the Colombian Congress,[14] and the scientific, technical and administrative standards for health research set forth in Resolution 8430 of 1993 of the Colombian Ministry of Health and Social Protection.[15]

This research project was approved by the Research Ethics Committee of the Hospital Universitario de La Samaritana Empresa Social del Estado through Minutes 06 of June 21, 2018, and all patients signed an informed consent in which they agreed to participate in the study voluntarily.

Results

Of the 66 patients included in the study, 35 (53.03%) were women. The average age of the participants was 65.5 years (range: 32-87 years and standard deviation: 13.6 years). The main causes of cirrhosis were chronic alcohol consumption (40.90%), autoimmune hepatitis (22.72%) and non-alcoholic steatohepatitis (NASH) (18.18%).

The severity of liver disease measured on the Child-Pugh score was classified as follows: class A: 40.90%, class B: 40.90%, and class C: 18.18%. EV were observed in 48 (73%) patients and mean platelet count, spleen diameter, and PC/SD ratio were 139.9×109/L, 125.5mm, and 1 211.9 n/mm3, respectively (Table 1). The results concerning the diagnostic performance of the test are shown in Table 2.

Table 1. Characteristics of patients with liver cirrhosis treated at Hospital Universitario La Samaritana Empresa social del Estado between July and December 2018.

Characteristics		n	%
Sex	Women	35	53.03%
	Men	31	46.96%
Mean age (years: mean and standard deviation)		65.5	13.6
Etiology of cirrhosis	Alcohol consumption	27	40.90%
	Autoimmune hepatitis	15	22.72%
	Non-alcoholic steatohepatitis	12	18.18%
	Primary biliary cirrhosis	6	9.09%
	Cryptogenic cirrhosis	2	3.03%
	Hepatitis B	4	1.51%
	Hepatitis C		1.51%
	Drug toxicity		1.51%
	Secondary biliary cirrhosis	1	1.51%
Child-Pugh classification	A	27	40.90%
	B	27	40.90%
	C	12	18.18%
Presence of varices		48	72.72%
Mean platelet count (mean and range)		139.9×10^9/L	122 590.98- 157 131.02
Mean spleen diameter (mean and range)		125.5mm.	119.71- 131.29
Average PC/SD ratio (mean and range)		1 212.9 n/mm^3	970.16- 1 453.64

Source: Own elaboration.

Table 2. Diagnostic performance of the platelet count/spleen diameter ratio (cut-off point <909) to detect esophageal varices in patients with liver cirrhosis treated at Hospital Universitario La Samaritana Empresa social del Estado between July and December 2018.

Measurement indicators	Positive for esophageal varices n=48	Negative for esophageal varices n=18
PC/SD ratio <909	29	4
PC/SD ratio >909	19	14
Sensitivity	0.60 (60 %)	-
Specificity	0.78 (78 %)	-
Positive predictive value	0.88 (88 %)	-
Negative predictive value	0.42 (42 %)	-
Prevalence of esophageal varices	0.73 (73 %)	-
Positive likelihood ratio	2.73	-
Negative likelihood ratio	0.51	-
Pretest probability	0.73 (73 %)	-
Positive posttest probability	0.88 (88 %)	-
Negative posttest probability	0.12 (12 %)	-
False positive rate	22%	-
False positive rate	39%	-

PC/SD ratio: platelet count/spleen diameter ratio.
Source: Own elaboration.

Discussion

Every year, about 2 million people die as a result of liver disease, and cirrhosis accounts for 3.5% of all causes of death worldwide, making it the eleventh leading cause of death in the world.[16] Mexico was the country with the highest mortality rate due to cirrhosis in 2010, with 36 157 deaths (mortality rate: 38.5/100 000 inhabitants) and Colombia showed a significant increase in deaths from this cause compared to 1980, going from 1 503 to 3 674 deaths (mortality rate: 10.4/100 000 inhabitants in 2010).[17,18]

In the present study, alcohol abuse was the most common cause of cirrhosis in the analyzed population (40.90%), followed by autoimmune hepatitis (22.72%) and non-alcoholic steatohepatitis (18%), which coincides with the results reported by Asrani *et al.*,[16] who found that the main etiologies of this condition worldwide are chronic alcohol consumption, non-alcoholic steatohepatitis, and chronic hepatitis B and C virus infections.

Since Giannini *et al.*[12] introduced the PC/SD ratio with a cut-off point <909 as a good predictor of the presence of EV in patients with cirrhosis, various studies have been conducted to analyze its effectiveness, yielding mixed results.

