Prediction of histopathological grades of liver pathology in cholestasis by direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level

(judul baru, judul asli saat submit mengalami revisi setelah komen dari reviewer)

Tanggal 13 Oktober 2022 corresponding author submit naskah:

SLJCH] Submission Acknowledgement - "COMPARISON BETWEEN DIRECT BILIRUBIN, ASPARTATE AMINOTRANSFERASE, ALANINE AMINOTRANSFERASE, AND ALBUMIN LEVEL WITH DIFFERENT HISTOPATHOLOGICAL GRADE OF LIVER BIOPSY IN CHILDREN WITH CHOLESTASIS"

Eksternal
Kotak Masuk

Sri Lanka Journal of Child Health <no-reply@ubiquitypartnernetwork.com> Kam, 13 Okt 2022, 06.31

kepada saya

Dear Dr Bagus Setyoboedi,

Thank you for submitting the manuscript, "COMPARISON BETWEEN DIRECT BILIRUBIN, ASPARTATE AMINOTRANSFERASE, ALANINE AMINOTRANSFERASE, AND ALBUMIN LEVEL WITH DIFFERENT HISTOPATHOLOGICAL GRADE OF LIVER BIOPSY IN CHILDREN WITH CHOLESTASIS" to Sri Lanka Journal of Child Health. With our online journal management system, you will be able to track its progress through the editorial process by logging in to the journal web site.

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Comparison between direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level with different histopathological grades of liver biopsy in children with cholestasis

Eksternal
Kotak Masuk

D

Dr. G.N. Lucas <drgnlucas@gmail.com> Min, 16 Okt 2022, 13.11

kepada saya

Dear Dr Bagus Setyoboedi
Could you please e-mail me a copy of the ethics clearance certificate
Regards
Dr G N Lucas
Joint Editor SLJCH

Tanggal 16 Oktober 2022 corresponding author membalas jawaban sertifikat kelayakan etik: 16 Okt 2022, 15.38

BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id>

kepada **G.N.**

Dear Lucas,

Here I send ethical clearance certificate of the study.

Best regards
Bagus Setyoboedi

Tanggal 16 Oktober 2022 corresponding author mendapatkan email dari editor untuk meminta data terkait sertifikat kelayakan etik:

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Dr. G.N. Lucas <drgnlucas@gmail.com> 16 Okt 2022, 21.03

kepada saya

The certificate is in Indonesian, I require the following information
1. The Institution granting ethical clearance
2. The reference number of the ethical clearance
3. The date of issue of the ethical clearance certificate
Regards
Dr Lucas

Tanggal 16 Oktober 2022 corresponding author membalas jawaban sertifikat kelayakan etik:

BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 16 Okt 2022, 21.24

kepada G.N.

Dear Lucas,
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2. The reference number is 259 / Panke.KKE / IV / 2017
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Bagus Setyoboedi

Tanggal 16 Oktober 2022 corresponding author mendapat balasan email dari editor tentang respon terhadap jawaban sertifikat kelayakan etik:

D

Dr. G.N. Lucas <drgnlucas@gmail.com> 17 Okt 2022, 09.35

kepada saya

Thanks
Dr Lucas

Tanggal 26 Oktober 2022 corresponding author mendapat email dari editor tentang komen reviewer:

D

Dr. G.N. Lucas <drgnlucas@gmail.com> Rab, 26 Okt 2022, 18.33

kepada saya

Dear Dr Bagus Setyoboedi
The following are the comments of the reviewer.

"1. Topic : suggest : **prediction of histopathological grades of liver pathology in cholestasis by direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level**
2. Methodology: unclear about the population – the indication for the biopsy, clinical diagnosis, the age group etc
3. Discussion : needs improvement – comparing with other studies and explanation of the findings
4. Conclusions ; Need rephrasing "

Please respond to the comments via direct e-mail.

Regards

Dr G N Lucas

Joint Editor SLJCH

Tanggal 12 November 2022 corresponding author mendapat email dari editor menanyakan kembali tentang komen reviewer:

D

Dr. G.N. Lucas <drgnlucas@gmail.com> 12 Nov 2022, 14.47

kepada **s.d.p.soegianto**, **sjamsul.arief**, saya

Dear All
There has been no response to my e-mail sent to the corresponding author on 26th October, not even an acknowledgement. If no response is obtained by 19th November your article will be rejected and archived.
Regards
Dr G N Lucas
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BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 12 Nov 2022, 17.25

kepada G.N.

Dear Lucas,

I am sorry for the late reply your mail. We still do the revision according to the reviewer comments.
Thank you for your understanding.

Regard
Bagus Setyoboedi

Tanggal 21 November 2022 corresponding author membalas email dari editor bahwa revisi komen reviewer dikirim dan judul sudah diubah sesuai komen reviewer:

BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 21 Nov 2022, 09.15

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Dear Lucas

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I hope that still have opportunity to publish it.

Regard
Bagus S

Tanggal 21 November 2022 corresponding author mendapat email dari editor tentang ORCHID author:

Dr. G.N. Lucas <drgnlucas@gmail.com> 21 Nov 2022, 20.55

kepada saya

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Dr Lucas

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kepada G.N.

Dear dr. Lucas

Tank you for your kindness to give us opportunity. Here are the Orchid number of the authors:
Bagus Setyoboedi
0000-0002-3923-6913

Sugi Deny Pranoto Soegianto
0000-0001-8162-6862

Sjamsul Arief
0000-0002-6372-2460

Best regard
Bagus S

Tanggal 22 November 2022 corresponding author mendapat email dari editor untuk melakukan revisi naskah yang akan terbit:

Prediction of histopathological grades of liver pathology in cholestasis by direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level

Eksternal
Kotak Masuk

D

Dr. G.N. Lucas <drgnlucas@gmail.com> Sel, 22 Nov 2022, 11.52

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Dear Dr Bagus Setyoboedi
Your article "Prediction of histopathological grades of liver pathology in cholestasis by direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level" has been

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kepada **G.N.**

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Bagus S

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2 pesan

Sri Lanka Journal of Child Health <no-reply@ubiquitypartnernetwork.com> 13 Oktober 2022 pukul 06.31
Balas Ke: bjcp@ymail.com
Kepada: bagus.setyoboedi@fk.unair.ac.id

Dear Dr Bagus Setyoboedi,

Thank you for submitting the manuscript, "COMPARISON BETWEEN DIRECT BILIRUBIN, ASPARTATE AMINOTRANSFERASE, ALANINE AMINOTRANSFERASE, AND ALBUMIN LEVEL WITH DIFFERENT HISTOPATHOLOGICAL GRADE OF LIVER BIOPSY IN CHILDREN WITH CHOLESTASIS" to Sri Lanka Journal of Child Health. With our online journal management system, you will be able to track its progress through the editorial process by logging in to the journal web site.

