

Gamma-glutamyl transpeptidase is a useful predictor in evaluating the prognosis in pediatric acute liver failure

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Research article

Keywords: Pediatric acute liver failure, prognosis, gamma-glutamyl transpeptidase, pediatric end-stage liver disease scoring system

Posted Date: December 9th, 2019

DOI: <https://doi.org/10.21203/rs.2.18355/v1>

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Abstract

Background and objective: Pediatric acute liver failure (PALF) progresses rapidly and has a poor prognosis. Therefore, simple, sensitive and specific clinical indicators are needed. Gamma-glutamyl transpeptidase (GGT) plays a role in predicting the prognosis in infantile cholestatic liver diseases. However, its role in predicting the prognosis in PALF remains unclear.

Methods: In present study, children with PALF were divided into a normal GGT group and a high GGT group using the GGT level of 50 U/L as the demarcation line. Age, sex, serum total bilirubin, direct bilirubin, albumin, total bile acid, international normalized ratio (INR) and pediatric end-stage liver disease (PELD) score were compared between the 2 groups. In addition, GGT level was subjected to receiver operating characteristic (ROC) curve analysis, and the area under the curve and the optimal diagnostic cutoff value were calculated.

Results: A total of 41 children with PALF were enrolled in the study. INR, PELD score and mortality rate were significantly higher in the normal GGT group in comparison to the high GGT group. GGT level had area under the ROC curve of 0.8194 (95% CI : 0.680-0.959); the optimal diagnostic cutoff values were 60 U/L. At the cutoff value, the sensitivity and specificity of GGT level in predicting the prognosis in PALF were 86.36% and 73.68% respectively.

Conclusion: GGT exhibited high sensitivity and specificity in predicting the prognosis in PALF. It can be used as one useful prognostic indicator of PALF.

Background

Pediatric acute liver failure (PALF) is a critical condition. Patients with PALF may rapidly develop massive necrosis of hepatocytes, significant abnormalities in blood coagulation function, cholestasis, and a substantial reduction in serum albumin (Alb) in a short period of time. The patients may even suffer serious complications such as hepatic encephalopathy, multiple organ dysfunction and disseminated intravascular coagulation. The PALF mortality rate is rather high[1, 2]. With the development and widespread application of liver transplantation technology, the PALF survival rate has reached 60–80% [3]. To distribute donor livers equitably and accurately, the pediatric end-stage liver disease (PELD) scoring system has been utilized clinically since 2002. The scoring system consists of 5 indices: age, total bilirubin (TB), albumin (Alb), international normalized ratio (INR) and growth retardation. Liver transplantation is prioritized based on the PELD score[4], which has achieved satisfactory outcomes in evaluating the condition and prognosis of patients with pediatric chronic liver diseases and acute liver failure[5–9]. In recent years, studies have found that the PELD scoring system has some limitations under certain circumstances. For example, children under 2 years of age with biliary atresia have a higher mortality rate during the waiting period for liver transplantation. Moreover, although children with PALF complicated by portal hypertension or hepatopulmonary syndrome may have low PELD scores, they still suffer a high risk of death[10, 11]. Therefore, the short-term mortality rate of children with PALF is

underestimated[12, 13]. Some studies suggest that bilirubin, Alb, INR, alanine aminotransferase (ALT), blood ammonia and alpha-fetoprotein (AFP) can be used as prognostic indicators[7, 14, 15]. The role of gamma-glutamyl transpeptidase (GGT) in the evaluation of the prognosis in PALF remains unclear. The present study retrospectively analyzed the clinical data of children with acute liver failure who were hospitalized and treated in our hospital between 2012 and 2018 and explored the role of GGT in predicting the prognosis in PALF.

Methods

Study subjects

The study subjects were children with PALF who were treated in a tertiary hospital between August 2010 and August 2018. All children aged 1 month to 14 years met the following criteria: (1) the child had no clear previous history of chronic liver disease; (2) biochemical markers indicated liver function damage; (3) the child had a bleeding time (due to liver injury) of ≥ 15 s or had an INR of ≥ 1.5 , which was accompanied by hepatic encephalopathy, or the child had an INR of ≥ 2.0 , regardless of whether she/he suffered concurrent hepatic encephalopathy; and (4) the coagulation abnormalities described above could not be corrected with vitamin K1.

