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ORIGINAL RESEARCH ARTICLE

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# Fibrinogen level among children with liver cirrhosis

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## Abstract

**Introduction** The liver has a major role in the production of coagulation factors, and cirrhotic patients have a series of coagulopathy disorders. The present study aimed to measure plasma fibrinogen levels in children with hepatic cirrhosis.

**Method** Patients younger than 18 years old after diagnosis of liver cirrhosis by biopsy were enrolled in the study. Laboratory data including hemoglobin, PT, PTT, INR, and liver function tests were recorded. Fibrinogen levels were measured using the Clauss method. PELD score for children less than 12 years and MELD Na for children over 12 years were used to measure the severity of the liver disease.

**Results** Fifty children with cirrhosis were studied. The mean fibrinogen level in the "PELD < 15" group was significantly higher than the other group ($P < 0.001$). There was no significant relationship between bleeding and fibrinogen levels. There was no significant relationship between PELD and bleeding in subjects ($P = 0.87$). The results of the study showed neither of these two factors (fibrinogen level and PELD) can play a predictive role in causing hemorrhage in patients.

**Conclusion** Our study has shown that fibrinogen level is significantly associated with severity of liver cirrhosis and decreases with more severe disease (PELD levels), but platelet and fibrinogen cannot predict the severity of bleeding in these patients.

**Keywords** Fibrinogen, Cirrhosis, Liver, Hemostasis

## Introduction

Cirrhosis is a liver condition that is the result of various reasons, including viral diseases, alcohol consumption, metabolic and autoimmune diseases, congenital disorders, and some unknown causes [1]. In advanced liver diseases, the coagulation system is troubled, and both procoagulant and anticoagulant factors plummet in production [1]. Patients with liver cirrhosis suffer from severe coagulopathy, bleeding, and also clotting which is caused by impaired production of coagulation factors, and the imbalance of the coagulation system along with the thrombocytopenia causes portal hypertension [1, 2]. It is now recognized that hemostasis is rebalanced in chronic liver disease [3].

Fibrinogen, or factor 1, which is the major participating protein in the clot (secondary hemostasis) and wound healing [1, 2] is a liquid glycoprotein with a weight of 340 kDa, made up of the combination of Bβ, Aα, and $\gamma$ in the hepatocytes [4, 5]. Fibrinogen can be seen in three forms with three different molecular weights: high molecular weight (two intact Aα chains), low molecular weight (a shortened Aα chain and the other left intact), and the other form with a molecular weight in which

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both of the Aα chains have been shortened [5]. The percentage of these forms in the body is 70, 26, and 4, respectively. Lighter types of fibrinogen are produced by the breaking of the heavier ones during the fibrinolytic process. Fibrinogen is also influenced by other proteolytic procedures such as thrombin and plasmin [5].

Because of the role of the liver in regulating fibrinolysis procedures, liver cirrhosis patients suffer from an increase in fibrinolysis [6]. In these patients, the proteolytic process can heavily be influenced, and the result of such changes can alter the blood fibrinogen measurements [5]. Carbonylation of the proteins will be increased in cirrhosis, and this will affect the function of fibrinogen [1]. Patients with liver cirrhosis go through certain degrees of disseminated vascular clotting along with reactive fibrinolysis — which is more than the primary fibrinolysis in this stage [5]. D-Dimer is another indicator of the breaking procedure of fibrin and the creation of clots [2].

The accelerated fibrinolysis in cirrhosis patients is observed in children with viral hepatitis, especially during the process of plasminogenesis [2]. In patients with advanced cirrhosis, fibrinogen is seen as low concentration, increased oxidation, hypersialyation, delayed conversion to fibrin, and decreased fibrin permeability [1, 2, 4]. In cirrhosis, fibrinogen can be within the normal range, but this does not rule out dysfunction [4]. There are limited papers published about coagulation factors and liver cirrhosis among pediatric patients, so the current study aimed to measure the relationship between plasma fibrinogen level and PELD score and MELD score. The presence of hypofibrinogenemia is assessed based on the score. To control the patient's bleeding, fibrinogen, or cryoprecipitate, is injected which is hoped to manage bleeding faster in smaller volumes.