Your submission will now be considered by our Editors. Research papers deemed appropriate for the journal will proceed directly to peer review, which generally take around 8 weeks to be completed. Non-research papers will undergo a full Editorial review process, which will take 2-3 weeks. Following the completion of the review, you will be contacted by journal staff with review feedback.

Thank you for considering this journal as a venue for your work. Please get in touch should you have any questions regarding your paper.

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BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 13 Oktober 2022 pukul 08.06
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[Kutipan teks disembunyikan]

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Comparison between direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level with different histopathological grades of liver biopsy in children with cholestasis

10 pesan

Dr. G.N. Lucas <drgnlucas@gmail.com> 16 Oktober 2022 pukul 13.10
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Joint Editor SLJCH

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Kepada: "Dr. G.N. Lucas" <drgnlucas@gmail.com>

Dear Lucas,

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Dr Lucas
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BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 16 Oktober 2022 pukul 21.09
Kepada: rendiskaji@yahoo.com

---------- Forwarded message ---------
From: **Dr. G.N. Lucas** <drgnlucas@gmail.com>
Date: Sun, Oct 16, 2022, 21:03
Subject: Re: Comparison between direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level with different histopathological grades of liver biopsy in children with cholestasis
To: BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id>

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BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 16 Oktober 2022 pukul 21.14
Draf Untuk: "Dr. G.N. Lucas" <drgnlucas@gmail.com>

Dear Lucas,
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1.
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BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 16 Oktober 2022 pukul 21.15
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Kepada: "Dr. G.N. Lucas" <drgnlucas@gmail.com>

Dear Lucas,
About the ethical clearance certificate:
1. Granting by the ethical committee of Dr. Soetomo Hospital in Surabaya Indonesia
2. The reference number is 259 / Panke.KKE / IV / 2017
3. The date of issue April 06, 2017

Thank you for your kind attention.

Regard.
Bagus Setyoboedi
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Rendi Aji <rendiskaji@yahoo.com> 17 Oktober 2022 pukul 02.55
Balas Ke: Rendi Aji <rendiskaji@yahoo.com>
Kepada: bagus.setyoboedi@fk.unair.ac.id

Dear
G.N. Lucas

Here the information for the ethical clearance

Institution : Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Number : 259/Panke.KKE/IV/2017
Date : 6 Aprl 2017

Thank you

Best regards
Bagus Setyoboedi

Sent from Yahoo Mail on Android
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Dr. G.N. Lucas <drgnlucas@gmail.com> 17 Oktober 2022 pukul 09.35
Kepada: BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id>

Thanks
Dr Lucas
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BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id>

Comparison between direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level with different histopathological grades of liver biopsy in children with cholestasis

6 pesan

Dr. G.N. Lucas <drgnlucas@gmail.com> 26 Oktober 2022 pukul 18.33
Kepada: BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id>

Dear Dr Bagus Setyoboedi
The following are the comments of the reviewer.

"1. Topic : suggest : prediction of histopathological grades of liver pathology in cholestasis by direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level
2. Methodology: unclear about the population – the indication for the biopsy, clinical diagnosis, the age group etc
3. Discussion : needs improvement – comparing with other studies and explanation of the findings
4. Conclusions ; Need rephrasing "

Please respond to the comments via direct e-mail.

Regards

Dr G N Lucas

Joint Editor SLJCH

Dr. G.N. Lucas <drgnlucas@gmail.com> 12 November 2022 pukul 14.47
Kepada: BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id>, s.d.p.soegianto@gmail.com, sjamsul.arief@yahoo.co.id

Dear All
There has been no response to my e-mail sent to the corresponding author on 26th October, not even an acknowledgement. If no response is obtained by 19th November your article will be rejected and archived.
Regards
Dr G N Lucas
Joint Editor SLJCH
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Kepada: "Dr. G.N. Lucas" <drgnlucas@gmail.com>

Dear Lucas,

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Thank you for your understanding.

Regard
Bagus Setyoboedi
[Kutipan teks disembunyikan]

BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 21 November 2022 pukul 09.15
Kepada: "Dr. G.N. Lucas" <drgnlucas@gmail.com>

Dear Lucas

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Dr. G.N. Lucas <drgnlucas@gmail.com> 21 November 2022 pukul 20.55
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Dear Dr Bagus Setyoboedi (corresponding author)
As indicated in the web site of the Sri Lanka Journal of Child Health, it is now necessary for us to have your internationally recognised ORCID ID (ORCID Identification Number) to be included in the manuscript. This number has a format such as **0000-0001-7789-8793**, which is the ORCID ID of Dr. B.J.C. Perera, the other Joint Editor.

Please be kind enough to send us the ORCID IDs of each of the authors.to be inserted into the metadata of the article in the journal web site. In case you do not have this number yet, please go to the website of ORCID (https://orcid.org/register) and register. This registration is free and would take only a couple of minutes.
The article will not be accepted for publication unless the ORCID IDs of all the authors are received.
Regards
Dr Lucas
[Kutipan teks disembunyikan]

BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id> 22 November 2022 pukul 08.11
Kepada: "Dr. G.N. Lucas" <drgnlucas@gmail.com>

Dear dr. Lucas

Tank you for your kindness to give us opportunity. Here are the Orchid number of the authors:
Bagus Setyoboedi
0000-0002-3923-6913

Sugi Deny Pranoto Soegianto

0000-0001-8162-6862

Sjamsul Arief
0000-0002-6372-2460

Best regard
Bagus S
[Kutipan teks disembunyikan]

BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id>

Prediction of histopathological grades of liver pathology in cholestasis by direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level

3 pesan

Dr. G.N. Lucas <drgnlucas@gmail.com> 22 November 2022 pukul 11.52
Kepada: BAGUS SETYOBOEDI <bagus.setyoboedi@fk.unair.ac.id>

Dear Dr Bagus Setyoboedi
Your article "Prediction of histopathological grades of liver pathology in cholestasis by direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level" has been accepted for publication in the Sri Lanka Journal of Child Health. The revised version is attached. If you wish to make any changes, please highlight the changes and e-mail it back to me.
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Kepada: "Dr. G.N. Lucas" <drgnlucas@gmail.com>

Dear dr. Lucas

Thank you very much, We do not have further revision for the manuscript.