After hospital admission, the children with PALF were given timely treatments, including supplementation with fat-soluble vitamins, promotion of bile acid metabolism, reduction in blood ammonia production, nutritional support, vital sign monitoring, and complication prevention. In addition, sever patients were given plasma exchange therapy if they had a serum TB level of > 200 $\mu\text{mol/L}$ or a TBA level of > 100 $\mu\text{mol/L}$, an ALT level of > 1000 U/L, and/or an INR of > 2.0 . The present study complied with the 1983 Declaration of Helsinki and was approved by the Ethics Committee of the Children's Hospital of Hebei Province. Informed consent was obtained from the children or their guardians. (No. 2016034).

Diagnosis of the etiology of PALF

(1) Infectious factors: The examination performed included tests for hepatitis A, hepatitis B, hepatitis C, hepatitis E, HIV, Treponema pallidum, Toxoplasma gondii, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), parvovirus B19 antibody and nucleic acids as well as blood, urine and stool cultures. (2) Metabolic disorder: The examination performed included a blood sugar test, blood ammonia test, lactic acid test, blood lipid test, ceruloplasmin test, serum copper test, 24-hour urinary copper test, alpha-fetoprotein test, thyroid function test, and hematuria tandem mass spectrometry. (3) Autoimmune factors: autoantibody levels, complement C3/C4 levels, erythrocyte sedimentation rate, anti-nuclear antibody levels, autoimmune liver disease antibody levels, and immunoglobulin levels were examined. (4) Hematological disease: Based on the conditions of the children, a blood smear test, blood lipid test, ferritin test, and bone marrow puncture examination were conducted. (5) Imaging examination: Ultrasonography of the liver and gallbladder, chest/spine X-ray, and cardiac echocardiography were performed. (6) Liver puncture examination: After the parents were informed and signed the consent form,

a portion of the children underwent percutaneous liver puncture biopsy. (7) Genetic testing: If the cause of the disease could not be identified by the above tests, whole exome examination was performed.

Clinical data

Various laboratory indicators of the children were collected at the time when the INR reached a peak value, including TB, direct bilirubin (DB), TBA, GGT, serum Alb and INR.

Patient grouping

The children were divided into a normal GGT group and a high GGT group based on the criterion that the upper normal limit (UNL) of GGT was 50 U/L.

Prognosis

The children were followed up until 3 weeks after the peak INR was reached. Native liver survival was considered a good prognosis, whereas death or accepting liver transplantation was considered a poor prognosis.

Ethical approval of the study

The study protocol was performed in compliance with the Declaration of Helsinki. Informed consent was obtained from the guardian of every participant.

Statistical methods

Analysis was performed using stata10.0 statistical software. Nonnormally distributed data are expressed using the median (interquartile range). Intergroup comparisons of the measurement data was performed using the Mann-Whitney U test (nonnormal distribution), whereas the count data were analyzed using Fisher's exact probability test. The Spearman rank test was employed to examine correlations. GGT was subjected to receiver operating characteristic (ROC) curve analysis, and the areas under the ROC curves and the optimal diagnostic cutoff value were calculated. A P value of less than 0.05 indicated that the difference was statistically significant.

Results

General information A total of 41 children with acute liver failure were enrolled in the present study. Among the 41 children, 19 (46.34%) were males, 19 (46.34%) were aged 1 month to 1 year, 7 (17.07%) were aged more than 1 year to 3 years, 4 (9.76%) were aged more than 3 years to 6 years, and 11 (26.83%) were aged more than 6 years to 11 years. There were 19 deaths (46.34%), among whom 10 were males. The parents of these children were not consanguineous.