## Material and methods

### Type of the study

The present study was cross-sectional and prospective.

### Place of the study

This study was carried out in the Department of Pediatric Hepatology of Nemazee Teaching Hospital a referral center for liver disease in Iran.

### Inclusion criteria and exclusion criteria

All cases under 18 afflicted with cirrhosis are studied carefully. After their diagnosis with biopsy, its etiology including viral hepatitis, autoimmune diseases, enzyme defects, Wilson's, hemochromatosis, and other unknown causes has been registered. Laboratory data including hemoglobin, INR, PTT, PT, and liver function tests were recorded. Fibrinogen level was measured using Clauss method. Children with incomplete laboratory were excluded.

To diagnose the severity of liver disease in children under 12, PELD (pediatric end-stage liver disease) criteria are used, and for those over 12, MELD Na criteria (model of end-stage liver disease) are used [7]. How they are measured is as follows:

- $\text{PELD score} = 10 \times ((0.480 \times \ln(\text{bilirubin})) + (1.857 \times \ln(\text{INR})) - (0.687 \times \ln(\text{albumin})) + \text{listing age factor} + \text{growth})$
- $\text{MELD-Na score} = 10 \times ((0.957 \times \ln(\text{creatinine})) + (0.378 \times \ln(\text{bilirubin})) + (1.12 \times \ln(\text{INR}))) + 6.43$
- $\text{MELD Na} = \text{MELD} - \text{Na} - [0.025 \times \text{MELD} \times (140 - \text{Na})] + 140$

### Statistical analysis

The collected data have been analyzed by SPSS, twenty-first version. In the descriptive section of this study, the mean, standard deviation, frequencies, and minimum and maximum amounts were reported. In the analytical section, to investigate and compare a quantitative factor among two groups, an independent *t*-test was used, and within three groups, one-way ANOVA along with a Bonferroni test was used. The analysis of the relationship between the two factors was done with chi-square or Fisher's exact test. The baseline in all of the tests was considered to be 0.05.

In the inferential section, to analyze the normalcy of the data, Kolmogorov–Smirnov and Shapiro–Wilk tests were used. To investigate and compare a quantitative factor among two groups, an independent *t*-test or its nonparametric equivalent test, Mann–Whitney *U* was used. The relationship between the two qualitative factors was investigated with chi-square or Fisher's exact test to study the linear relation and also to determine the predictive role of fibrinogen, PELD criteria in causing bleeding in individuals from binary logistic regression fibrinogen on bleeding, and PELD amount on the causation of bleeding.

## Result

Fifteen children with liver cirrhosis have participated in this research. The age of the children in this study is 1.5 months to 204 months (17 years) with an average age of $56.5 \pm 56$ (mean $\pm$ SE) months. Of patients, 28 (56%) are boys, and 22 (44%) are girls. The average age of boys is $49.19 \pm 10.86$ months (mean $\pm$ SE), and the average age of girls is $65.93 \pm 12.63$ months (mean $\pm$ SE).

There is not a significant difference between the age of the girls and the boys who are being studied according to the independent *t*-test ($P = 0.239$ and $U = 165$).

**Table 1** The distribution of age variable data among gender groups

| | Sex | Shapiro–wilk | | | Kolmogorov–Smirnov | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | df | Sig | Statistic | df | Sig |
| Age | Boy | 0.278 | 28 | 0.000 | 0.787 | 28 | 0 |
| | Girl | 0.193 | 22 | 0.032 | 0.879 | 22 | 0.110 |