In Brazil, Mattos *et al.*,[19] in a study conducted in 164 patients with cirrhosis (56.7% men) with an average age of 56.6 years and in whom the main cause of cirrhosis

was viral infection (43.9%), found that the PC/SD ratio had a sensitivity of 77.5%, a specificity of 45.5%, a PPV of 79.5% and a NPV of 42.6%, and concluded that this is not a suitable method for the diagnosis of EV.

In Peru, Mosqueira et al.,[20] conducted a study in 47 patients with cirrhosis with an average age of 60.7 years and in whom alcohol consumption was the main cause of cirrhosis (25.5%) and reported that the PC/SD ratio had a sensitivity of 40%, a specificity of 75%, a PPV of 82% and a NPV of 30%, concluding that the diagnostic effectiveness of this ratio is not acceptable.

In Cuba, Infante-Velazquez et al.,[21] in a study of 102 patients with cirrhosis (54% men) with an average age of 55.8 years and in whom the main cause of cirrhosis was viral hepatitis, described that the PC/SD ratio had a sensitivity of 93%, a specificity of 45%, a PPV of 38.8% and a NPV of 97%, concluding that the cut-off point of 909 for this test was effective as a method to identify the presence of EV in their study population and that it is also an effective strategy for reducing health care costs and is therefore considered a safe alternative in countries with limited economic resources.

In Mexico, González et al.,[22] in a cross-sectional study conducted in 91 patients with cirrhosis (55% men) with an average age of 53 years and in whom the main cause of cirrhosis was alcohol consumption (45%), found that the PC/SD ratio with a cut-off point of 884.3 had a sensitivity of 84%, a specificity of 70%, a PPV of 94% and a NPV of 40%, and concluded that this ratio is a good diagnostic tool.

Given the disparity in the reported results, Chen et al.,[23] published a meta-analysis in 2017 that comprised 49 studies (22 prospective studies) in 6 274 patients with cirrhosis, whose condition was associated with alcohol consumption, schistosomiasis, and hepatitis B and C. The authors found that the cut-off point of the PC/SD ratio was <909 in 19 studies (38%), with a sensitivity of 84%, a specificity of 80%, an LR+ of 3.95 and an LR- of 0.23. Chen et al.,[23] also reported that, despite the high heterogeneity of the results of the analyzed studies, the PC/SD ratio can be used to identify patients with EV, especially in cases of viral hepatitis cirrhosis, due to its high sensitivity.

Finally, Sami et al.,[24] also in a systematic review and meta-analysis that comprised 21 studies (2 471 patients) aimed at identifying all primary studies that reported accuracy using EGD as the gold standard, found that 9 publications (823 patients) evaluated the PC/SD ratio, of which 5 had a cut-off point <909 and that sensitivity for this test was 87%, specificity was 71%, LR+ was 3.1, and LR- was 0.18. They concluded that this ratio is the most accurate noninvasive method for the diagnosis of EV.

The present study differs from those cited above in that women here made up the majority of patients (53%), viral etiology was the least common cause of cirrhosis (3%), and cirrhosis in most patients was related to diseases of immunological origin, such as autoimmune hepatitis (22.72%) and primary biliary cirrhosis (9.09%), followed by NASH (18.18%).

Similarly, most patients were classified as class A and class B on the Child-Pugh score (n=27 and n=27, respectively), the mean platelet count was >100x10⁹/L, and the mean spleen diameter was 125.5mm, a figure close to the upper limit for the diagnosis of splenomegaly (120mm).

It should be noted that although the sensitivity, specificity, and NPV for the PC/SD ratio to detect EV (cut-off 909) were low, the PPV was high (88%), suggesting that there is a high probability of identifying patients with EV with a PC/SD ratio <909, but this is merely an assumption.

Limitations

Some of the main limitations of the present study were its small sample size, the use of secondary information, and the retrospective nature of the study, since it is expected that the data record is reliable throughout the period studied in order to obtain results and draw conclusions.

Conclusion

The low sensitivity, specificity and NPV found in the present study suggest that the PC/SD ratio (cut-off point <909) may not be a useful diagnostic test for the detection of EV in patients with cirrhosis.

Conflicts of interest

None stated by the authors.

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Acknowledgments

References

1. Groszmann RJ, García-Tsao G, Boch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patient with cirrhosis. N Eng J Med. 2005;353(21):2254-61. https://doi.org/fw8hxz.

2. D´Amico G, Luca A. Natural history, Clinical-hemodynamic correlations. Prediction of the risk of bleeding. Baillieres Clin Gastroenterol. 1997;11(2):243-56. https://doi.org/bj4d22.

3. Abradales JG, Villanueva C, Bañares R, Aracil C, Catalina MV, Garci A-Pagán JC, et al. Hepatic-venous pressure gradient and prognosis in patient with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol. 2008;48(2):229-36. https://doi.org/bnmfn2.