Regard
Bagus S
[Kutipan teks disembunyikan]

Prediction of histopathological grades of liver pathology in cholestasis by direct bilirubin, aspartate aminotransferase, alanine aminotransferase and albumin level

***Bagus Setyoboedi[1], Sugi Deny Pranoto Soegianto[2], Sjamsul Arief[1]**

Sri Lanka Journal of Child Health, 2023; **52**:

Abstract

Background: Liver biopsy, a routine diagnostic procedure in Dr. Soetomo General Hospital Surabaya, is a valuable tool in the diagnosis, prognosis, and management of parenchymal liver disease. However, the correlation between histopathological features and direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) and albumin level has not yet been established.

Objectives: To correlate various histopathological features with direct bilirubin, AST, ALT and albumin level of children with cholestasis.

Method: This is a retrospective study of 51 cases of cholestasis diagnosed and treated from January 2011 to December 2016. All biopsies were reviewed and graded by a semi-quantitative scoring system according to Muthukanagarajan *et al* and categorized into fibrosis, bile duct proliferation, cholestasis and duct plate malformation. Degrees of all features were compared with direct bilirubin, AST, ALT, and albumin level. Statistical analysis used one way ANOVA, Kruskal-Wallis and unpaired t-test. $p<0.05$ was considered significant.

Results: There were 30 males and 21 females with a median age of 3 (1-9) months and a mean weight of 5 (1.41) kg. Degree of fibrosis was negative (47%), mild (22%), moderate (31%) and severe (0%). Bile duct proliferation was negative (57%), mild (21%), moderate (14%) and severe (8%). Cholestasis was negative in 0%, mild in 14%, moderate in 69% and severe in 18%; duct plate malformation was negative in 63% and positive in 37%. Direct bilirubin level showed significant difference with degree of duct proliferation ($p=0.024$). There was no significant difference of AST level with all degrees of histopathological grade. ALT level showed significant difference with degree of fibrosis ($p=0.043$). Albumin level showed significant difference with degree of fibrosis ($p=0.000$), degree of duct proliferation ($p=0.006$) and duct plate malformation ($p=0.037$).

Conclusions: This study showed that while the direct bilirubin level was significantly associated with the degree of duct proliferation and the ALT level was significantly associated with the degree of fibrosis, the albumin level was significantly associated with the degree of fibrosis, degree of duct proliferation and degree of duct plate malformation

(Key words: Histopathology, Cholestasis, Bilirubin, Albumin, Transaminase)

Introduction

Liver biopsy is still the standard procedure for obtaining liver tissue for histopathological examination and a valuable tool in the diagnosis, prognosis and management of many parenchymal liver disease[1]. Liver biopsy is the cornerstone of the diagnostic work-up of infants with cholestatic jaundice, and it is standard practice in most paediatric centres to obtain a percutaneous liver biopsy before surgical intervention[2]. The role of liver biopsy has also evolved into a prognostic tool in a variety of liver diseases, providing information such as histologic grades of inflammation and staging of fibrosis. Histologic assessment of the liver remains an essential tool in establishing the diagnosis in numerous paediatric diseases, in combination with various clinical and laboratory data[3]. However, correlation between histopathological features and direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) and albumin level have not yet been established.

[1]*Department of Child Health, Faculty of Medicine, Universitas Airlangga / Dr. Soetomo General Hospital, Surabaya, Indonesia,* [2]*Department of Clinical Medicine, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, Kupang, Indonesia*

**Correspondence:*
bagus.setyoboedi@fk.unair.ac.id

https//orcid.org/0000-0002-3923-6913

(Received on 12 October 2022: Accepted after revision on 22 November 2022)

The authors declare that there are no conflicts of interest

Personal funding was used for the project.

Objectives

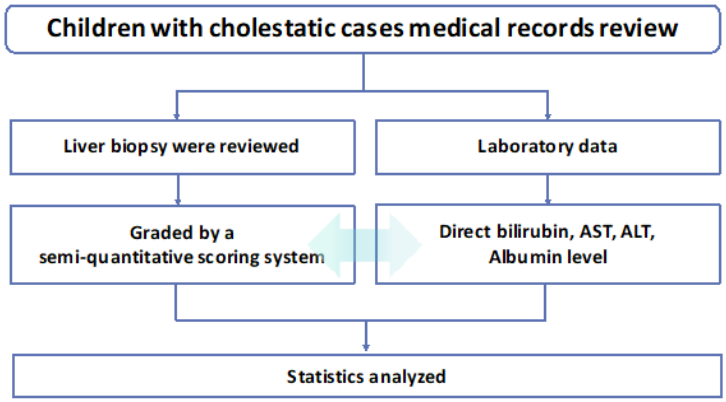
To correlate various histopathological features with direct bilirubin, AST, ALT, and albumin level of children with cholestasis.

Method

Design: A retrospective study was carried out from medical records in the Hepatology Outpatient Clinic, Dr. Soetomo Hospital from 1st January 2011 to 31st December 2016.

Inclusion criteria: Infants with clinical sign of cholestasis (jaundice, pale stools, abdominal distension and dark urine) and direct bilirubin >1 mg/dl, who were suspected of biliary atresia, neonatal hepatitis, Alagille Syndrome, α-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis or secondary cholestasis due to other causes and who underwent percutaneous liver biopsy, were enrolled in this study.

Exclusion criteria: Infants with incomplete laboratory data and biopsy results were excluded from the study.



Study protocol

Liver biopsy review and grading: All liver biopsy results were reviewed by the pathologist who examined them previously and graded using the semi-quantitative scoring system of Muthukanagarajan SJ *et al*[4].