Causes of PALF The causes of PALF included hereditary metabolic diseases (13 children, 31.70%), infectious factors (11 children, 26.83%), drug, mushroom and other organic compound poisoning (6 children, 14.63%), autoimmune liver disease (2 children, 4.88%), hematological disease (1 child, 2.44%), and ischemic liver disease (1 child, 2.44%). The etiology of PALF was unclear in 7 children (17.07%). The results are shown in Table 1.

Comparison of the clinical indicators between the groups of children with different GGT levels

In the present study, the UNL of GGT, 50 U/L, was used as the demarcation line. Fourteen children had GGT levels less than 50 U/L; these children were included in the normal GGT group. The remaining 27 children constituted the high GGT group. Compared to the high GGT group, INR, PELD score and mortality rate were significantly elevated in the normal GGT group (INR: 5.76 vs 2.45, $P=0.0042$; PELD score: 37.95 vs 23.40, $P=0.0002$; mortality rate: 78.57% vs 29.63%, $P=0.004$) (Table 2).

Table 2 Comparison of clinical data between the groups with different GGT levels

	Normal GGT group (n=14)	High GGT group (n=27)	Statistics	<i>P</i> value
	Median (range)	Median (range)		
Age(month)	9 (4, 84)	18 (6, 69)	-0.110 ^a	0.9123
Sex				
Male	6	13	1.000 ^b	0.504
Female	8	14		
Prognosis				
Death	11	8	0.007 ^b	0.004
Survival	3	19		
TB	173.4 (124.1, 297.8)	145.5 (82.9, 225.1)	0.742 ^a	0.4579
DB	95.65 (70.8, 145.2)	122.5 (65.2, 183.6)	-0.577 ^a	0.5637
Alb	30.15 (23, 36.6)	29 (24.2, 37.7)	-0.130 ^a	0.8966
INR	5.76 (3.55, 6.54)	2.45 (2.04, 4.17)	2.860 ^a	0.0042
TBA	106.4 (61.5, 127.9)	173.8 (76.7, 323)	-1.650 ^a	0.0990
PELD score	37.95 (31.3, 41.2)	23.4 (18.2, 31.6)	3.765 ^a	0.0002

Note: TB, serum total bilirubin; DB, serum direct bilirubin; Alb, serum albumin; INR, international normalized ratio of prothrombin time; TBA, serum total bile acid; PELD:

model of pediatric end-stage liver disease; ^a represents the Z value; ^b indicates Fisher's exact test.

Comparison of the GGT levels in children with PALF in different prognosis groups

The children with PALF were divided into a death group and a survival group based on different prognoses. The death group had a GGT level of 36 U/L (22, 73), whereas the survival group had a GGT level of 91.5 U/L (74, 170). The difference between the 2 groups was statistically significant ($P=0.0115$) (Table 3).

Table 3 GGT levels in children with PALF in different prognosis

	Death group (n=19)	Survival group (n=22)	Statistics	P value
	Median (range)	Median (range)		
GGT	36 (22, 73)	91.5 (74, 170)	-3.492	0.0005

Abbreviation: GGT=Gamma-glutamyl transpeptidase

The correlation between serum GGT level and PELD score

Serum GGT level and PELD score displayed a nonbivariate normal distribution. Based on the Spearman rank correlation test, the Spearman correlation coefficient between GGT level and PELD score was -0.3908. There was a significant negative correlation between the GGT level and PELD score ($P=0.0005$) (Figure 1).

ROC curve analysis

ROC curve analysis was performed on the GGT levels in children with PALF. The area under the ROC curve was 0.8197 (95% CI: 0.680, 0.959) (Figure 2). The optimal diagnostic cutoff value was 60 U/L. At this cutoff value, the sensitivity of GGT level for predicting the prognosis in PALF was 86.36%; the specificity was 73.68%.

Discussion

PALF is a severe condition with a high mortality rate. The results of the present study indicated that hereditary metabolic liver disease was the main cause of PALF. The mortality rate of the children with PALF who did not undergo liver transplantation was 46.34%. GGT could serve as one of the useful indicators of poor prognosis in children with PALF. Good sensitivity and specificity were achieved when a GGT level of 60 U/L was used as the cutoff to predict poor prognosis.

