http:// ijp.mums.ac.ir
Original Article (Pages: 16396-16401)

The Value of Serum D-dimer in Predicting Mortality of Children with Liver Cirrhosis: A Prospective Study

Fatemeh Kanaani Nejad [1], * Seyed Mohsen Dehghani [2,3], Fereshteh Karbasian [4]

[1] MD, Medical Imaging Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

[2] MD, MPH, Professor of Pediatrics Shiraz Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

[3] Pediatric Gastroenterology, Hepatology, and Nutrition Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4] MD, Fellowship of pediatric gastroenterology and hepatology, Department of pediatric gastroenterology, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Background: Liver cirrhosis is one of the major causes of mortality worldwide. Finding new methods to stratify patients with liver cirrhosis can affect the treatment plan and improve the outcomes. The present study aimed to determine the prognostic value of the serum D-dimer level in pediatric patients with liver cirrhosis.

Method: All cirrhotic pediatric patients admitted to Namazi Hospital (Shiraz, Iran) between November 2020 and November 2021 underwent serum D-dimer level testing on admission and were prospectively analyzed for 90 days. The Mann-Whitney U test was used to evaluate the correlation between D-dimer level and patient mortality. In addition, ROC (Receiver Operating Curve) analysis was used to evaluate the specificity and sensitivity of the D-dimer level in predicting mortality.

Result: In total, 38 patients with cirrhosis were included in this study. The serum D-dimer level was significantly correlated with the mortality of children with liver cirrhosis (P = 0.01), and the area under the ROC of the serum D-dimer level for this prediction was 0.777 (P = 0.01). The best cut-off D-dimer value was 1641.5 ng/ml, which offered a sensitivity of 70.0% and specificity of 82.14% for predicting mortality. We detected no significant correlation between the D-dimer level and the PELD (Pediatric End-stage Liver Disease) or MELD (Model for End-stage Liver Disease) score.

Conclusion: The D-dimer level is significantly associated with the mortality of children with cirrhosis. Therefore, D-dimer testing can be used as a stratification marker to prioritize patients waiting on the liver transplant list.

Key Words: D-dimer, Liver Cirrhosis, Pediatric Patients, Prognostic Factor.

* Please cite this article as: Kanaani Nejad F, Dehghani SM, Karbasian F. The Value of Serum D-dimer in Predicting Mortality of Children with Liver Cirrhosis: A Prospective Study. Int J Pediatr 2022; 10 (7):16396-16401. DOI: **10.22038/ijp.2022.65695.4953**

****Corresponding Author:***

Seyed Mohsen Dehghani, MD, MPH, Professor of Pediatrics Shiraz Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. Email: sm.dehghani70@gmail.com

Received date: May.23,2022; Accepted date:Jun.25,2022

1- INTRODUCTION

Liver cirrhosis is a leading cause of DALYs (Disability Adjusted Life Years) and mortality (1). Accurate prognostic scoring systems can help physicians make better diagnoses and select more effective therapies for patients. Furthermore, it will enhance the ability to predict mortality using easily accessible laboratory parameters similar to those used to create the PELD (Pediatric End-stage Liver Disease) and MELD (Model for End-stage Liver Disease) scores.

The D-dimer is a soluble fibrin degradation product, widely recognized as a marker of activation of coagulation and fibrinolysis and employed to safely rule-out venous thromboembolism and pulmonary embolism (2, 3). Recently, it has been indicated that a higher D-dimer level correlates not only with homeostatic abnormalities but also with profound systemic inflammation, sepsis, and multi-organ injuries (4). Studies suggest a strong correlation between higher serum D-dimer levels and the presence of ascites and SBP (spontaneous bacterial peritonitis) in patients with liver failure (5, 6).

The serum D-dimer level increases significantly in patients with liver cirrhosis, gradually rising even further as the degree of liver dysfunction increases in severity (7, 8). Hence, it may be a prognostic factor negatively associated with the outcome of liver cirrhosis. There are retrospective studies investigating the correlation of the D-dimer level with the Child-Pugh and MELD scores, indicating its association with the degree of liver dysfunction and suggesting its potential for use as a prognostic and stratification marker in liver cirrhosis or decompensated liver failure (4, 9, 10).

Fibrinolytic activity, as evidenced by a high level of D-dimer, is also detected in pediatric patients with chronic liver disease (particularly if cirrhotic) (11). However, the association between D-dimer level and mortality in children with cirrhosis is yet to be explored. Hence, this study aimed to evaluate the correlation between the D-dimer level, the PELD/MELD scores, and the mortality rate of children with liver cirrhosis.