The scoring system for *grading the extent of fibrosis* includes:

- Grade I (mild) fibrosis comprised cases with portal fibrous expansion to porto-portal bridging fibrosis involving 50% or less of portal tracts.
- Grade II (moderate) fibrosis included cases with porto-portal bridging fibrosis involving greater than 50% of portal tracts without nodular hepatic architecture.
- Grade III (severe) fibrosis included cases with porto-portal and porto-central bridging fibrosis involving greater than 50% of portal tracts associated with nodular hepatic architecture.

Bile duct proliferation refers to the presence of greater than 5 bile ducts per portal tract and was graded according to a semi-quantitative scoring system.

- Presence of 5 to 9 bile ducts per portal tract was graded as mild.
- Greater than or equal to 10 bile ducts per portal tract was graded as moderate.
- An average number of bile ducts per portal tract greater than or equal to 10 but the ducts were elongated attenuated and angulated was graded as severe bile duct proliferation.

Portal and periportal inflammation was graded as:

- Mild if cells were present in less than one third of portal tracts.
- Moderate if cells were present in more than one third to two-thirds of portal tracts.
- Severe when dense packing of cells was present in more than two-thirds of portal tracts.

Cholestasis was graded as:

- Absent.
- Mild (accumulation of bile in centrilobular hepatocytes).
- Moderate (accumulation of bile in centrilobular and periportal hepatocytes or even in portal tracts).
- Severe (showed presence of bile infarcts).

Duct plate malformation was identified by the presence of numerous unusual curved and concentric bile ducts arranged around a fibrous or a central vascular core in the portal tract. Histopathological examination of the biliary remnant showed fibro-inflammatory obliteration of the duct, apoptotic degeneration of the residual bile

duct epithelium and variable degrees of periductal inflammation[4].

Ethical issues: Study protocol was approved by the Institutional Ethics Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (No. 259 / Panke.KKE / IV / 2017) on 06 April, 2017. Being a retrospective study, informed written consent was not feasible.

Statistical analysis: This was performed with SPSS, version 20 (SPSS Inc, Chicago, Illinois, USA). One way ANOVA, Kruskal-Wallis and unpaired t-test were used to compare the variables and a value of $p<0.05$ was considered significant.

Results

There were 30 males and 21 females with a median age of 3 (1-9) months and a mean weight of 5 (1.41) kg. The follow up of all samples showed that 8 infants died and 4 infants underwent the Kasai procedure.

Degree of fibrosis was 47% negative, 22% mild, 31% moderate and 0% severe. *Bile duct proliferation* was 57% negative, 21% mild, 14% moderate and 8% severe; *Cholestasis* was 0% negative, 14% mild, 69% moderate and 18% severe. *Duct plate malformation* was 63% negative and 37% positive. (Figure 1).

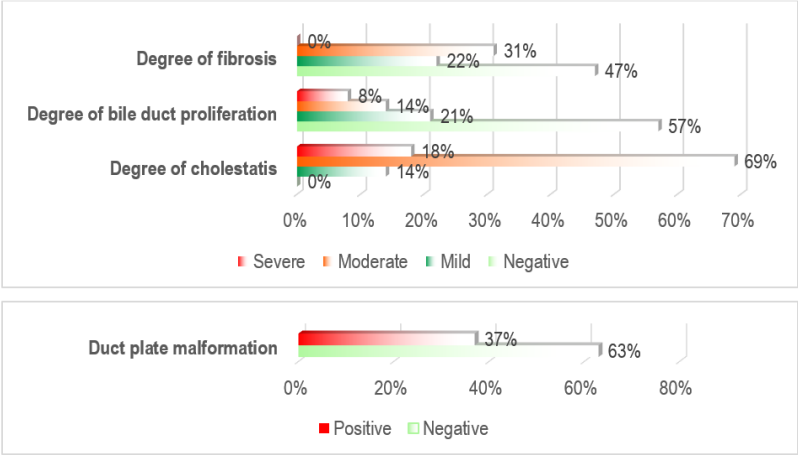


Figure 1: ***Distribution of clinicopathological features***

Direct bilirubin level showed a significant difference with degree of duct proliferation (p=0.024). There was no significant difference of AST level with all degrees of histopathological grades. ALT level showed significant difference with degree of fibrosis (p=0.043). Albumin level showed significant difference with degree of fibrosis (p=0.000), degree of duct proliferation (p=0.006) and duct plate malformation (p=0.037). (Tables 1-4)

Table 1: ***Comparison of histopathological features with direct bilirubin***

Histopathological feature	Direct bilirubin (mg/dl)	p-value
Degree of fibrosis: Mean (SD)		
Negative	7.66 (5.07)	
Mild	7.48 (3.28)	0.336[1]
Moderate	9.79 (5.40)	
Severe	-	
Degree of bile duct proliferation: Median (min-max)		
Negative	7.01 (1.5-23.87)	
Mild	6.99 (2.40-14.01)	**0.024**[2]
Moderate	10.97 (10.71-25.02)	
Severe	6.5 (2.48-11.70)	
Degree of cholestasis: Mean (SD)		
Negative	-	
Mild	8.64 (3.49)	
Moderate	7.67 (4.72)	0.327[1]
Severe	10.40 (6.17)	
Duct plate malformation: Mean (SD)		
Negative	8.11 (4.39)	0.754[3]
Positive	8.59 (5.71)	

p<0.05 significant; one way ANOVA test[1], Kruskal Wallis test[2], Unpaired t-test[3]

Table 2: ***Comparison of histopathological features with aspartate transaminase***

Histopathological feature	Aspartate transaminase (mg/dl)	p-value
Degree of fibrosis: Median (min-max)		
Negative	190.00 (21.00-1517.00)	
Mild	246.00 (113.00-738.00)	0.514[1]
Moderate	228.00 (122.00- 499.00)	
Severe	-	
Degree of bile duct proliferation: Median (min-max)		
Negative	207.00 (21.00-1517.00)	
Mild	221.00 (122.00- 499.00)	0.728[1]
Moderate	272.00 (167.00-444.00)	
Severe	260.25 (184.00-446.00)	
Degree of cholestasis: Median (min-max)		
Negative	-	
Mild	242.00 (113.00-760.00)	
Moderate	207.00 (21.00-1517.00)	0.542[1]
Severe	311.00 (169.70-446.00)	
Duct plate malformation: Mean (SD)		
Negative	266.18 (182.30)	0.316[2]
Positive	345.97 (309.96)	

p<0.05 significant; Kruskal Wallis test[1], Unpaired t-test[2]

