Introduction

Liver cirrhosis has been established as a condition where normal liver parenchyma was replaced with connective tissue producing nodule formation. Since it disrupts liver function, the term used to describe the condition is the end-stage of chronic liver disease. The etiologic factor can occur because of viral infection, excessive alcohol consumption or cryptogenic agent (no defining cause) (1, 2). In 2010, the disease contributed to 49,538 deaths of U.S. citizens with a male predominance (3). Meanwhile, there is no major difference compared with developing regions. Indonesia had 9% of citizens, or 1,284,000 people of the total viremic population with cirrhosis in 2014 and it is expected to increase to 15% in 2030. Although, Indonesia reduced its HBsAg endemicity to moderate level in 2013 but it still faces multiple problems related to cirrhotic complications. In addition, the number of decompensated liver cirrhotic...
Material and Methods

Patients

The cross-sectional study was carried out in one of tertiary referral hospital in the western part of Sumatera Island, Haji Adam Malik General Hospital, Medan, Indonesia, between May 2016 and May 2017. The non-random and consecutive sampling method was used to include suitable patients in the study based on their date of admission to the hospital. The exclusion criteria in the study were malignancy condition, or severe comorbidity, for instance end-stage renal disease and chronic pulmonary obstructive disorder, blood transfusion in the previous three months, positive HIV status, dyslipidemia and diabetes mellitus, acute liver failure, and pregnancy. Patients admitted to the internal medicine hospitalisation ward and diagnosed with decompensated liver cirrhosis were automatically considered for the study after satisfying the inclusion criteria and signing the written informed consent without coercion.

Several laboratory findings were noted from the medical record registry, such as serum iron parameters, thrombocyte, international normalised ratio, bilirubin, serologic marker related to viral cirrhosis, and endoscopy for the presence of esophageal varices.

CTP Score

The five indicators included in CTP score were assessed using physical and ultrasonography examination for ascites and encephalopathy while bilirubin, albumin, and INR were noted from the Haji Adam Malik medical record registry on the admission day. CTP score was calculated using the free online calculator provided by MdCacl (https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality). CTP score was then divided into three class, A (5–6), B (7–9), and C (10–15). Thereafter, the mean difference of demographical characteristic comparison in each class and correlation analysis between serum ferritin and CTP score were carried out.

Statistical analysis

The analysis was performed using Statistical Package for the Social Science (SPSS Inc., Chicago, IL) version 12.0 and depicted in percentage and medians or means with standard deviation. The data was not normally distributed, it was statistically proven based
on the Kolmogorov-Smirnov normality test. Consequently, the data was analysed using non-parametric test (Kruskal-Wallis test). In exception to age variables, the data normal distribution was obtained; it was analysed using ANOVA test. The correlation between the serum ferritin level and CTP score was evaluated using Spearman correlation test (P-value < 0.05 was stated as significant results statistically with 95% confidence interval). Furthermore, the study was approved by the Medical Research Ethical Committee, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia (letter number: 544/TGL/KEPK FK USU-RSUPHAM/2017) and it was in accordance with the Declaration of Helsinki for medical research involving human subjects.

Results

The study enrolled 54 decompensated liver cirrhotic patients, 17 females and 37 males, with a mean age of 52.76 ± 12.57 years. Most patients had viral-related cirrhosis of hepatitis B and C since the serologic marker for viral infection was positive (HBsAg and anti-HCV) (n = 30 patients, non-hepatitis B and C patients were 24). The baseline characteristic was presented in Table 1 including several laboratory results and serum iron parameters and esophageal variceal findings. F3 Beppu classification for esophageal varices was the predominant grade (n = 22, 40.7%) followed by F2 (n = 16, 29.6%). In further analysis, the study obtained significant findings of mean difference using Kruskal-Wallis test, since the data was not distributed normally, such as gender and CTP score in accordance with serum ferritin (trichotomous cut-off values: ferritin under 200, 200–400, and over 400). In addition, creatinin and bilirubin levels were consistently and descriptively higher in patients with ferritin levels more than 400 µg/L. The other findings consisting of albumin, INR, and creatinin were also depicted in Table 1. Thus, the serum ferritin levels were significantly correlated with CTP score (r = 0.487; P = 0.000) (Figure 1).