a, Lilliefors significance correction

**Table 2** Descriptive study of various laboratory parameters in children

| | Min | Max | Mean | SE | Median |
|---|---|---|---|---|---|
| WBC (µL) | 9.05 | 0.89 | 10.46 | 27 | 1.5 |
| Hb (g/dL) | 8.75 | 0.27 | 8.82 | 13.3 | 5.6 |
| Plt (µL) | 82,500 | 14,678 | 117,922 | 513,000 | 12,000 |
| PT (seconds) | 23.2 | 1.85 | 26.25 | 61 | 12 |
| PTT (seconds) | 54 | 3.61 | 59 | 130 | 25 |
| INR | 2.4 | 0.45 | 3.47 | 14 | 1 |
| AST (units/L) | 137.5 | 54.33 | 254.52 | 2600 | 12 |
| ALT (units/L) | 85.5 | 45.69 | 170.18 | 2110 | 4 |
| Total bilirubin (mg/dL) | 16.4 | 2.19 | 21.18 | 58 | 0.6 |
| Direct bilirubin (mg/dL) | 8.95 | 0.98 | 10.38 | 24 | 0.1 |
| Creatinine (mg/dL) | 0.1 | 0.09 | 0.3 | 3.8 | 0.1 |
| Albumin (g/dL) | 3 | 0.09 | 2.98 | 4.8 | 1.7 |
| Fibrinogen level (mg/dL) | 95 | 6.67 | 102.62 | 197 | 24 |

The results of the age normality test based on gender are defined in Table 1.

As is presented in Table 1, the variable of age in both sexes is separate to be analyzed for the test. The results of the Kolmogorov–Smirnov and Shapiro–Wilk tests individually are authentic to either verify or reject the normality. The level of significance which is shown in the table indicates that the gender and the ages are not normal compared to each other ($P<0.05$). Accordingly, the nonparametric Mann–Whitney test is used to compare the average age between the genders.

The age of the control group was between 2 and 180 months. Twenty-four of them are boys with an average age of $11.23\pm24$, and 26 of them are girls with an average age of $9.66\pm26$. It is noteworthy that among 50 (100%), in 15 of them (30%), bleeding tested positive. In 44 (88%), jaundice was positive; in 33 people (66%), hepatomegaly was positive; in 28 people (56%), splenomegaly was positive; and in 39 people (78%), ascites was positive.

Table 2 describes the descriptive minimum, maximum, average, standard error, and median for different laboratory parameters in children afflicted with liver cirrhosis. The amount of standard error is equivalent to the standard deviation divided by the average.

It is worth mentioning that among 50 (100%), 39 of them (78%) had a Plt less than 150,000, and 11 (22%) had a Plt more or equal to 150,000.

As is shown in Table 3, among 46 people whose PELD factor was measured, 33 people (7.71%) had a PELD larger than 15, and 13 people (3.28%) had lower than 15 PELD amounts.

PELD score $<15$ was seen in 13 (28.3%) of children, and $PELD>=15$ was seen in 33 (71.7%) of the children. Fibrinogen level was $141.54\pm49.05$ mg/dL in $PELD<15$ and $89.58\pm39.21$ mg/dL in $PELD>=15$ group ($P<0.001$).

*However, all those 4 individuals for whom MELD Na was measured had severe liver cirrhosis.

In Table 4, the results of the independent *t*-tests are presented to evaluate and compare fibrinogen in two levels of cirrhosis (based on PELD criteria). This table shows the amount in both of the groups of the PELD classification, average, and standard deviation in each group. The achieved result based on the statistical indicator T and also *P*-value shows that the average fibrinogen in the group with PELD $<15$ is significantly higher than others ($P<0.001$).

**Table 3** Results of fibrinogen normality test in individuals based on PELD

| | PELD | Shapiro–Wilk | | | Kolmogorov–Smirnov | | |
|---|---|---|---|---|---|---|---|
| | | Sig | df | Statistic | Sig | df | Statistic |
| Fibrinogen level | PELD $<15$ | 0.2 | 13 | 0.155 | 0.184 | 13 | 0.910* |
| | PELD $>=15$ | 0.2 | 33 | 0.122 | 0.070 | 33 | 0.941* |

* This is a lower bound of the true significance

a, Lilliefors significance correction

**Table 4** The relationship between bleeding in children and their fibrinogen levels

| Fibrinogen classification bleeding | Fib < 100 (mg/dL) ($n=27$) | Fib > = 100 (mg/dL) ($n=23$) | Total | *p*-value |
|---|---|---|---|---|
| Negative | 18 (36) | 17 (34) | 35 (70) | 0.58 |
| Positive | 9 (18) | 6 (12) | 15 (30) | |

The results of the average normality test on the level of fibrinogen are presented in Table 3 classified based on PELD.

