Appropriate timing to start and optimal response evaluation of high-dose corticosteroid therapy for patients with acute liver failure

Keisuke Kakisaka[1)], Kojiro Kataoka[1)], Yuji Suzuki[1)], Hidekatsu Kuroda[1)], Yasuhiro Takikawa[1)]

[1)]Division of Hepatology, Department of Internal Medicine, Iwate Medical University, Morioka, Japan

Address for correspondence:
Keisuke Kakisaka, MD, PhD
School of Medicine, Iwate Medical University
19-1 Uchimaru, Morioka 0208505, Japan
Tel.: +81-19-651-5111
Fax: +81-19-652-6664
E-mail: keikaki@iwate-med.ac.jp

Short title: **Appropriate timing** of high-dose corticosteroid therapy for ALF

Word counts: 3715

Abstract

Background: Corticosteroid therapy has been commonly administered to patients with acute liver injury (ALI)/acute liver failure (ALF) in Japan to prevent the development of hepatic encephalopathy, but the **appropriate timing** to start corticosteroid therapy has not been determined **and optimal response evaluation of the therapy** has not been conducted. We prospectively investigated the optimal timing to start therapy on the established severity indication: the Japan Hepatic Encephalopathy Prediction Model (JHEPM) and prothrombin time (PT). Methods: This prospective observational study enrolled 469 patients with ALI/ALF from 2004 to 2015. We evaluated 44 patients with ALF on high-dose corticosteroid therapy before hepatic coma development. The predictive performance for coma development was assessed using the receiver operator curve method in both PT and JHEPM probability the day before administering high-dose corticosteroid therapy. Results: Among these patients, nine developed hepatic coma after the therapy. Selection bias was adjusted using propensity score method. High-dose corticosteroid therapy tended to decrease the risk of coma development although there was no statistical significance. The cut-off value of 53%, 1.95, and 39% in JHEPM probability, PT-international normalized ratio (PT-INR), and PT activity, respectively, showed high sensitivity and specificity. Conclusion: We propose the **appropriate timing** to start high-dose corticosteroid therapy in patients with ALI/ALF; 40% of JHEPM probability, 1.53 of PT-INR, and 52% of PT because these values were theoretically discriminated at 98% coverage to the patients with coma. Because the study contained selection bias, the **appropriate timing for therapy** should be confirmed

in a future prospective study.

Key Words: ALF, Japan hepatic encephalopathy model, JHEPM, corticosteroid, LOHF

Abbreviations: Acute liver failure (ALF), acute liver injury (ALI), alanine aminotransferase (ALT), aspartate transaminase (AST), area under the receiver operating characteristic curve (AUROC), Japan Hepatic Encephalopathy Prediction Model (JHEPM), creatinine (Cre), prothrombin time activity (PT), prothrombin time-international normalized ratio (PT-INR), receiver–operator curve (ROC), total bilirubin (TBil), white blood cell counts (WBC).

Introduction

Acute liver failure (ALF) is manifested by the presence of coagulopathy (prothrombin [PT] international normalized ratio [PT-INR] > 1.5 or PT < 40%) occurring within 8 weeks of the first onset of symptoms in patients without underlying liver disease[1]. Progression of liver failure leads to impairment of the detoxification process, which results in hepatic coma. Patients with ALF with coma are further subdivided into acute and subacute types; the acute type was defined as the development of coma within 10 days from the onset of symptoms, and the subacute type was defined as the development of coma more than 10 days after onset of symptoms. Although ALF patients with coma are treated under intensive care, such as artificial liver support, their mortality still remains high without liver transplantation[2]. Liver transplantation drastically improved the survival rate of patients with ALF with coma, but donor shortage delays liver transplantation.

In contrast, patients with ALF without coma do not need intensive care and special therapy, and their mortality remains low. Therefore, an early evaluation of liver damage severity in patients with ALI/ALF in the pre-coma stage and early initiation of treatment to prevent coma-development may be a more effective approach in decreasing the morbidity and mortality in patients with ALI/ALF[3] than improving intensive care for patients with ALF with coma. We investigated the effect of high-dose corticosteroid administration in preventing coma development in patients with ALI/ALF from this point of view.