In the present study, 13 children (31.70%) had hereditary metabolic liver disease, including hepatolenticular degeneration (5 children), citrin deficiency (4 children), progressive familial intrahepatic cholestasis (PFIC) type II (1 child), medium-chain acyl-coenzyme A dehydrogenase deficiency (1 child), mitochondrial DNA depletion syndrome (1 child), and homocysteinemia (1 child). 3 died among the 13 children. PALF caused by hereditary metabolic liver diseases showed a better prognosis than did PALF resulting from other causes, which was consistent with the findings of previous studies[16, 17]. Vomiting and retarded growth and development represent clues for early diagnosis of hereditary metabolic diseases. Mother's history of spontaneous abortion, sibling death, similar disease in siblings, significant increase in blood lactate, ammonia and INR, and moderate elevation of ALT and TB levels also provide diagnostic clues for identification of PALF caused by hereditary metabolic diseases[18–20]. Infectious factors are common causes of PALF in developing countries, among which viral hepatitis is most common[21, 22]. In the present study, 11 children had infection-induced PALF, among whom 5 had bacterial sepsis-induced multiple organ failure, 2 had EBV infection, 2 had measles, 1 had HSV infection, and 1 had CMV infection. However, there was no case of PALF caused by hepatitis A to E viral hepatitis, which is inconsistent with the results reported in the literature[23]. The underlying reasons for the contradictory result are that measures to block mother-to-child transmission of hepatitis B virus (HBV) and improve vaccination procedures for HBV have gradually advanced in China. The present study failed to identify the causes of PALF in 7 children (17.07%). With the continuous improvement of diagnostic techniques, some children with PALF of unknown etiology were eventually diagnosed as having autoimmune liver diseases, mitochondrial diseases and other metabolic diseases[24–26].

In 2002, PELD scores started to be used to evaluate children with chronic liver failure who were under 12 years of age awaiting liver transplantation. At a cutoff value of 33, PELD score showed a sensitivity of 81% and a specificity of 86% in predicting a poor prognosis, the area under the curve was 0.88[6]. Núñez-Ramos et al. found that at a cutoff value of 28, PELD score exhibited a predictive sensitivity of 72.7% and a specificity of 100% in predicting a poor prognosis[27]. Patients with high scores had an increased risk

of death. In the present study, a significant negative correlation was found between the GGT level and PELD score, which may indicate that low GGT level is also efficient in predicting the prognosis in PALF.

In a variety of pediatric intrahepatic cholestasis liver diseases, low GGT levels also play a prognostic role. Wang et al. found that low GGT levels were significantly correlated with hepatic inflammation in infantile idiopathic cholestasis. The transaminase level was significantly elevated in children with infantile idiopathic cholestasis with a GGT level lower than 100 U/L, and the liver biopsy showed severe inflammation[28]. Lu et al. analyzed 135 children with cholestasis of different causes. It was found that patients with GGT level between 75 and 300 U/L tended to have a good prognosis. However, among the patients with low GGT level (< 100U/L), about 47.4% patients had poor prognosis[29]. In the children with citrin deficiency, the death group had a GGT level of 87.43 ± 71.78 IU/L, which was significantly lower than the survival group (223.37 ± 125.91 IU/L). The results indicate that GGT is an indicator of poor prognosis in children with citrin deficiency[30]. In neonatal sepsis-related cholestasis, GGT showed a sensitivity of 69% and a specificity of 68% in predicting a poor prognosis when the cutoff value was set to 85.5 U/L[31]. In the present study, GGT exhibited a sensitivity of 86.36% and a specificity of 73.68% in predicting a poor prognosis in PALF when the cutoff value was 60 U/L. The area under the ROC curve was 0.819.