The results of Table 3 reveal the normality of the fibrinogen factor classified in groups of PELD ($P>0.05$). In this case, using a parametric independent *t*-test to compare the average fibrinogen among the PELD groups is allowed.

Fibrinogen ± SE level among the case and control group was 102.62 ± 6.66 and 390.98 ± 2.77, respectively ($p=0.00$).

In Table 4, the results of the chi-square test are used to investigate the relationship between bleeding in children and the level of fibrinogen in them. As can be seen, there is no noteworthy relationship between bleeding and the level of fibrinogen. The analysis of the frequency inside the table is quite telling of the same issue.

Among 15 children who had bleeding, 9 of them had a low level of fibrinogen, and 6 had a high level of fibrinogen. These frequencies are low to make the test meaningful. The average level of fibrinogen in children with bleeding is 103.47 ± 73.6 (mg/dL) and in those without bleeding is 102.47 ± 14.65 (mg/dL).

In Table 5, the results of the chi-square are used to investigate the relationship between the bleeding in children with $PELD<15$ and $15\leq PELD$. As can be seen, there is no significant relationship between the level of PELD and bleeding in individuals ($P=0.87$).

Table 6 shows the number, amount, average, standard deviation, and levels of fibrinogen at different levels of etiology. As can be seen, most of the studied cases were afflicted with underlying biliary atresia disease (22 people); the average of fibrinogen is 12.52 ± 73.107 mg/dL. The second most prevalent underlying disease is related to Wilson's in 10 individuals with average fibrinogen of 58.54 ± 7.77 mg/dL.

**Table 5** The relationship between bleeding and different levels of liver cirrhosis based on PELD

| Bleeding | PELD < 15 | PELD > = 15 | Total ($n=46$) | p-value |
|---|---|---|---|---|
| Negative | 9 (19.6) | 22 (47.8) | 31 (67.4) | 0.87 |
| Positive | 4 (8.7) | 11 (23.9) | 15 (32.6) | |

**Table 6** Evaluation and comparison of mean fibrinogen levels based on etiology

| | *n* | Fibrinogen level mg/dL (mean ± SD) |
|---|---|---|
| Autoimmune hepatitis | 4 | 95.25 ± 31.02 |
| Wilson | 10 | 77.7 ± 54.58 |
| Cystic fibrosis | 1 | 105 |
| Biliary atresia | 22 | 107.73 ± 52.12 |
| Galactosemia | 1 | 118 |
| Other | 12 | 115 ± 34.45 |

Using the Pearson correlation test, the relation between fibrinogen and PELD is investigated. Considering that the *P*-value is 0.067, no significant relationship is seen.

Logistic regression of the influence of PELD and fibrinogen on bleeding was shown in Table 7. In this table, the PELD effects on bleeding are also presented. The results of each of these factors' separate analyses show that none of these two (fibrinogen level and PELD) cannot predict bleeding in patients.

The study of the effects of fibrinogen on bleeding shows that the decrease in fibrinogen does not increase the chance of bleeding ($P=0.58$). Moreover, the study of the PELD effect on bleeding shows that the higher the PELD is does not necessarily mean that the risk of bleeding is increased ($P=0.87$).

Reference groups in logistic models are meant to be groups that are referential ones with which other groups are compared. For instance, the reference group in the analysis of the effect of fibrinogen is a group with fibrinogen higher than 100. In other words, if the binary logistic regression analysis above is meaningful, to interpret the odds ratio (OR), we need to compare the chance of bleeding in the group with low fibrinogen to the chance of bleeding in the group with fibrinogen above 100.

## Discussion

In our research, there is not a significant relationship between bleeding in children with their fibrinogen level and PELD. The results of the analyses of the binary

**Table 7** Binary logistic regression to investigate the influence of fibrinogen and PELD on bleeding

| Relevant factor | Category | Number | *OR* | CI 95% for OR | *p*-value |
|---|---|---|---|---|---|
| Fibrinogen | Fib < 100 | 27 | 1.42 | 0.43–4.83 | 0.58 |
| | Fib > = 100 | 23 | 1 | | |
| PELD | PELD < 15 | 13 | 1 | 0.28–4.48 | 0.87 |
| | PELD > = 15 | 33 | 1.13 | | |