Table 3: ***Comparison of histopathological features with alanine transaminase***

Histopathological feature	Alanine transaminase (mg/dl)	p-value
Degree of fibrosis: Mean (SD)		
Negative	206.58 (143.87)	
Mild	211.90 (124.63)	**0.043**[1]
Moderate	198.63 (59.48)	
Severe	-	
Degree of bile duct proliferation: Median (min-max)		
Negative	165.0 (11.0-624.0)	
Mild	193.0 (89.0-314.0)	0.57[2]
Moderate	206.0 (110.0-338.0)	
Severe	225.5 (158.1-264.0)	
Degree of cholestasis: Mean (SD)		
Negative	-	
Mild	201.86 (114.03)	
Moderate	203.43 (127.34)	0.965[1]
Severe	214.88 (83.19)	
Duct plate malformation: Mean (SD)		
Negative	206.62 (136.97)	0.901[3]
Positive	202.90 (76.00)	

p<0.05 significant; one way ANOVA test[1], Mann-Whitney test[2], Unpaired t-test[3]

Table 4: ***Comparison of histopathological features with albumin***

Histopathological feature	Albumin (mg/dl)	p-value
Degree of fibrosis: Median (min-max)		
Negative	3.83 (2.70-6.20)	
Mild	3.80 (3.00-4.37)	**0.001**[1]
Moderate	2.95 (2.24-3.90)	
Severe	-	
Degree of bile duct proliferation: Median (min-max)		
Negative	3.82 (2.70-6.20)	
Mild	3.40 (2.70-4.37)	**0.006**[1]
Moderate	3.40 (2.24-3.90)	
Severe	2.73 (2.60-3.40)	
Degree of cholestasis: Median (min-max)		
Negative	-	
Mild	3.70 (2.70-4.56)	
Moderate	3.70 (2.70-6.20)	0.175[1]
Severe	3.40 (2.24-4.00)	
Duct plate malformation: Median (min-max)		
Negative	3.75 (2.70-6.20)	**0.037**[2]
Positive	3.40 (2.24-5.10)	

p<0.05 significant; Kruskal Wallis test[1], Mann-Whitney test[2]

Discussion

Traditional serological markers of liver function viz. 'liver function tests' give little indication of the various underlying pathological processes, including fibrosis[5]. The present method of subjective assessment of liver fibrosis and architecture by a single pathologist is reasonable in the daily diagnostic situation, but application of grading and staging scoring systems is inappropriate routinely. Histopathological stage scoring is sufficient for many clinical trials, and is the correct approach for observational studies[5].

The serum bilirubin levels showed statistically significant differences in early and advanced stages of liver damage[6]. Conjugated hyperbilirubinaemia characteristically occurs in parenchymal liver disease and biliary obstruction[7]. In our study, the direct bilirubin level showed a significant difference with the degree of duct proliferation (p=0.024). Hyperbilirubinaemia is directly proportional to the degree of histological injury of hepatocytes[8]. The presence of conjugated hyperbilirubinaemia almost always signifies the existence of liver disease. Both hepatocellular and cholestatic liver injury may lead to elevated serum bilirubin levels[9].

We found there was no significant difference of AST level with all degrees of histopathological grade. AST is present in a wide variety of tissues like the heart, skeletal muscle, kidney, brain and liver. Large increases in mitochondrial AST occur in serum after extensive tissue necrosis[8]. The ensuing centrilobular necrosis results in a rapid rise in aminotransferases, with AST value greater than ALT in the initial days of hepatic injury[9]. Initial portal and periportal fibrosis of varying degree may progress to cirrhosis[10]. In this study, ALT level showed a significant difference with the degree of fibrosis (p=0.043). ALT is primarily localized to the liver and more frequently increased as compared to AST. ALT also may reflect the extent of hepatocellular necrosis[8]. Relative levels of alkaline phosphatase elevation could be used as markers to indicate cholestatic problems, whereas elevated ALT or AST levels would indicate hepatocellular injury[11].

Albumin is quantitatively the most important protein in plasma synthesized by the liver and is a useful indicator of hepatic function. Low albumin suggests underlying poor synthetic activity of the liver and thereby underlying end-stage liver disease[7-9,12]. Albumin level in this study showed a significant difference with the degree of fibrosis (p=0.001), degree of duct proliferation (p=0.006) and duct plate malformation (p=0.037). In one study, all the cases with duct plate malformation had very severe fibrosis with nodular transformation of the liver and also had increased biliary proliferation[4]. Serum concentration of albumin depends upon several other factors such as nutritional, hormonal, sepsis, systemic inflammatory disorders, urinary and gastrointestinal losses. These should be considered when interpreting low albumin levels in patients with chronic liver disease[7].

Conclusions

This study showed that while the direct bilirubin level was significantly associated with the degree of duct proliferation and the ALT level was significantly associated with the degree of fibrosis, the albumin level was significantly associated with the degree of fibrosis, degree of duct proliferation and degree of duct plate malformation.

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KOMITE ETIK PENELITIAN KESEHATAN
RSUD Dr. SOETOMO SURABAYA

KETERANGAN KELAIKAN ETIK
(" ETHICAL CLEARANCE ")

259 / Panke.KKE/ IV / 2017

KOMITE ETIK RSUD Dr. SOETOMO SURABAYA TELAH MEMPELAJARI SECARA SEKSAMA RANCANGAN PENELITIAN YANG DIUSULKAN, MAKA DENGAN INI MENYATAKAN BAHWA PENELITIAN DENGAN JUDUL :

" Hubungan antara Profil Klinis Kolestasis pada Anak dengan Histopatologi Hati di RSUD Dr. Soetomo Surabaya "

PENELITI UTAMA : Dr. Bagus Setyoboedi, dr., Sp.A (K)

PENELITI LAIN : 1. Sjamsul Arief, dr., Sp.A (K), MARS
2. Sugi Deni Pranoto Soegianto, dr

UNIT/ LEMBAGA/ TEMPAT PENELITIAN : RSUD Dr. Soetomo Surabaya

DINYATAKAN LAIK ETIK

SURABAYA, 06 APR 2017

KETUA

RSUD Dr. Soetomo Komite Etik Penelitian Kesehatan

(Dr. Elizeus Hanindito, dr., Sp.An, KIC,KAP)
NIP. 19511007 197903 1 002

PREDICTION OF HISTOPATHOLOGICAL GRADES OF LIVER PATHOLOGY IN CHOLESTASIS BY DIRECT BILIRUBIN, ASPARTATE AMINOTRANSFERASE, ALANINE AMINOTRANSFERASE AND ALBUMIN LEVEL

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Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, Kupang, Indonesia

ABSTRACT

Background: Liver biopsy, a routine diagnostic procedure in Dr. Soetomo General Hospital Surabaya, is a valuable tool in the diagnosis, prognosis, and management of parenchymal liver diseases. However, analysis between histopathological features with direct bilirubin, aspartat transaminase (AST), alanin transaminase (ALT) and albumin level have not yet established.