GGT is mainly present in the cytoplasm of hepatocytes and bile duct epithelium. It facilitates the transport of the antioxidant glutathione into cells. Factors such as drugs, alcohol, viral infection and inflammatory reaction cause fluctuations in GGT levels. The lower GGT level in the children with PALF with a poor prognosis may result from liver dysfunction-caused failure of bile salt pumps. Moreover, since the decrease in the GGT level is accompanied by reduced glutathione synthesis, both the protective antioxidant capacity and the bile acid metabolic activity decline, leading to further aggravation of liver failure. It should be noted that GGT levels remain normal in some cholestatic liver diseases, such as PFIC (type 1, type 2 and type 4,5,6), bile acid synthesis deficiency and arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome.

The present study was a retrospective analysis, and the obtained conclusions have certain limitations. It is necessary to expand the sample size for further investigation. A portion of the children did not undergo liver puncture examination. Possible correlations between GGT levels in children with PALF and the severity of liver tissue lesions should be determined. In addition, the causes of PALF remain unclear in certain children. To clarify the cause, further improvement of the detection techniques is necessary. As a simple, low-cost noninvasive examination, GGT level is one of the useful indicators for predicting prognosis in PALF.

Conclusion

We found that the poor prognosis cases had a lower level of GGT, which had a significant negative correlation with PELD score. ROC analysis indicated that the diagnostic cutoff value of GGT was 60 U/L.

By the using of this cutoff value, the sensitive and specificity were 86.36% and 73.68%, respectively. It is possible to be a well predictor to evaluate the prognosis of PALF patients

List Of Abbreviations

PALF: Pediatric acute liver failure

GGT: Gamma-glutamyl transpeptidase

INR: International normalized ration

PELD: Pediatric end-stage liver disease

ROC: Receiver operating characteristic

ALT: Alanine aminotransferase

AFP: Alphafetoprotein

CMV: Cytomegalovirus

EBV: EpsteinBarr virus

HSV: Herpes simplex virus

Declarations

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Children's Hospital of Hebei Province (approval no. 2016034). Informed consent was obtained from the children or their guardians.

Consent for publication

All authors have contributed to and agreed on the content of the manuscript.

Availability of data and materials

The data analyzed in this study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

Conflict of Interest

All authors declare no conflict of interest related to this article.

Funding

None

Authors' contributions

Haiyan Fu conceived the study. Haiyan Fu and Ruiqin Zhao both conducted diagnoses of PALF patients and wrote the manuscript in this study. All the authors managed the patients, collected patient data, conducted statistical analyses.

Acknowledgements

We thank all the parents of the cases who participated the study.

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Table

Table 1 Causes of PALF

Causes of PALF	1 month - 3 years (n=26)	>3 years - 6 years (n=6)	>6 years - 14 years (n=9)	Number of deaths
Hereditary metabolic liver disease (n=13)				
Hepatolenticular degeneration		1	4	2
Citrin deficiency	4			0
PFIC type II	1			0
Medium-chain acyl-CoA dehydrogenase deficiency	1			0
Mitochondrial DNA depletion syndrome	1			1
Homocysteinemia	1			0
Infectious factor (n=11)				
Bacterial sepsis	4		1	3
EB	2			0
HSV	1			1
Measles	1	1		0
CMV	1			0
Poisoning factor (n=6)				
Traditional Chinese medicine		1		0
Drug Hypersensitivity syndrome	1			0
Mushroom		1	1	2
Other poisons			2	2
Hematological disease (n=1)				
Langerhans cell histiocytosis	1			1
Autoimmune liver disease (n=2)				
Autoimmune hepatitis type 1			1	1
Autoimmune sclerosing		1		0

cholangitis

Ischemia (n=1)

After rod

1

1

disease/cardiopulmonary

resuscitation

Unknown cause (n=7)

7

5

Abbreviations: PALF=pediatric acute liver failure; PFIC= progressive familial intrahepatic cholestasis; EB=Epstein-Barr virus; HSV=herpes simplex virus; CMV=cytomegalovirus (CMV)