2- MATERIALS AND METHODS

2-1. Study Design and participants

In this prospective hospital-based study, we enrolled all children below 18 years old admitted due to liver cirrhosis (based on clinical, histological, or radiographic evidence) to the pediatric gastroenterohepatology ward of Namazi Educational Hospital affiliated with Shiraz University of Medical Sciences, Shiraz, Iran, from November 2020 to November 2021.

The exclusion criteria were: (i) patients diagnosed with a malignancy in current or previous admissions; (ii) patients with venous or arterial thrombosis in color Doppler sonography in the current admission; and (iii) suspicious or confirmed cases of coronavirus disease 2019 (COVID-19) in the current admission.

We were aware that D-dimer test results could be affected by COVID-19; therefore, we excluded patients who had a positive PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or had symptoms of COVID-19 on admission.

2-2. Data Collection

The following data were collected from patients' electronic records in the hospital information system: age, gender, etiology of liver disease, presence of ascites, hepatic encephalopathy, survival, and paraclinical data such as CBC (complete blood count), INR (international normalized ratio), serum creatinine, serum electrolytes, and liver function tests including total and direct bilirubin,

albumin, ALT (alanine transaminase), AST (aspartate aminotransferase), and ALP (alkaline phosphatase). To determine the serum D-dimer level, 2 ml of peripheral blood was collected in a coagulation tube containing 3.2% sodium citrate ahead of analysis with the VIDAS® D-Dimer Exclusion™ II test (bioMérieux Inc., USA). Results equal to or above 500 ng/ml were considered positive in this method. The clinical information and index test results were not available to the assessors of the reference standard, and the clinical information and reference standard results were not available to the performers and readers of the index test. The PELD/MELD scores were calculated with MDCalc Medical Calculator (version 4.0.4) developed by MD Aware, LLC.

The patients enrolled in this study were followed for 90 days after D-dimer testing to evaluate whether they survived or not. The report of the mortality rate among the participants is based on this 90-day follow-up.

2-3. Data Analysis

Continuous data are presented as the mean ± SD (Standard Deviation) and were compared using Spearman's rank correlation coefficient test. Categorical data are expressed as frequencies, compared by the use of the Mann-Whitney U test. The correlation of D-dimer level with the PELD/MELD scores was evaluated using Spearman's rank correlation coefficient test. The ROC (receiver operating curve) analysis was employed to evaluate the specificity and sensitivity of D-dimer for predicting mortality. The optimal cut-off value was defined as the value at which the specificity plus sensitivity was maximal. In addition, the AUROC (area under the ROC) and the 95% confidence intervals (CIs) were also calculated. A two-sided P-value of <0.05 was considered to indicate a statistically significant difference.

All statistical analyses were performed using SPSS software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). There was no missing data among the patients enrolled in this study. The appropriate sample size was calculated with the $\mathbf{n = Z_{\omega/2}^2\, \sigma^2/d^2}$ formula.

3- RESULTS

During enrollment, among 45 patients, 38 were deemed eligible for inclusion in the current study. The participants' laboratory test results are provided in **Table 1**.

Table-1: Laboratory tests results calculated as mean ± standard deviation (SD).

Laboratory Test	Result (mean± SD)	Reference Range
White blood cell count,10^9/l	10.02±8.05	4-10
Hemoglobin level, g/dl	9.42±2.23	13-17
Platelet count,10^9/l	122.65±82.69	135-350
Albumin, g/dl	2.87±0.63	3.5-5.5
Total bilirubin, mg/dl	16.70±18.06	0.1-1.2
Direct bilirubin, mg/dl	7.83±7.41	<=0.3
Alanine Transaminase, U/l	217.55±307.64	9-50
Aspartate Aminotransferase, U/l	127.97±228.60	15-40
Alkaline Phosphatase, U/l	1043.57±908.47	45-125
INR	2.74±1.33	0.9-1
Creatinine *, mg/dl	0.24±0.26	0.8-1
Serum Sodium, mEq/l	134.92±5.20	136-145
D-Dimer, ng/ml	1445.52±938.56	0-500

* Creatinine level is not reliable in icteric patients

The mean age of children in this study was 6.69 ± 5.27 years. The majority of the participants were males (20/38 patients, 52.63%). In the current study, 28.94% of patients (11/38) presented with SBP, and 55.26% (21/38) presented with ascites at the time of admission.