Objectives: To analyze various histopathological features with direct bilirubin, AST, ALT and albumin level of cholestasis children.

Methods: This is retrospective study of 51 cases of cholestasis diagnosed and treated from January 2011 to December 2016. All biopsy were reviewed and graded by a semi-quantitative scoring system according to Muthukanagarajan *et al.* (categorized into fibrosis, bile duct proliferation, cholestasis, and duct plate malformation). Degree of all features were compared with direct bilirubin, AST, ALT, and albumin level. Statistics analyzed using one way anova test, Kruskal-Wallis, unpaired *t* test. $p<0.05$ was considered significant.

Results: There were 30 males and 21 females with characteristic: age 3(1-9) month old, weight 5 (1.41) kg. Degree of fibrosis: 47% negative, 22% mild, 31% moderate, 0% severe; Bile duct proliferation: 57% negative, 21% mild, 14% moderate, 8% severe; Cholestasis: negative 0%, mild 14%, moderate 69%, severe 18%; Duct plate malformation: 63% negative, 37% positive. Direct bilirubin level showed significant difference with degree of duct proliferation (P=0.024). There was no significant difference of AST level with all degree of histopathological grade. ALT level showed significant difference with degree of fibrosis (P=0.043). Albumin level

showed significant difference with degree of fibrosis (P=0.000), degree of duct proliferation (p0.006) and duct plate malformation (P=0.037).

Conclusion: Direct bilirubin, ALT, and albumin level had a distinction of histopathological grade in different features of children with cholestasis.

Keywords: *histopathology, cholestasis, bilirubin, albumin, transaminase*

INTRODUCTION

Liver biopsy is still the criterion standard procedure for obtaining liver tissue for histopathological examination and a valuable tool in the diagnosis, prognosis, and management of many parenchymal liver diseases.[1] Liver biopsy is a cornerstone of the diagnostic work-up of infants with cholestatic jaundice, and it is standard practice in most pediatric centers to obtain a percutaneous liver biopsy before surgical intervention.[2]

The role of liver biopsy has also evolved into a prognostic tool in a variety of liver diseases providing information such as histologic grades of inflammation and staging of fibrosis. Histologic assessment of the liver remains an essential tool in establishing the diagnosis in numerous pediatric diseases in combination with various clinical and laboratory data.[3] However, analysis between histopathological features with direct bilirubin, aspartat transaminase, alanin transaminase and albumin level have not yet established.

The purpose of this study to analyze various histopathological features with direct bilirubin, aspartate aminotransferase, alanine aminotransferase, and albumin level of cholestasis children.

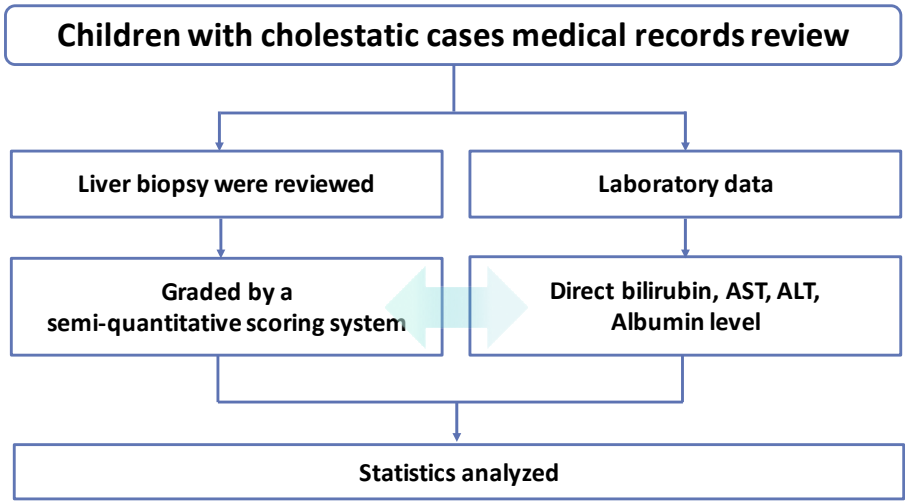
METHODS

Design

A retrospective study was done from medical records in Hepatology Outpatient Clinic Dr. Soetomo Hospital between Januari 1st 2011 to December 31st 2016. Study protocol were approved by the local Ethical Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia.

Patients

Children under 1 year old with clinical sign of cholestatic jaundice (jaundice, pale stool, abdominal enlargement and dark urine) and direct bilirubin >1 mg/dl who are suspected of biliary atresia, viral infection cholestasis, Alagille Syndrome, α-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis and secondary cholestasis due to other causes who went percutaneous liver biopsy were enrolled this study. Percutaneus liver biopsy was performed to explore the clinical diagnosis and to make decision further management of this patients. We excluded incomplete data of biopsy result and laboratory result.



There were 30 males and 21 females with age characteristic 3(1-9) month old and body weight 5 (1.41) kg. The follow up of all sample shows that 8 patients died, 4 patient went to kasai procedure.

Liver biopsy review and grading

We review all liver biopsy result to pathologist who examined previously and graded using semi quantitative scoring system by Muthukanagarajan et al., 2016.

The scoring system for grading the extent of fibrosis includes:

1. Grade I (mild) fibrosis comprised cases with portal fibrous expansion to porto-portal bridging fibrosis involving less than 50% of portal tracts.
2. Grade II (moderate) fibrosis included cases with porto-portal bridging fibrosis involving greater than 50% of portal tracts without nodular hepatic architecture.