*Ref* Reference group

logistic regression neither did nor confirm any predictive role for the level of fibrinogen and PELD for bleeding in patients. However, patients with $PELD \leq 15$ is noticeably less than those with $PELD < 15$. Our study is in line with other studies. De Maat et al. have shown that in patients with mild or average cirrhosis, the level of fibrinogen is as much as (or just a little more than) normal people, but in severe cases, the level of fibrinogen changes drastically [5]. In the research of Rizzo et al., fibrinogen level in patients with mild cirrhosis was more than in healthy people, but in severe patients, the level of fibrinogen was meaningfully less [4]. In Arif et al., the level of fibrinogen in the patients in the initial and final stages was less than the control group, and in the advanced patients, it was more than the control group [8]. In the study by Peng et al., fibrinogen level was significantly decreased among patients with liver cirrhosis compared to healthy control [9]. As mentioned above, fibrinogen level was increased among patients with cirrhosis in most of the studies while significantly decreased in Peng et al. study [9]; these differences may be due to sampling size and stage of disease.

However, in the study of Violi et al., there was a significant relationship between bleeding and fibrinogen level, and it is declared that cirrhosis patients who have had a history of gastrointestinal bleeding had a less level of fibrinogen [10]. Moreover, Takerar et al. showed that the low level of fibrinogen can predict a need for further blood transfusion during a liver transplant, but platelet count was not a predictor [11].

In the current study, 78% of the patient had thrombocytopenia. In the research of Violi et.al., among the patients with cirrhosis, 40% had an unusual bleeding time (more than 10 min), and 42% had a platelet count of less than 100,000/μL. Patients with severe liver failure had fewer platelet counts and longer bleeding times compared to milder failures. Bleeding duration is significantly related to platelet counts and fibrinogen. These data show that in cirrhosis, the deterioration of the function of platelets relates to the function of the liver. The inverse correlation between bleeding duration and fibrinogen suggests that low levels of this coagulant parameter may be partly responsible for platelet dysfunction [12].

The perception of hemostasis in patients with cirrhosis has changed with the concept of the re-imbalanced profile of the hemostatic concept [11]. Most studies that describe the risk of bleeding in cirrhosis and thrombocytopenia have not considered the amount of fibrinogen. Maximum amplitude in thromboelastography is a combination of platelet-fibrinogen interaction and can be used to assess clot strength. The evaluation of maximum amplitude in thromboelastography shows that even if there is a low platelet count if the fibrinogen is normal or high, sufficient clot strength will be achieved [11]. The combination of low platelet count and low fibrinogen always results in low maximum amplitude. And it is strongly associated with an increased tendency to bleed [13]. Velik-Salchner et al. showed improvement in clotting disorder and reduced blood loss in thrombocytopenia with increased fibrinogen [14]. A study by Takrar et al. showed that a 1 g increase in fibrinogen significantly altered the volume of blood injected into cirrhotic patients during orthopedic liver transplantation [11]. Studies have shown an increased risk of hemorrhage associated with an invasive approach with a low platelet count (less than $10^9 \times 75$/L), but it should be noted that these studies failed to assess the contribution of fibrinogen to clot strength in cases of thrombocytopenia [15]. In the study by Jarasvaraparn et al., they showed children with liver cirrhosis had more defects in fibrinogen and platelet compared to healthy control [16].

## Conclusion

The present study has shown that fibrinogen levels are significantly associated with the severity of liver cirrhosis and decrease further as the disease becomes more severe (PELD level). According to our information, the present study is the only research conducted in this field on children and is, therefore, new research. It is suggested that in subsequent similar studies, fibrinogen functional tests be used to measure its efficacy in patients with liver cirrhosis.

### Limitation

This is a single-center study and limited sample size. The control group was not included in this study.

#### Abbreviations

| | |
|---|---|
| AST | Aspartate aminotransferase |
| ALT | Alanine aminotransferase |
| Hb | Hemoglobin |
| MELD | Model for end-stage liver disease |
| PELD score | Pediatric end-stage liver disease score |
| PLT | Platelet |
| WBC | White blood cell |

#### Authors' contributions

NH and SMD supervised the research and follow up with the patients. SHH revised the proposal and data analysis. HJ review the literature and revised the manuscript. All authors reviewed the manuscript. The authors read and approved the final manuscript.