Discussion

In the study, the significant and positive correlation between serum ferritin levels and CTP score was evident among decompensated liver cirrhosis patients in the study. While, several laboratory findings tend to be varied with ferritin levels based on descriptive analysis, most findings had higher levels in accordance with high serum ferritin levels (> 400 µg/L), particularly CTP score. Therefore, it can be confirmed that a patient with hyperferritinemia has a tendency to have a higher CTP score with moderate correlation. Hepatocellular including chronic active hepatitis B and liver cirrhosis is the second most common etiology propagated by certain mechanism producing hyperferritinemia (16).

Iron overload adds the liver insults by inducing secretion of pro-inflammatory cytokine and producing inflammation and necrosis of liver cells (17). Ferritin as cytosolic protein egress into the vascular system as it leaks from necrotic liver cells, and hyperferritinemia will ensue. Therefore, the serum ferritin level,

| Variables          | Ferritin < 200 (n = 22) | Ferritin 200–400 (n = 5) | Ferritin > 400 (n = 27) | P-value |
|--------------------|-------------------------|--------------------------|-------------------------|---------|
| Age (years)a       | 52.55±13.15             | 58.4±11.19               | 51.89±12.50             | 0.574d  |
| Gender             |                         |                          |                         |         |
| Male/Female        | 15/7                    | 0/5                      | 22/5                    | 0.002a  |
| Albumin            | 2.45 (1.5–3.3)          | 1.9 (1.6–3.1)            | 2.2 (1.7–3.7)           | 0.419   |
| INRb               | 1.28 (0.99–1.84)        | 1.54 (1.07–2.96)         | 1.32 (0.81–2.45)        | 0.266   |
| Creatinine         | 0.9 (0.6–2.37)          | 0.88 (0.55–2.06)         | 1.18 (0.52–13.58)       | 0.198   |
| Total bilirubin    | 1.01 (0.3–4.6)          | 1.9 (0.6–16.3)           | 2.41 (0.29–29.8)        | 0.183   |
| CTP scorec         | 8 (6–12)                | 9 (7–12)                 | 10 (5–12)               | 0.018a  |
| CTP class (A/B/C)  | 1/18/3                  | 0/3/2                    | 1/12/14                 | 0.089   |

The data is presented in ‘mean (standard deviation) and median or interquartile range, ’International normalised ratio,’ Child-Turcote-Pugh score, ’Age variable was analysed using ANOVA test, the rest variables using Kruskal-Wallis test.
Similarly found a significant correlation between hyperferritinemia and CTP score \( (r = 0.392, P = 0.009) \) by enrolling 51 patients with liver cirrhosis. In other perspectives, ferritin and CTP score were associated with poor prognosis through multivariate analysis among waiting list pre-transplant patients independently (24). Buyukasik et al. (25) showed that higher level of serum ferritin was confined to CTP class C patients \( (A/B/C= 198±25/161±161/366±396) \). Although, the relationship between ferritin and prognosis or the outcome still becomes inconsistent. There was a finding that ferritin could not be used solely to predict prognosis and the clinical outcome. Uchino et al. (26) stated that serum ferritin did not affect the prognosis among hepatocellular carcinoma patients who underwent radiofrequency ablation (RFA), in addition, there were lower serum ferritin levels among CTP score class C and it is more likely affected by tumor size and liver function (27).