3. Grade III (severe) fibrosis ranged from porto-portal and porto-central bridging fibrosis involving greater than 50% of portal tracts associated with nodular hepatic architecture.

Bile duct proliferation refers to presence of greater than 5 bile ducts per portal tract and is graded according to a semi-quantitative scoring system.

1. Presence of 5 to 9 bile ducts per portal tract is graded as mild.
2. Greater than or equal to 10 bile ducts per portal tract is graded as moderate.
3. An average number of bile ducts per portal tract greater than or equal to 10 but the ducts are elongated attenuated and angulated is graded as severe bile duct proliferation.

Portal and periportal inflammation is graded as :

1. Mild if cells are present in less than one third of portal tracts.
2. Moderate if cells are present in more than one third to two-thirds of portal tracts.
3. Severe when dense packing of cells present in more than two-thirds of portal tracts.

Cholestasis was graded as :

1. Absent.
2. Mild (accumulation of bile in centrolobular hepatocytes).
3. Moderate (accumulation of bile in centrolobular and periportal hepatocytes or even in portal tracts).
4. Severe (shows presence of bile infarcts).

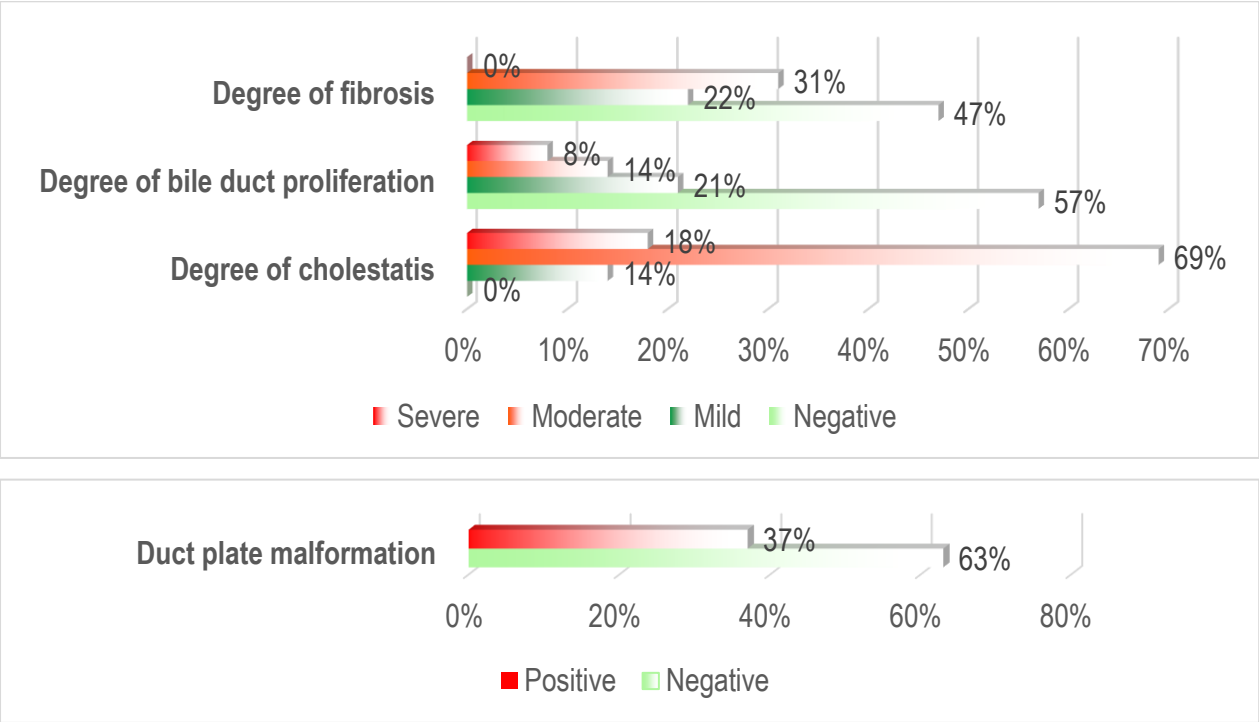
Duct plate malformation is identified by presence of numerous unusual curved and concentric bile ducts arranged around a fibrous or a central vascular core in the portal tract. Histopathological examination of the biliary remnant will show fibroinflammatory obliteration of the duct, apoptotic degeneration of the residual bile duct epithelium and variable degrees of periductal inflammation.[4]

Statistical analysis

Statistical analyses were performed with SPSS, v.20 (SPSS Inc, Chicago, Illinois, USA). one way anova test, Kruskal-Wallis, unpaired *t* test was used to compare the variables and a value of $P<0.05$ was considered significant.

RESULTS

There were 30 males and 21 females with characteristic: age 3(1-9) month old, weight 5 (1.41) kg. Degree of fibrosis: 47% negative, 22% mild, 31% moderate, 0% severe; Bile duct proliferation: 57% negative, 21% mild, 14% moderate, 8% severe; Cholestasis: negative 0%, mild 14%, moderate 69%, severe 18%; Duct plate malformation: 63% negative, 37% positive. (Graphic 1).



Graphic 1. Distribution of clinicopathological features.

Direct bilirubin level showed significant difference with degree of duct proliferation (P=0.024). There was no significant difference of AST level with all degree of histopathological grade. ALT level showed significant difference with degree of fibrosis (P=0.043). Albumin level showed significant difference with degree of fibrosis (P=0.000), degree of duct proliferation (p0.006) and duct plate malformation (P=0.037). (Table 1-4)

Table 1. Comparison histopathological features with direct bilirubin

Degree of fibrosis	Direct bilirubin (mg/dl), mean (SD)	P
Negative	7.66 (5.07)	0.336[1*]
Mild	7.48 (3.28)	
Moderate	9.79 (5.40)	
Severe	-	

Degree of bile duct proliferation	Direct bilirubin (mg/dl), median (min-max)	P
Negative	7.01(1.5-23.87)	0.024[2*]
Mild	6.99(2.40-14.01)	
Moderate	10.97(10.71-25.02)	
Severe	6.5 (2.48-11.70)	

Degree of cholestasis	Direct bilirubin (mg/dl), mean (SD)	P
Negative	-	
Mild	8.64 (3.49)	0.327[1*]
Moderate	7.67 (4.72)	
Severe	10.40 (6.17)	