4. North Italian Endoscopy Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Eng J Med. 1988;319(15):983-9. https://doi.org/fh8jvj.

5. Reverter F, Tandon P, Agustín S, Turón F, Casu S, Bastiampillai R, et al. A MELD-base model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology. 2014;146(2):412-19.e3. https://doi.org/f2pk6r.

6. de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2010;53(4):762-8. https://doi.org/fdwff6.

7. 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(3):743-52. https://doi.org/f3hvgt.

8. Sharma SK, Aggarwal R. Prediction of large esophageal varices in patients with cirrhosis of the liver using clinical, laboratory and imaging parameters. J Gastroenteroly Hepatol. 2007;22(11):1909-15. https://doi.org/bz85nk.

9. Gentile I, Viola C, Graf M, Liuzzi R, Quarto M, Cerini R, et al. A simple noninvasive score predicts gastresophageal varices with chronic viral hepatitis. J Clin Gastroenterol. 2009;43(1):81-7. https://doi.org/c3735t.

10. Sen S, Griffith WJ. Non-invasive prediction of oesophageal varices in cirrhosis. World J Gastroenterol. 2008;14(15):2454-5. https://doi.org/c7d7fx.

11. Giannini E, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut. 2003;52(8):1200-5. https://doi.org/dr342h.

12. Giannini EG, Botta F, Borro P, Dubelco P, Testa E, Mansi C, et al. Application of the platelet count/spleen diameter ratio to rule out the presence of oesophageal varices in patients with liver cirrhosis: a validation study based follow-up. Dig Liver Dis, 2005;37(10):779-85. https://doi.org/dhjdtr.

13. World Medical Association (WMA). WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. Fortaleza: 64th WMA General Assembly; 2013.

14. Colombia. Congreso de la República. Ley 23 de 1981 (febrero 18): Por la cual se dictan normas en materia de ética médica. Bogotá. D.C.: Diario Oficial 35711; febrero 27 de 1981.

15. Colombia. Ministerio de Salud y Protección Social. Resolución 8430 de 1993 (octubre 4): Por la cual se establecen las normas científicas, técnicas y administrativas para la investigación en salud. Bogotá D.C.; octubre 4 de 1993.

16. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151-71. https://doi.org/gfj27b.

17. Mokdad AA, López AD, Shahraz S, Lozano R, Mokdad AH, Sttanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med. 2014;12:145. https://doi.org/f6h8g2.

18. Torres-Poveda K, Burguete-García AI, Madrid-Marina V. Liver cirrhosis and hepatocellular carcinoma in Mexico: impact of chronic infection by hepatitis viruses B and C. Ann Hepatol. 2011;10(4):556-8.

19. Mattos AZ, Mattos AA, Vianna FF, Musskopf MI, Pereira-Lima JC, Maciel AC. Platelet count/spleen diameter ratio: analysis of its capacity as a predictor of the existence of varices esophageal varices. Arq Gastroenterol. 2010;47(3):275-8. https://doi.org/b9f4r4.

20. Mosqueira J, Montiel JB, Rodríguez D, Monge E. Evaluación del test diagnóstico índice número de plaquetas/diámetro mayor del bazo, como predictor de la prevalencia de várices esofágicas en cirrosis hepática. Rev Gastroenterol. Perú. 2011;31(1):11-6.

21. Infante-Velázquez M, Rosado-Vargas FC, Pérez-Lorenzo M, Samada-Suárez M, Hernández-Amarán M. Cociente conteo de plaquetas/diámetro bipolar del bazo menor de 909 para predecir várices esofágicas. Rev Cub Med Mil. 2013;42(4):451-6.

22. González-Ojeda A, Cervantes-Guevara G, Chávez-Sánchez M, Dávalos-Cobián C, Ornelas-Cázares S, Macías-Amezcua MD, et al Platelet count/spleen diameter ratio to predict esophageal varices in Mexican patients with hepatic cirrhosis. World J Gastroenterol. 201428;20(8):2079-84. https://doi.org/f5tqgp.

23. Chen R, Deng H, Ding X, Xie Ch, Wang W, Shen Q. Platelet Count to Spleen Diameter Ratio for the Diagnosis of Gastroesophageal Varices in Liver Cirrhosis: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2017;2017:7407506. https://doi.org/f9ss72.

24. Sami S, Harman D, Ragunath K, Böhning D, Parkes J, Guha I. Non-invasive tests for the detection of oesophageal varices in compensated cirrhosis: systematic review and meta-analysis. United European Gastroenterol J. 2018;6(6):806-18. https://doi.org/gdwf2.