The study also did not escape certain limitations. First, the causal relationship between ferritin and certain dependent variables could not be described since it was designed as a cross-sectional (point-time design). Second, serum ferritin levels would be affected by the presence of C282Y homozygosity producing iron...
overload (28) but the study did not perform the screening test to exclude the positive samples. Finally, the study also did not provide the output related to prognosis and outcome. Therefore, further studies exploring the accurate cut-off point of hyperferritinemia for certain poor clinical scenario should be carried out. One study had found that a significant cut-off value of serum ferritin levels (as much as 400 µg/L) could be used to predict one-month mortality in decompensated liver cirrhotic patients (29). In a larger study, 200 µg/L had been proved to predict 180-day and 1-year mortality among liver transplantation waiting list patients (30). Notwithstanding these findings, the precise cut-off value of serum ferritin remains uncertain.

Conclusions

The study concluded that ferritin is an important biomarker that represents CTP score as an indirect scheme to predict prognosis and mortality among decompensated liver cirrhotic patients. Ferritin level is easily affected by several factors; therefore, longitudinal studies inevitably need to provide evidence of ferritin cut-off value related to prognosis and outcome since hyperferritinemia is a hallmark of liver inflammation instead of iron overload among decompensated cirrhotic patients.

Acknowledgements

None.

Ethics of Study

The study was approved by the Medical Research Ethical Committee, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia (letter number: 544/TGL/KEPK FK USU-RSUPHAM/2017) and it was in accordance with the Declaration of Helsinki for medical research involving human subjects.

Conflict of Interest

None.

Funds

None.
5. Scrutton J, Wallace J, Wait S. Situation analysis of viral hepatitis in Indonesia: a policy. [Internet]. New York: Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP); 2018 July. [Retrieved 2018 Dec 2]. Available from: www.healthpolicypartnership.com/wp-content/uploads/hepatitis/Situation_analysis_of_viral_hepatitis_in_Indonesia.pdf

6. Garcia-Tsao G. The child-Turcotte classification: from gestalt to sophisticated statistics and back. *Dig Dis Sci*. 2016;61(11):3102–3104. https://doi.org/10.1007/s10620-016-4319-7

7. Hong SH, Kim JE, Cho ML, Heo YJ, Choi JH, Choi JH, et al. Comparison of the Child-Turcotte-Pugh classification and the model for end-stage liver disease score as predictors of the severity of the systemic inflammatory response in patients undergoing living-donor liver transplantation. *J Korean Med Sci*. 2011;26(10):1333–1338. https://doi.org/10.3346/jkms.2011.26.10.1333

8. Durand F, Valla D. Assessment of the prognosis of cirrhosis: child–Pugh versus MELD. *J Hepatol*. 2005;42(1):100–107. https://doi.org/10.1016/j.jhep.2004.11.015

9. Peng Y, Qi X, Guo X. Child–Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. *Medicine*. 2016;95(8):1–29. https://doi.org/10.1097/MD.0000000000002877

10. Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. *Blood reviews*. 2009;23(3):95–104. https://doi.org/10.1016/j.bire.2008.08.001

11. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: past, present and future. *Biochim Biophys Acta*. 2010;1800(8):760–769. https://doi.org/10.1016/j.bbagen.2010.03.011

12. Wessling-Resnick M. Iron homeostasis and the inflammatory response. *Ann Rev Nutr*. 2010;30:105–122. https://doi.org/10.1146/annurev.nutr.012809.104804

13. Milice S, Nikolasevic I, Orlic L, Devcic E, Starcevic-Cizmarevic N, Stimac D, et al. The role of iron and iron overload in chronic liver disease. *Medical Sci Monit*. 2016;22:2144–2151. https://doi.org/10.12659/MSM.896494

14. Koperdanova M, Cullis JO. Interpreting raised serum ferritin levels. *BMJ*. 2015;351:h3692. https://doi.org/10.1136/bmj.h3692

15. Abby Philips C, Sahney A. Oesophageal and gastric varices: historical aspects, classification and grading: everything in one place. *Gastroenterol Report*. 2016;4(3):186–195. https://doi.org/10.1093/gastro/gow018

16. Moore Jr C, Ormseth M, Fuchs H. Causes and significance of markedly elevated serum ferritin levels in an academic medical center. *J Clin Rheumatol*. 2013;19(6):324–328. https://doi.org/10.1097/RHU.0b013e31829ce01f