The most common etiologies of liver cirrhosis were unknown (10/38 patients; 26.31%), Wilson's disease (7/38 patients; 18.42%), and biliary atresia (6/38 patients; 15.78%), followed by PFIC (progressive familial intrahepatic cholestasis) and congenital hepatic fibrosis. Other less common etiologies were autoimmune hepatitis, neonatal hepatitis, primary sclerosing cholangitis, and Niemann-Pick disease. The 90-day mortality rate was 26.31% (10/38) among the patients enrolled in this study.

The mean D-dimer level was 1445.52 ng/ml (reference range: 0-500 ng/ml). In addition, the mean MELD and MELD-Na scores (in 9/38 patients) were 25.22 and 24.77, respectively. The mean PELD score (in 29/38 patients) calculated for children younger than 12 years was 24.36.

The correlation between D-dimer level and mortality was investigated by the Mann-Whitney U test, indicating a significant correlation (P = 0.01). The specificity and sensitivity of the D-dimer level for predicting the mortality of children with liver cirrhosis were determined, and the AUROC was calculated. The AUROC of the D-dimer level for this prediction was 0.777 (95% CI: 0.612-0.942; P = 0.01). The best cut-off D-dimer value was 1641.5 ng/ml, offering a sensitivity of 70.0% and specificity of 82.14% for predicting the mortality of children with cirrhosis. The ROC curve is demonstrated in **Fig. 1**.

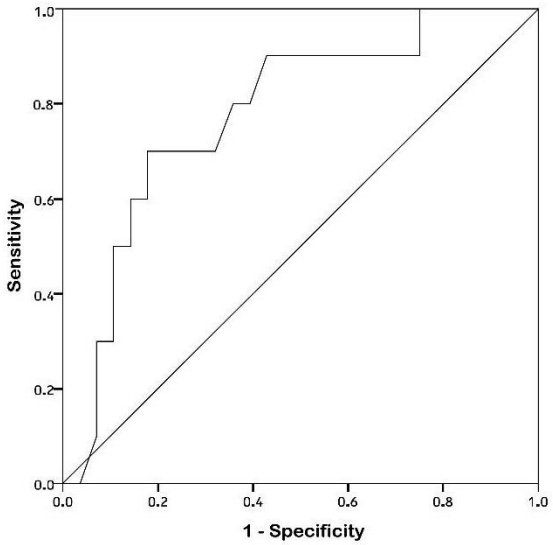

Fig. 1: The ROC curve

The correlation between D-dimer and the PELD/MELD scores was investigated using the Spearman test, which revealed no significant correlation. The same was true for the potential correlations between all laboratory test results and the serum D-dimer level.

4- DISCUSSION

In recent decades, transplantation has transformed end-stage liver disease in

children from a fatal to fixable condition. However, 1 in 10 infants and 1 in 20 children listed for liver transplants in the United States die on the waiting list (12, 13). Although the primary goal of patient prioritization ranking is to minimize waiting list mortality, some studies indicate the insufficiency of the PELD score in predicting mortality among children with the end-stage liver disease (14). Therefore, more studies on different objective and paraclinical parameters may enhance the ability to predict mortality in the current scoring systems.

The current study found that a higher serum D-dimer level can predict the mortality of children with liver cirrhosis. Therefore, it can be suggested as a prognostic and stratification marker for children suffering from this condition. There are limited studies on serum D-dimer levels of pediatric patients with cirrhosis. El-Sayed et al. showed a significantly higher D-dimer level in patients with liver cirrhosis of Child-Pugh class A and B compared with non-cirrhotic and control groups. In that study, the D-dimer level correlated positively with the prothrombin time and negatively with platelet count and prothrombin concentration. They concluded that fibrinolytic activity, as evidenced by high D-dimer levels, is detected in pediatric patients with chronic liver disease, particularly if cirrhotic (11).

There are also studies on the role of D-dimer level in predicting the in-hospital mortality in liver cirrhosis among adults. Li Y et al., in a retrospective study, showed that the serum D-dimer level correlated with the Child-Pugh (correlation coefficient 0.219; $P < 0.001$) and MELD scores (correlation coefficient 0.207; $P < 0.001$) in patients with cirrhosis. They also reported that the AUROC of D-dimer level for predicting the in-hospital mortality of liver cirrhosis was 0.729 ($P < 0.0001$), while the best cut-off D-dimer value was 280 ng/ml, with a sensitivity of 86.84% and a specificity of 49.17% (9). Our study on pediatric patients showed a higher level of D-dimer as the best cut-off compared with their adult population, but also with greater specificity.