Figures

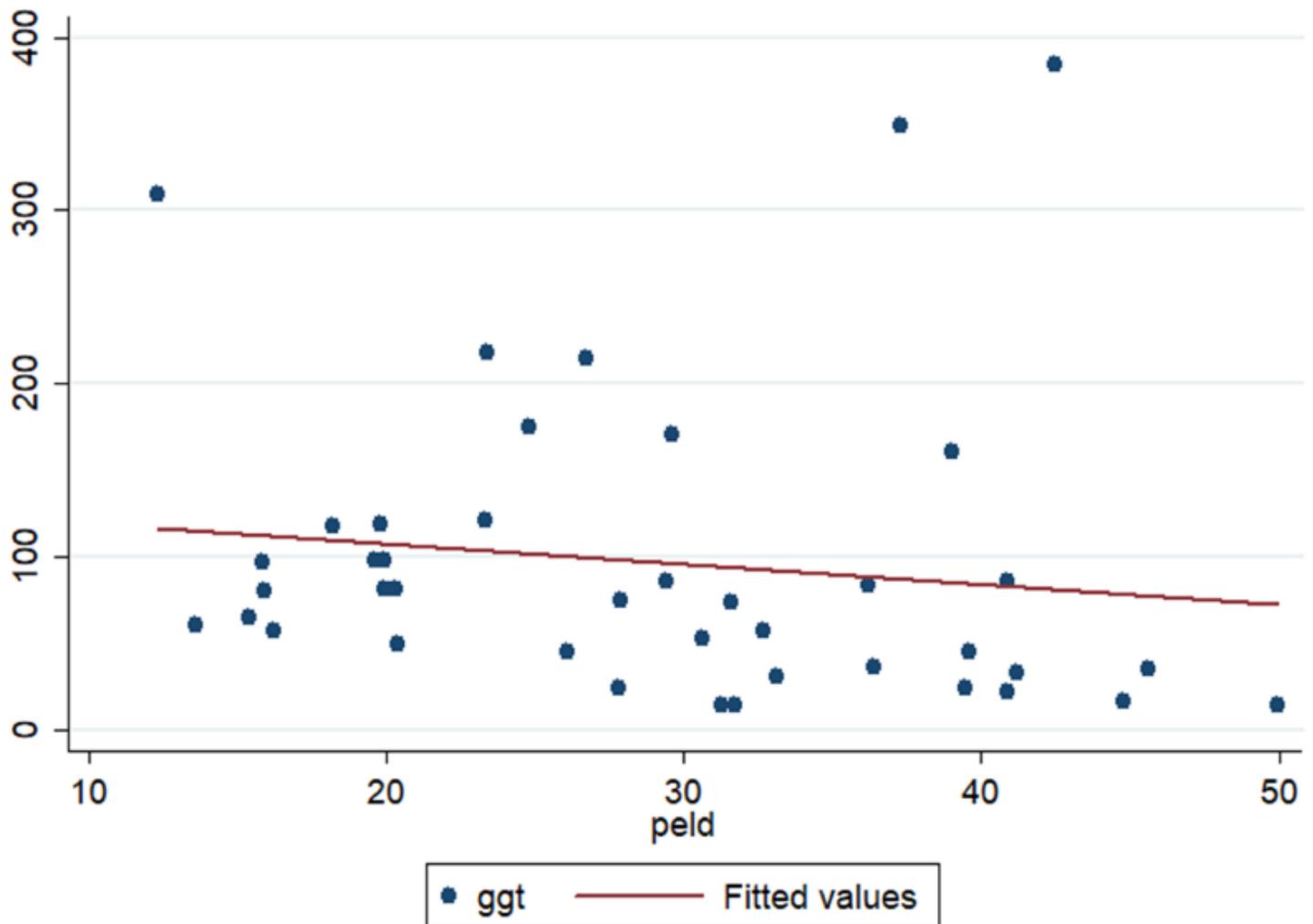


Figure 1

significant correlation between GGT level and PELD score. GGT: Gamma-glutamyltransferase PELD: pediatric end-stage liver disease