High-dose corticosteroid therapy is widely used for acute liver injury (ALI),

including ALF in Japan, although the efficacy of high-dose corticosteroid therapy to ALF has still been controversial[4-7]. Among the various etiologies of ALF, autoimmune hepatitis (AIH)-associated ALF may be a good indication for corticosteroid therapy, considering its pathophysiological mechanism[8-10]. In contrast, the efficacy of corticosteroid in ALF due to other causes is uncertain. Corticosteroid suppresses immunological activity and prevents further liver inflammation through an alteration in the ALF pathomechanism[11]. A previous study from the USA reported a beneficial effect of corticosteroid therapy for ALF in selected patients, who presented higher transaminase levels and lower MELD scores[12]. Furthermore, the study also reported that no survival benefit was observed with corticosteroid therapy once patients have progressed to ALF with coma[12]. These data suggested that early intervention with corticosteroid therapy would prevent ALF progression.

For early intervention in patients with ALI/ALF, we have been working through a referral system for patients with ALI[9, 13-15]. In this system, the Japan Hepatic Encephalopathy Prediction Model (JHEPM) is used for the evaluation of the probability of coma development in patients with ALF. For example, physicians in a general hospital in our region who want to refer a patient with ALI/ALF to our institute can discuss the treatment strategy with us based on the JHEPM-derived probability of coma development through the fax-mediated system. When the patient's JHEPM probability exceeds 20%, we recommend transferring the patient to our hospital for intensive care[13]. Using the JHEPM probability and reference system of the patient, we widely follow patients with ALI around our region and can determine the prognosis of

patients with ALI/ALF regardless of transferring.

To improve the survival rate of patients with ALF, the **appropriate timing and optimal response evaluation of** high-dose corticosteroid therapy for patients with ALF in the pre-coma stage needs to be established. We aimed to confirm the efficacy of high-dose corticosteroid therapy for ALF in preventing coma development in patients with ALF and to predict the patients who are likely to develop hepatic coma after the therapy. Therefore, we prospectively observed the clinical course of patients with ALF who were treated with high-dose corticosteroid therapy. Using these data, we estimated the optimal timing for the initiation of high-dose corticosteroid therapy to patients with ALF.

Subjects and Methods

Subjects: Our database listed 469 patients who consulted our department for further evaluation of liver dysfunction between April 2004 and March 2015 (Figure 1). The inclusion criteria for registration to the database were as follows: the absence of a diagnosis of either chronic hepatitis or liver cirrhosis, acute liver injury (aspartate transaminase [AST] > 200 IU/L or alanine transaminase [ALT] > 300 IU/L) and prolonged prothrombin time (PT-INR > 1.2 or PT activity < 80%). After registration, laboratory data and physical findings were serially reported from regional hospitals. The JHEPM probability was calculated by using these data of each report. A 20% JHEPM probability was assumed as the time to start intensive care based on our previous study[13]. Seventy-six of 328 patients exceeded 20% of JHEPM in the present study. When some patients were continually treated in regional hospitals, we kept in close contact with the regional hospital and corrected clinical findings, including physical findings and laboratory data.

After registration to the list in the referral system, 126 patients met the definition of either ALF or late-onset hepatic failure (LOHF). The definition of ALF was previously mentioned above and obtained from a previous study[14]. LOHF was defined as ALF and coma development more than 8 weeks, but less than 24 weeks from the onset of the first symptom[14, 16]. We excluded 5 patients because the aim of the present study was evaluation of the therapy for prevention of hepatic coma and these patients were administered high-dose corticosteroids after the onset of coma. To confirm the potential selective bias of patients with high-dose corticosteroid therapy, 121 patients

with ALF or LOHF were analyzed with adjustment of data by propensity scoring. To evaluate efficacy of high-dose corticosteroid therapy, patients with ALF (n = 43) or LOHF (n = 1) were included (Figure 1 and Table 1). The details of the etiology of the liver disease in each patient are summarized in Table 1. All protocols reported in this study were approved by the Institutional Review Board of Iwate Medical University (approval number: H20-36).