17. Ramm GA, Ruddell RG. Hepatotoxicity of iron overload: mechanisms of iron-induced hepatic fibrogenesis. *Sem Liver Dis*. 2005;25(4):433–449. https://doi.org/10.1055/s-2005-923315

18. Kowdley KV. Iron overload in patients with chronic liver disease. *Gastroenterol Hepatol*. [Internet]. 2016 [Retrieved 2018 December 3];12(11):695–698. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5193089/pdf/GH-12-695.pdf

19. Seeff LB, Everson GT, Morgan TR, Curto TM, Lee WM, Ghany MG, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol*. 2010;8(10):877–883. https://doi.org/10.1016/j.cgh.2010.03.025

20. Vagu C, Sultana C, Ruta S. Serum iron markers in patients with chronic hepatitis C infection. *Hepat Mon*. 2013;13(10):e13136. https://doi.org/10.5812/hepatmon.13136

21. Radicheva MP, Andonova AN, Milcheva HT, Ivanova NG, Kyuchukova SG, Nikolova MS. Serum markers of iron metabolism in chronic liver diseases. *Maced J Med Sci*. 2018;6(6):1010–1016. https://doi.org/10.3889/oamjms.2018.251

22. Gao YH, Wang JY, Liu PY, Sun J, Wang XM, Wu RH, et al. Iron metabolism disorders in patients with hepatitis B-related liver diseases. *World J Clin Cases*. 2018;6(13):600–610. https://doi.org/10.12998/wjcc.v6.i13.600
23. Ripoll C, Keitel F, Hollenbach M, Greinert R, Zipprich A. Serum ferritin in patients with cirrhosis is associated with markers of liver insufficiency and circulatory dysfunction, but not of portal hypertension. *J Clin Gastroenterol.* 2015;49(9):784–789. https://doi.org/10.1097/MCG.000000000000283

24. Al-Freah MA, Kriese S, Foxton MR, Quaglia A, Bomford A, Heaton ND, et al. The association of pretransplant ferritin level with waiting list and post-transplant survival. Does ferritin actually predict outcome? *Transpl Int.* 2013;26(11):1070–1079. https://doi.org/10.1111/tri.12164

25. Buyukasik NS, Nadir I, Akin FE, Cakal B, Kav T, Ersoy O, et al. Serum iron parameters in cirrhosis and chronic hepatitis: detailed description. *Turk J Gastroenterol.* 2011;22(6):606–611. https://doi.org/10.4318/tjg.2011.0323

26. Uchino K, Tateishi R, Nakagomi R, Fujiwara N, Minami T, Sato M, et al. Serum levels of ferritin do not affect the prognosis of patients with hepatocellular carcinoma undergoing radiofrequency ablation. *PloS One.* 2018;13(7):e0200943. https://doi.org/10.1371/journal.pone.0200943

27. Wei Y, Ye W, Zhao W. Serum iron levels decreased in patients with HBV-related hepatocellular carcinoma, as a risk factor for the prognosis of HBV-Related HCC. *Front Physiol.* 2018;9(66):1–10. https://doi.org/10.3389/fphys.2018.00066

28. Adams P. Management of elevated serum ferritin levels. *Gastroenterol Hepatol.* [Internet]. 2008 [Retrieved 2018 December 4];4(5):333. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3093720/pdf/GH-04-333.pdf

29. Umer N, Makki MU, Kiran SK, Jadoon NA. Serum ferritin as a predictor of 30 days mortality in patients of decompensated chronic liver disease. *J Ayub Med Coll Abbottabad.* [Internet]. 2017 [Retrieved 2018 December 4];29(3):415–418. Available from: jamc.ayubmed.edu.pk/index.php/jamc/article/download/2229/1055

30. Walker NM, Stuart KA, Ryan RJ, Desai S, Saab S, Nicol JA, et al. Serum ferritin concentration predicts mortality in patients awaiting liver transplantation. *Hepatology.* 2010;51(5):1683–1691. https://doi.org/10.1002/hep.23537