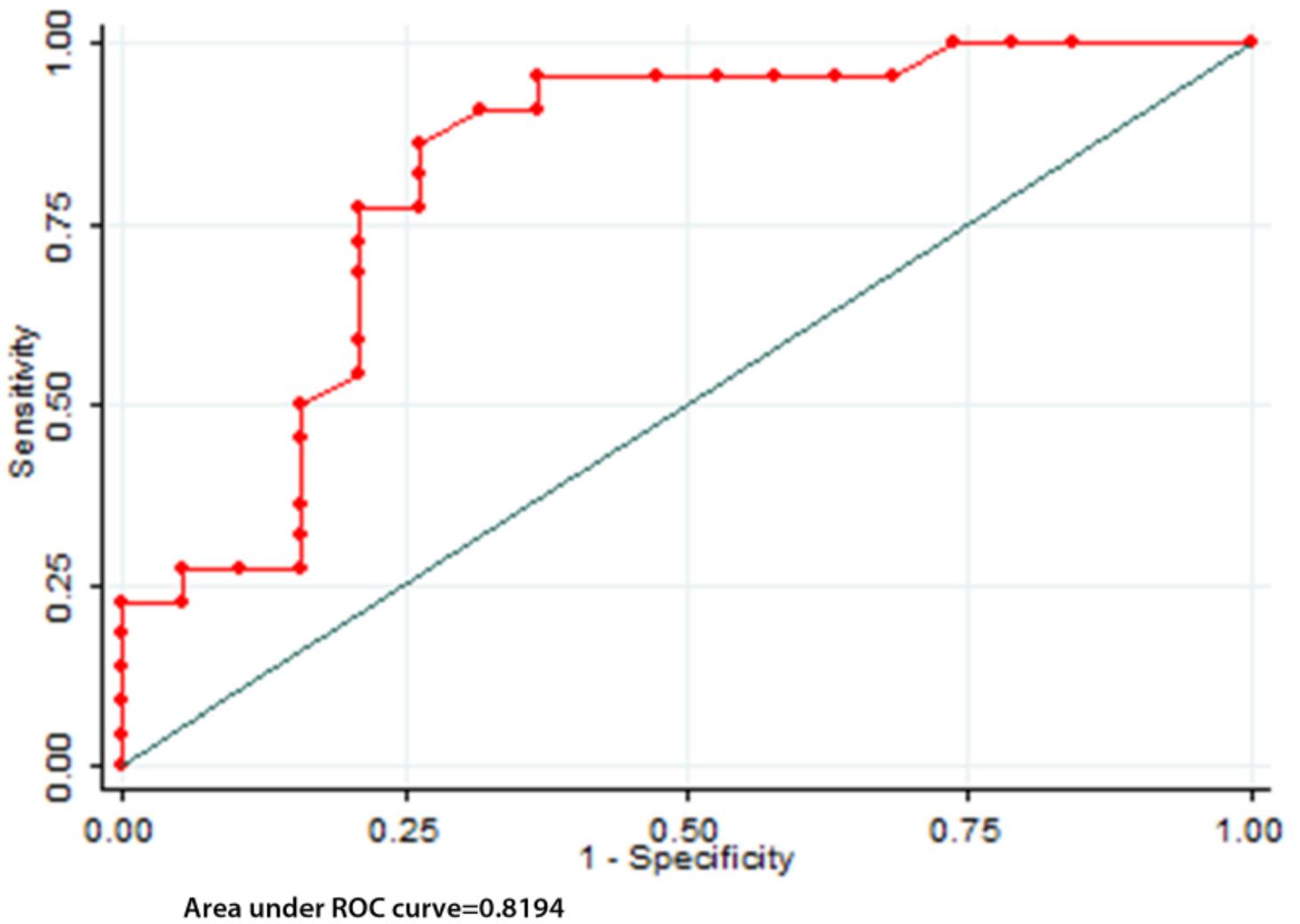


Figure 2

ROC curve analysis of serum GGT. ROC: Receiver operating characteristic GGT: Gamma-glutamyltransferase