Prediction models for coma development in ALF: The JHEPM probability was calculated for each patient based on the results of a hematological examination and the reported etiology of liver failure on admission [15]. The formula is as follows: JHEPM = [0.692 loge (1 + TBil (mg/dL))] − 0.065 PT (%) + [1.388 age (years)] + [0.868 etiology] − 1.156. In this formula, age is 1 in patients older than 50 years, and etiology is 1 when the cause of a non-acetaminophen-induced liver injury flared up because of type B hepatitis, auto-immune hepatitis, or unknown causes, and 0 for other causes. The JHEPM value is calculated as follows: $p = 100/(1 + e^{\lambda})$.

Protocol of high-dose corticosteroid therapy: High-dose corticosteroid therapy involved the administration of 1000-mg methylprednisolone infusion on 3 consecutive days. The indication of the therapy was dependent on the physician's decision.

Laboratory data: White blood cell counts (WBC), plasma PT time, and serum levels of ALT, AST, creatinine (Cre), and total bilirubin (TBil) were analyzed by using an autoanalyzer (JCA-BM2250, JEOL, Tokyo, Japan). PT activity was measured by using RecombiPlastin (Werfen Japan, Tokyo, Japan), Thromborel S (SYSMEX Co., Kobe, Japan), or Thrombocheck PT (SYSMEX Co.) kits. To compare these values during

high-dose corticosteroid therapy, they were measured the day before administering high-dose corticosteroid therapy, and 4 or 7 days after the therapy.

Statistical analysis: The results are expressed as the mean and standard deviation. All statistical analyses were performed by using SPSS 17.0 software program (SPSS Inc., Chicago, IL, USA). Non-parametric tests (Kruskal–Wallis followed by Dunn multiple comparisons) were used to evaluate the statistical significance of the results. A two-sided p value of <0.05 was considered statistically significant. The predictive performance for coma development was assessed by using the receiver operator curve (ROC) method in both prothrombin and JHEPM probability the day before high-dose corticosteroid therapy, and 4 and 7 days after the treatment. The cut-off values for coma-development were estimated by using the area under the ROC (AUROC) method.

Assemble study using propensity score: To reduce selection bias among the patients receiving high-dose corticosteroid therapy and those without the therapy, propensity score was calculated using the data from the 121 patients in the present study (Figure 1). Possible confounders in propensity score were chosen by comparison between the patients with high-dose corticosteroid therapy and those without the therapy (Supplemental Table). Sex, liver atrophy, autoimmune hepatitis, and serum ALT level were selected by logistic regression analysis and used for calculating propensity score for high-dose corticosteroid therapy. The odds ratio of high-dose corticosteroid therapy to the development of hepatic coma was analyzed by binomial logistic regression with data adjusted by propensity score.

Results

High-dose corticosteroid therapy might reduce the risk of hepatic coma in patients with ALF. To confirm the beneficial effect of high-dose corticosteroid therapy, we estimated the odds ratio of the therapy to the development of hepatic coma in the ALF. We noticed that there might be selection bias among the patients with treatment, although the present study was a prospective, non-randomized observational study. To reduce these risks, we performed a propensity score analysis. The odds ratio (95% confidence interval) of high-dose corticosteroid therapy to the development of hepatic coma was lower in the adjusted data by propensity score than that in the data before adjusting [1.48 (0.48-4.902) vs. 2.22 (0.787-6.247)], although there was no statistical significance.

High-dose corticosteroid therapy may lead to early recovery of liver function in the patients with ALF. To evaluate the efficacy of high-dose corticosteroid therapy for increasing prothrombin activity, the hallmark of protein synthesis in the liver, we evaluated the serial changes of PT activity in the patients with ALF or LOHF (Supplemental figure). The first time-point of the patients without therapy was defined as the day of recognition by the referral system of the patient. In patients treated by high-dose corticosteroid therapy, PT activity 4 days and 7 days after therapy were significantly improved compared with PT before therapy. In contrast, only PT activity 7 days after recognition showed a significant improvement compared with PT activity before recognition.