Duct plate malformation	Direct bilirubin (mg/dl), mean (SD)	P
Negative	8.11 (4.39)	0.754[3*]
Positive	8.59 (5.71)	

P value significant if < 0,05
One way anova test[1] Kruskal-Wallis test[2] Unpaired *t* test[3]

Table 2. Comparison histopathological features with AST

Degree of fibrosis	AST (mg/dl), median (min-max)	P
Negative	190.00 (21.00-1517.00)	0.514[1*]
Mild	246.00 (113.00-738.00)	
Moderate	228.00 (122.00-499.00)	
Severe	-	

Degree of bile duct proliferation	AST(mg/dl), median (min-max)	P
Negative	207.00(21.00-1517.0)	0.728[1*]
Mild	221.00 (122.00-499.00)	
Moderate	272.00 (167.00-444.00)	
Severe	260.25(184.00-446.00)	

Degree of cholestasis	AST(mg/dl), median (min-max)	P
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Moderate	207.00 (21.00-1517.00)	
Severe	311.00 (169.70-446.00)	

Duct plate malformation	AST (mg/dl), mean (SD)	P
Negative	266.18 (182.30)	0.316[2*]
Positive	345.97 (309.96)	

P value significant if < 0,05
Kruskal-Wallis test[1] Unpaired *t* test[2]

Table 3. Comparison histopathological features with ALT

Degree of fibrosis	ALT (mg/dl), mean (SD)	P
Negative	206.58 (143.87)	0.043[1*]
Mild	211.90 (124.63)	
Moderate	198.63 (59.48)	
Severe	-	

Degree of bile duct proliferation	ALT(mg/dl), median (min-max)	P
Negative	165.0(11.0-624.0)	0.57[2*]
Mild	193.0(89.0-314.0)	
Moderate	206.0(110.0-338.0)	
Severe	225.5(158.1-264.0)	

Degree of cholestasis	ALT(mg/dl), mean (SD)	P
Negative	-	
Mild	201.86 (114.03)	0.965[1*]
Moderate	203.43 (127.34)	
Severe	214.88 (83.19)	

Duct plate malformation	ALT (mg/dl), mean (SD)	P
Negative	206.62 (136.97)	0.901[3*]
Positive	202.90 (76.00)	

P value significant if < 0,05
One way anova test[1] Mann-Whitney test[2] Unpaired *t* test[3]

Table 4. Comparison histopathological features with Albumin

Degree of fibrosis	Albumin (mg/dl), median (min-max)	P
Negative	3.83 (2.70-6.20)	0.001[1*]
Mild	3.80 (3.00-4.37)	
Moderate	2.95 (2.24-3.90)	
Severe	-	

Degree of bile duct proliferation	Albumin (mg/dl), median (min-max)	P
Negative	3.82(2.70-6.20)	0.006[1*]
Mild	3.40(2.70-4.37)	
Moderate	3.40(2.24-3.90)	
Severe	2.73 (2.60-3.40)	

Degree of cholestasis	Albumin (mg/dl), median (min-max)	P
Negative	-	
Mild	3.70 (2.70-4.56)	0.175[1*]
Moderate	3.70 (2.70-6.20)	
Severe	3.40 (2.24-4.00)	

Duct plate malformation	Albumin (mg/dl), median (min-max)	P
Negative	3.75 (2.70-6.20)	0.037[2*]
Positive	3.40(2.24-5.10)	

P value significant if < 0,05
Kruskal-Wallis test[1] Mann-Whitney test[2]

DISCUSSION

Traditional serological markers of liver function "liver function tests" give little indication of the various underlying pathological processes, including fibrosis.[5] The present method of subjective assessment of liver fibrosis and architecture by a single pathologist is reasonable in the daily diagnostic situation, but application of grading and staging scoring systems is inappropriate routinely. Histopathological stage scoring is sufficient for many clinical trials, and is the correct approach for observational studies.[5]

The serum bilirubin levels showed statistically significant difference in early and advanced stages of liver damages.[6] Conjugated hyperbilirubinemia characteristically occurs in parenchymal liver disease and biliary obstruction.[7] In our study, Direct bilirubin level showed significant difference with degree of duct proliferation (P=0.024). Hyperbilirubinemia is directly proportional to the degree of histological injury of hepatocytes.[8] The presence of conjugated hyperbilirubinemia almost always signifies the existence of liver disease. Both hepatocellular and cholestatic liver injury may lead to elevated serum bilirubin levels.[9]

We found there was no significant difference of AST level with all degree of histopathological grade. AST is present in a wide variety of tissues like the heart, skeletal muscle, kidney, brain and liver. Large increases in mitochondrial AST occur in serum after extensive tissue necrosis.[8] The ensuing centrilobular necrosis results in a rapid rise in aminotransferases, with AST value greater than ALT in the initial days of hepatic injury.[9] Initial Portal and periportal fibrosis of varying degree that may progress to cirrhosis.[10] In this study, ALT level showed significant difference with degree of fibrosis (P=0.043). ALT is primarily localized to the liver and more frequently increased as compared to AST. ALT is also may reflect the extent of hepatocellular necrosis.[8] Relative levels of ALP elevation could be used

as markers to indicate cholestatic problems, whereas elevated ALT or AST levels would indicate hepatocellular injury.[11].

Albumin is quantitatively the most important protein in plasma synthesized by the liver and is a useful indicator of hepatic function. Low albumin suggests underlying poor synthetic activity of liver and thereby underlying end-stage liver disease. [7–9,12] Albumin level in this study showed significant difference with degree of fibrosis (P=0.001), degree of duct proliferation (P=0.006) and duct plate malformation (P=0.037). In one study, all the cases with duct plate malformation had very severe fibrosis with nodular transformation of liver and also had increased biliary proliferation.[4] Serum concentration of albumin depends upon several other factors such as the nutritional, hormonal factors, sepsis, systemic inflammatory disorders, urinary and gastrointestinal losses. These should be considered when interpreting low albumin levels in patients with chronic liver disease.[7]

In conclusion, this study showed that direct bilirubin, ALT, and albumin level had a distinction of histopathological grade in different features of children with cholestasis. The liver function tests and the histopathological features were found to have a better correlation. Injury to liver causes alteration in both functional as well as structural organisation. Hence a liver function test should be able to identify the presence of liver parenchymal or biliary, assess its severity and should provide prognostic information.[7]

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