Our findings indicate the prognostic value of the D-dimer level in pediatric patients with liver cirrhosis. Although we identified an accurate cut-off point, our AUROC was 0.777, meaning that this prognostic value may be moderate. The major advantage of the current study was its prospective nature, which minimizes patient selection bias. However, considering that a small number of patients were included in the study, bias may still affect our results.

5- CONCLUSION

In conclusion, higher D-dimer levels predicted an increased 90-day mortality risk due to liver cirrhosis in pediatric patients. Further prospective cohort studies with a greater number of enrolled cases are thus warranted to confirm the present findings. Interestingly, we found no correlation between higher D-dimer levels and PELD/MELD scores, which should be reevaluated in upcoming studies.

6- ETHICAL CONSIDERATIONS

At the time of admission, consent was obtained from the patients' guardians. The Ethics Committee of Shiraz University of Medical Sciences approved the present study before the study began. Protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration.

7- ACKNOWLEDGMENT

Prof. Mahmoud Haghighat and Asst. Prof. Iraj Shahramian supported our study. There is no real or perceived conflict of interest in any aspect of this study.

8- REFERENCES

1. Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, Murray CJL, Naghavi M. Liver cirrhosis

mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med. 2014; 12:145.

2. Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. J Am Coll Cardiol. 2017; 70(19):2411-20.

3. Le Gal G, Righini M, Wells PS. D-dimer for pulmonary embolism. Jama. 2015; 313(16):1668-9.

4. Qi T, Zhu C, Lu G, Hao J, He Q, Chen Y, Zhou F, Chen J, Hou J. Elevated D-dimer is associated with increased 28-day mortality in acute-on-chronic liver failure in China: a retrospective study. BMC Gastroenterol. 2019; 19(1):20.

5. Mikuła T, Sapuła M, Jabłońska J, Kozłowska J, Stańczak W, Krankowska D, Stańczak W, Krankowska D, Wiercińska-Drapało A. Significance of Heparin-Binding Protein and D-dimers in the Early Diagnosis of Spontaneous Bacterial Peritonitis. Mediators Inflamm. 2018; 2018:1969108.

6. Spadaro A, Tortorella V, Morace C, Fortiguerra A, Composto P, Bonfiglio C, Alibrandi A, Luigiano C, Caro GD, Ajello A, Ferrau O, Freni MA. High circulating D-dimers are associated with ascites and hepatocellular carcinoma in liver cirrhosis. World J Gastroenterol. 2008; 14(10):1549-52.

7. Saray A, Mesihovic R, Gornjakovic S, Vanis N, Mehmedovic A, Nahodovic K, Glavas S, Papovic V. Association between high D-dimer plasma levels and ascites in patients with liver cirrhosis. Med Arch. 2012; 66(6):372-4.

8. Dai J, Qi X, Li H, Guo X. Role of D-dimer in the Development of Portal Vein Thrombosis in Liver Cirrhosis: A Meta-analysis. Saudi J Gastroenterol. 2015; 21(3):165-74.

9. Li Y, Qi X, Li H, Dai J, Deng H, Li J, Peng Y, Liu X, Sun X, Guo X. D-dimer level for predicting the in-hospital mortality in liver cirrhosis: A retrospective study. Exp Ther Med. 2017; 13(1):285-9.

10. Gürsoy S, Başkol M, Torun E, Yurci A, Soyuer I, Eser B, Güven K, Ozbakir O, Yücesoy M. Importance of anticoagulant proteins in chronic liver diseases. Turk J Gastroenterol. 2005; 16(3):129-33.

11. El-Sayed R, El-Karaksy H, El-Raziky M, El-Hawary M, El Koofy N, Helmy H, Fahmy M. Assessment of coagulation and fibrinolysis in children with chronic liver disease. Blood Coagul Fibrinolysis. 2013; 24(2):113-7.

12. Leung DH, Narang A, Minard CG, Hiremath G, Goss JA, Shepherd R. A 10-Year united network for organ sharing review of mortality and risk factors in young children awaiting liver transplantation. Liver Transpl. 2016; 22(11):1584-92.

13. Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, Wainright J L, Snyder J J, Israni A K, Kasiske B L. OPTN/SRTR 2016 Annual Data Report: Liver. Am J Transplant. 2018; 18 Suppl 1:172-253.

14. Swenson SM, Roberts JP, Rhee S, Perito ER. Impact of the Pediatric End-Stage Liver Disease (PELD) growth failure thresholds on mortality among pediatric liver transplant candidates. Am J Transplant. 2019; 19(12):3308-18.