Clinical characteristics of ALF patients with high-dose corticosteroid therapy

in the present study: Based on the patient characteristics shown in Table 1, 35 patients with ALF without coma and 9 patients, including 1 with LOHF, developed coma after high-dose corticosteroid therapy (Table 1). Because we focused on the therapeutic indication of high-dose corticosteroid therapy for prevention of coma development, the patients were divided into groups based on coma development. The survival rate in patients with ALF without coma was higher than those with ALF with coma, which was similar to previous reports[1, 2, 13]. In laboratory data before high-dose corticosteroid therapy, the serum levels of AST, ALT, Cre, TBil, and WBC in patients with coma were not significantly different from those observed in patients without coma. The patients with coma showed higher levels of both PT-INR and JHEPM probability, and showed lower levels of plasma PT activity compared with the patients without coma (Table 2). Therefore, we focused on JHEPM, PT activity, and PT-INR as predictors of hepatic coma to establish indication of the treatment. No complications, such as infection, associated with high-dose corticosteroid therapy were observed. All 10 patients with HBV received nucleotide analog (NA) on the first day of high-dose corticosteroid therapy. No patients, including the 11 AIH patients, received other immunosuppressive drugs during hospitalization (Table 1).

Patients with more than 40% JHEPM, more than 1.31 PT-INR, or less than 50% PT had coma development. We evaluated both JHEPM and PT values the day before therapy to assess the appropriate timing to start high-dose corticosteroid therapy for patients with ALF. When the incidence rate of coma was compared using JHEPM, coma development was observed in patients with more than 40% JHEPM (Figure 2A).

Coma development presented in patients with more than 1.31 PT-INR (Figure 2B) or less than 50% PT activity the day before the therapy (Figure 2C). Based on the low values of JHEPM, PT-INR, and PT activity, coma prevalence tended to increase. Of the 9 patients with coma, 5 developed hepatic coma within 3 days of steroid pulse initiation (data not shown).

PT activity was a good predictor for coma-development in patients with ALF with high-dose corticosteroid therapy: Because factors associated with PT, JHEPM, PT-INR, and PT activity showed a significant difference among these patients with/without coma, we did not perform multivariate analysis to identify predictive factors in hepatic coma development. We analyzed JHEPM, PT-INR, and PT activity by using the ROC method to confirm the predictive ability for the onset of coma. The AUROC presented good predictive ability in JHEPM, PT-INR, and PT activity (0.898, 0.857, and 0.873, respectively). When the cut-off values were 53.6%, 1.95, and 39.4% of JHEPM, PT-INR, and PT activity, respectively, all parameters showed high sensitivity (0.89, 0.89, and 0.89, respectively) and specificity (0.77, 0.86, and 0.71, respectively; Figure 3).

PT improved drastically after steroid pulse therapy in patients without coma, but not in patients with coma: Because PT was a good parameter for the evaluation of liver physiological function, we serially observed the change of both PT-INR and PT activity. Both PT-INR and PT activity significantly improved after steroid pulse therapy in patients without coma. In contrast, these parameters in patients with coma were not improved (Figure 4A and B). These data suggested that patients with coma had a poor

response to steroid pulse therapy.

PT activity 4 days after high-dose corticosteroid therapy was useful as an ***evaluation of the response to therapy****.* Although prevention of disease progression contributes to improve the outcome of patients with ALF, poor responders to steroid pulse therapy should also be focused on. We considered that the patient might require liver transplantation if the patient developed hepatic coma after high-dose corticosteroid therapy. For the reason mentioned above, a prediction for the development of hepatic coma after high-dose corticosteroid therapy was required. We evaluated both PT activity and PT-INR 4 and 7 days after initiation of the therapy to confirm the predictive ability of PT activity for hepatic coma development after high-dose corticosteroid therapy. All values were analyzed by using the ROC method. All values showed lower sensitivity compared with PT activity before the therapy (Figures 3 and 5). However, both PT-INR and PT activity 4 days after the therapy showed higher specificity compared with PT before the therapy (0.91 and 0.94, respectively). These data indicated that the PT value after 4 days of the therapy was useful for excluding patients who did not develop hepatic coma.