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#### Availability of data and materials

Data was available with the authors.

## Declarations

#### Ethics approval and consent to participate

This study was approved by the ethical committee of the Shiraz University of Medical Sciences. All methods were performed following the relevant

guidelines and regulations (Declaration of Helsinki for experiments involving humans). Informed consent was signed by parents or legal guardians.

**Consent for publication**
Nothing to declare.

**Competing interests**
The authors declare that they have no competing interests.

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**References**

1. Gligorijević N, Minić S, Križáková M, Katrlik J, Nedić O (2018) Structural changes of fibrinogen as a consequence of cirrhosis. Thromb Res 166:43–49
2. El-Sayed R, El-Karaksy H, El-Raziky M, El-Hawary M, El Koofy N, Helmy H, Fahmy M (2013) Assessment of coagulation and fibrinolysis in children with chronic liver disease. Blood Coag Fibrinol 24(2):113–117
3. Kujovich JL (2015) Coagulopathy in liver disease: a balancing act. Hematology Am Soc Hematol Educ Program 2015:243–249
4. Rizzo K, Vella K, Zammit D, Gatt P, Grima C, Inguanez MB, Gerada J, Ellul P, Vassallo M, Azzopardi N (2019) Fibrinogen measurement in liver disease: validation of the functional fibrinogen thromboelastography assay and a novel mathematical predictive model. Blood Transfus 17(3):237–246
5. de Maat MP, Nieuwenhuizen W, Knot EA, van Buuren HR, Swart GR (1995) Measuring plasma fibrinogen levels in patients with liver cirrhosis. The occurrence of proteolytic fibrin (ogen) degradation products and their influence on several fibrinogen assays. Thromb Res 78(4):353–362
6. Lisman T, Porte RJ (2010) Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 116(6):878–885
7. Freeman RB Jr, Wiesner RH, Roberts JP, McDiarmid S, Dykstra DM, Merion RM (2004) Improving liver allocation: MELD and PELD. Am J Transplant 4(Suppl 9):114–131
8. Arif S, Khan AS, Khan AR (2002) Changes in fibrinogen level in liver cirrhosis. J Ayub Med Coll Abbottabad 14(2):19–21
9. Peng J, He G, Chen H, Kuang X (2021) Study on correlation between coagulation indexes and disease progression in patients with cirrhosis. Am J Transl Res 13(5):4614–4623
10. Violi F, Leo R, Basili S, Ferro D, Cordova C, Balsano F, Group C (1994) Association between prolonged bleeding time and gastrointestinal hemorrhage in 102 patients with liver cirrhosis: results of a retrospective study. Haematologica 79(1):61–65
11. Thakrar SV, Mallett SV (2017) Thrombocytopenia in cirrhosis: impact of fibrinogen on bleeding risk. World J Hepatol 9(6):318–325
12. Violi F, Leo R, Vezza E, Basili S, Cordova C, Balsano F (1994) group C: Bleeding time in patients with cirrhosis: relation with degree of liver failure and clotting abnormalities. J Hepatol 20(4):531–536
13. Klein A, Arnold P, Bingham R, Brohi K, Clark R, Collis R, Gill R, McSporran W, Moor P, Rao Baikady R (2016) AAGBI guidelines: the use of blood components and their alternatives 2016. Anaesthesia 71(7):829–842
14. Velik-Salchner C, Haas T, Innerhofer P, Streif W, Nussbaumer W, Klingler A, Klima G, Martinowitz U, Fries D (2007) The effect of fibrinogen concentrate on thrombocytopenia. J Thromb Haemost 5(5):1019–1025
15. Giannini EG, Greco A, Marenco S, Andorno E, Valente U, Savarino V (2010) Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol 8(10):899–902
16. Jarasvaraparn C, Rusch C, Nadler M, Drobish J, Stoll J, Doyle MB, Khan A, Kulkarni S (2022) Characterization of biomarkers of hemostasis and bleeding-related outcomes in children with cirrhosis. J Pediatr Gastroenterol Nutr 75(4):506–513

## Publisher's Note