Discussion

This prospective, non-randomized, and observational study showed that 1) PT activity and JHEPM probability, predicted coma development in patients with ALF who were treated with steroid pulse therapy, 2) patients with ALF with coma who showed a poor response to steroid pulse therapy, and 3) PT 4 days after high-dose corticosteroid therapy was a good parameter for **evaluating the response to therapy and** identification of patients who did not develop hepatic coma.

ALF with coma shows high mortality, and liver transplantation is required in some cases. Performing liver transplantation is difficult in Japan due to shortage of liver donors, medical cost, or surgical risk for donors if the graft comes from a living donor[3, 16]. For the reasons mentioned above, steroid therapy is widely used as treatment for ALF in Japan[7, 16]. Serial changes of PT occurred in both the patients with high-dose corticosteroid therapy and those without therapy. As a result, PT activity 4 days after the therapy significantly improved compared with that before the therapy (Supplemental figure). In contrast, PT 4 days after recognition did not show significant improvement. These data would indicate that high-dose corticosteroid therapy leads to quicker recovery of liver function in the patients with ALF, although there might be a selection bias. We evaluated whether high-dose corticosteroid therapy prevented the development of hepatic coma in the patients with ALF. Although there was no statistical significance regarding the beneficial effect of the therapy in the evaluation, high-dose corticosteroid therapy might show a tendency of risk reduction for hepatic coma in the patients with ALF.

Previous reports denied the efficacy of steroid therapy to patients with ALF[4-6, 16]. Most patients treated in these studies seemed to be started on steroids in an advanced stage[4, 5, 17]. We considered that the earlier steroid therapy initiation may result in the better response in the therapy for patients with ALF. In fact, Karkhanis et al reported that steroid therapy significantly decreased the mortality in patients with ALF who were administered steroids in the stage with serum AST level higher than 1000 U/L and MELD probability lower than 40[12]. Thus, the **appropriate** timing in initiating steroid pulse therapy for ALF needs to be established. To establish the criteria for high-dose corticosteroid therapy, we proposed the following values of JHEPM, PT-INR, and PT activity as the **appropriate timing to start high-dose corticosteroid therapy**: 40%, 1.53, and 52%, respectively. These values were calculated by mean ± 2 × standard deviation of each value because these values theoretically discriminated 98% coverage to patients with coma (Table 2).

Because prothrombin has a half-life of 1.5–5 h, PT activity and PT-INR are used as a highly sensitive marker of protein synthesis in the liver[18]. In the present study, several assays were used for PT evaluation. Although each assay might vary, the difference, if any, would be small[19]. Therefore, PT activity was maintained without revision, although we recognize this potential limitation. Functional hepatocyte mass assessed with scintigraphy correlated with the PT activity value, and the value of the scintigraphy and PT activity decreased in patients with ALI/ALF based on the functional and hepatocyte loss of the liver[20]. The PT activity of the patients with coma in the present study was maintained at a low level after steroid therapy (Figure 4A and

B). Considering that patients who receive steroid therapy at lower PT level showed higher rate of coma development, we speculate that steroid therapy could inhibit liver damage, but not directly promote regaining liver function. In fact, we have previously reported that insufficient regeneration of the liver in ALF patients showed poor prognosis[14]. When PT activity was considered as an indicator of physiological liver function, liver injury with low PT activity displayed insufficient liver function, which induced hepatic coma. As shown in Figure 2C, hepatic coma developed in the patients with PT less than 49% or a PT-INR of more than 1.31. These data suggest that patients who did not meet the definition of ALF might progress to ALF with coma. Based on these findings, patients with ALI/ALF might be treated according to this proposed timing.

One patient developed hepatic coma despite no indication by 4-day PT activity after treatment that would have predicted coma onset (Figure 5). The patient was diagnosed with LOHF, which is an uncommon form of liver failure and shows extremely poor prognosis[16, 21]. Because hepatic coma in patients with LOHF only appears in the late phase of the disease, PT activity after treatment did not predict coma onset at the late phase of the LOHF. To avoid this issue in future research, examining the clinical course of deceased patients with ALF and LOHF might be of assistance[14]. In the results of the previous study, the deceased patients showed not only delayed recovery of liver function but also impaired liver regeneration[14]. This idea of impaired regeneration, which may lead to liver atrophy, would be a good candidate for the prediction of LOHF in future study.

There were several limitations in the present study. Firstly, there was selection bias of the patients with high-dose corticosteroid therapy. Although logistic regression analysis with propensity scoring was used for evaluation of the therapeutic effect on the prevention of hepatic coma, high-dose corticosteroid therapy only showed a tendency for decreasing the risk of hepatic coma onset without statistical significance. Secondly, there was no criterion on the indications for high-dose corticosteroid therapy. The study design was observational because indication criteria of high-dose corticosteroid therapy were absent and there was no previous study for reference with these criteria. Finally, there was no discussion on etiology because the number of the patients with each etiology was small. To clarify the specific effect of high-dose corticosteroid therapy on each etiology, a larger population of patients with ALF undergoing the therapy and a well-designed study with solid indication for therapy will be needed.

Acknowledgements

The authors declare that they have no conflicts of interest. We thank Koko Motodate for providing excellent secretarial support. This study was supported in part by Grants-in-Aid from the Ministry of Health, Labor and Welfare of Japan to the Intractable Hepatobiliary Diseases Study Group (JP16K21307 and JP16K09370).

References

1. Sugawara K, Nakayama N,Mochida S. Acute liver failure in Japan: definition, classification, and prediction of the outcome. J Gastroenterol 2012;47:849-861.
2. Oketani M, Ido A,Tsubouchi H. Changing etiologies and outcomes of acute liver failure: A perspective from Japan. J Gastroenterol Hepatol 2011;26 Suppl 1:65-71.
3. Yamashiki N, Sugawara Y, Tamura S, et al. Outcomes after living donor liver transplantation for acute liver failure in Japan: results of a nationwide survey. Liver Transpl 2012;18:1069-1077.
4. Ware AJ, Jones RE, Shorey JW, et al. A controlled trial of steroid therapy in massive hepatic necrosis. Am J Gastroenterol 1974;62:130-133.
5. Gregory PB, Knauer CM, Kempson RL, et al. Steroid therapy in severe viral hepatitis. A double-blind, randomized trial of methyl-prednisolone versus placebo. N Engl J Med 1976;294:681-687.
6. Redeker AG, Schweitzer IL,Yamahiro HS. Letter: Randomization of corticosteroid therapy in fulminant hepatitis. N Engl J Med 1976;294:728-729.
7. Fujiwara K, Yasui S, Yonemitsu Y, et al. Efficacy of high-dose corticosteroid in the early stage of viral acute liver failure. Hepatol Res 2014;44:491-501.
8. Ohira H,Takahashi A. Current trends in the diagnosis and treatment of autoimmune hepatitis in Japan. Hepatol Res 2012;42:131-138.
9. Kakisaka K, Kataoka K, Suzuki Y, et al. Necrotic cell death and suppression of T-cell immunity characterized acute liver failure due to drug-induced liver injury. Cytokine 2016;86:21-28.
10. Yasui S, Fujiwara K, Yonemitsu Y, et al. Clinicopathological features of severe and fulminant forms of autoimmune hepatitis. J Gastroenterol 2011;46:378-390.
11. Coutinho AE,Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol 2011;335:2-13.
12. Karkhanis J, Verna EC, Chang MS, et al. Steroid Use in Acute Liver Failure. Hepatology 2014;59:612-621.
13. Takikawa Y, Endo R, Suzuki K, et al. Early prediction of short-term development of hepatic encephalopathy in patients with acute liver disease unrelated to paracetamol. A prospective study in Japan. J Hepatol 2009;51:1021-1029.
14. Kakisaka K, Kataoka K, Onodera M, et al. Alpha-fetoprotein: A biomarker for the recruitment of progenitor cells in the liver in patients with acute liver injury or failure. Hepatol Res 2014;45:E12-20.
15. Kakisaka K, Kataoka K, Kuroda H, et al. Predictive formula for acute liver failure is useful for predicting the prognosis of patients with acute-on-chronic liver failure. Hepatol Res 2016;46:459-467.
16. Oketani M, Ido A, Nakayama N, et al. Etiology and prognosis of fulminant hepatitis and late-onset hepatic failure in Japan: Summary of the annual nationwide survey between 2004 and 2009. Hepatology Research 2013;43:97-105.
17. Randomised trial of steroid therapy in acute liver failure. Report from the European Association for the Study of the Liver (EASL). Gut 1979;20:620-623.
18. Franchini M,Lippi G. Prothrombin complex concentrates: an update. Blood Transfus 2010;8:149-154.

19. Takikawa Y, Harada M, Wang T, et al. Usefulness and accuracy of the international normalized ratio and activity percent of prothrombin time in patients with liver disease. Hepatol Res 2014;44:92-101.
20. Kudo M, Todo A, Ikekubo K, et al. Quantitative assessment of hepatocellular function through in vivo radioreceptor imaging with technetium 99m galactosyl human serum albumin. Hepatology 1993;17:814-819.
21. Kakisaka K, Kuroda H, Abe T, et al. Hepatic Hemodynamics and Elevation of Liver Stiffness as Possible Predictive Markers of Late-onset Hepatic Failure. Intern Med 2016;55:1091-1095.

Figure Legends

Figure 1. Flow chart over eligible patients with acute liver failure treated with high-dose corticosteroid therapy.

Figure 2. Incidence rate of hepatic coma in patients classified by the Japan Hepatic Encephalopathy Prediction Model (JHEPM), prothrombin international normalized ratio (PT-INR), and prothrombin (PT) activity.

A, B and C: Forty-four patients are classified by JHPEM (A), PT-INR (B), and PT activity (C), and demonstrated the incidence rate in the population of each class.

Figure 3. Prediction of hepatic coma development is analyzed by receiver operating characteristic curve by using JHEPM, PT-INR, and PT.

The area under the ROC (AUROC) value was 0.898 for the JHEPM, 0.857 for PT-INR, or 0.873 for PT. The distinction for prediction of hepatic coma for sensitivity, specificity, positive predictive value, and negative predictive value were 0.89, 0.77, 0.50 and 0.96 for the JHEPM, respectively, 0.89, 0.86, 0.62 and 0.97 for PT-INR, respectively, and 0.89, 0.71, 0.47 and 0.96 for PT, respectively, when the cutoff values were 53.6 for the JHEPM, 1.96 for PT-INR and 39.4 for PT.

Figure 4. Serial changes of PT and PT-INR are compared between patients with coma and those without coma.

A and B: Forty-four patients are divided into the following two groups: 35patients

without coma and 9 patients with coma. Serial changes in PT-INR (A) and PT (B) are presented as line charts. Y axis indicates each value. X axis indicates time-points of each evaluation. Statistical significance was evaluated using the Friedman test, and defined as a p value <0.05. No significant difference is presented as n.s.

Figure 5. Prediction of hepatic coma development is analyzed by receiver operating characteristic curve by using PT 4 and 7 days after high-dose corticosteroid therapy.
The area under the ROC (AUROC) values of prediction of hepatic coma were evaluated using PT-INR (A) and PT (B). A: AUROC values were 0.843 for PT-INR measured 4 days after the treatment, and 0.908 for PT-INR measured 7 days after the treatment. B: AUROC values were 0.905 for PT measured 4 days after the treatment, and 0.898 for PT measured 7 days after the treatment.

Supplemental Figure Legend. Serial changes of PT and PT-INR are compared between patients with high-dose corticosteroid therapy (Pulse) and those without the Pulse.

A and B: One hundred twenty-one patients were divided into the following two groups: 77 patients without high-dose corticosteroid therapy and 44 patients with the therapy. Serial changes in PT-INR (A) and PT (B) are presented as line charts. Y axis indicates each value. X axis indicates timepoints of each evaluation. Statistical significance was evaluated using the Friedman test, and defined as a p value <0.05. No significant difference is presented as n.s.

Figure 1

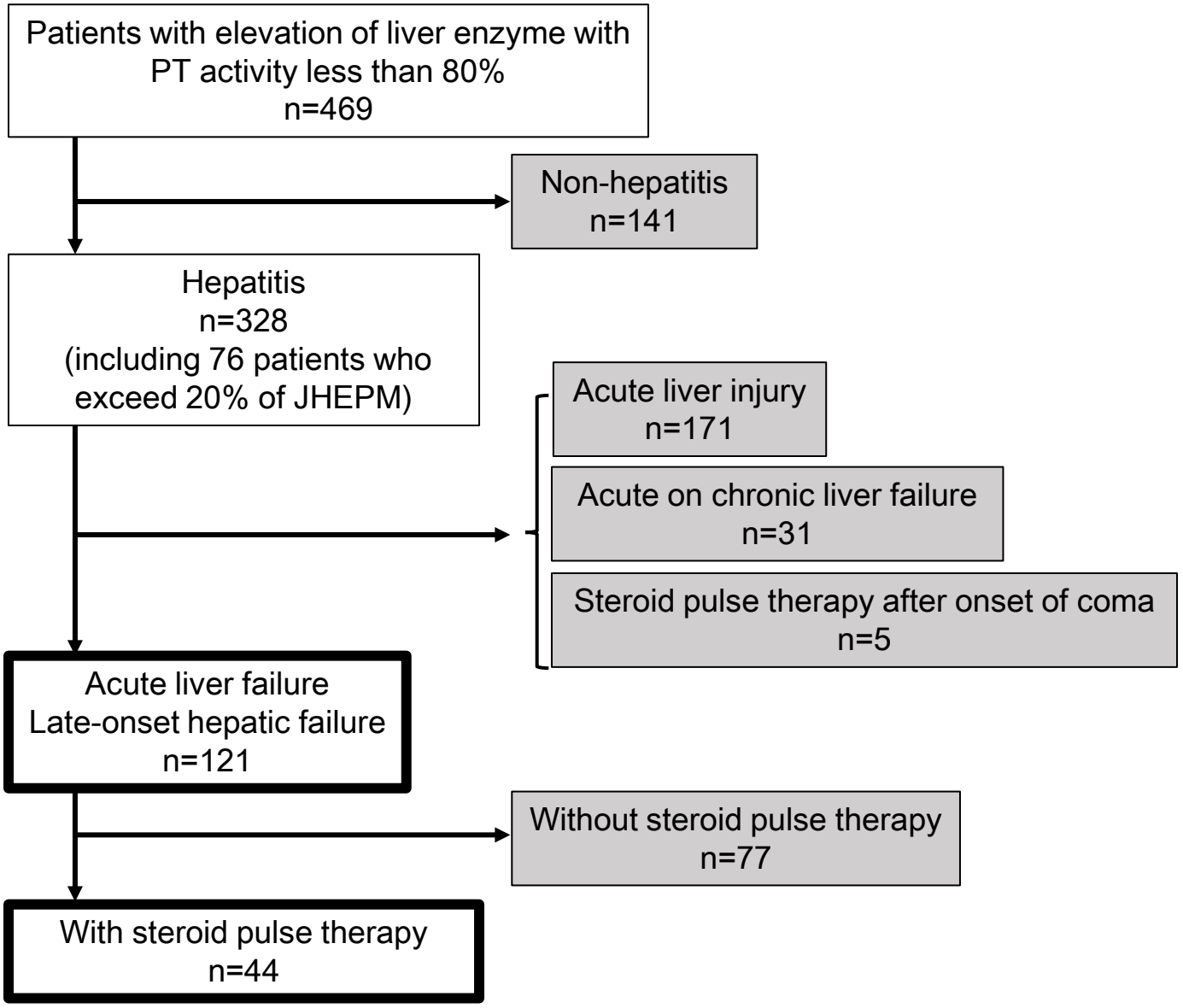

Patients with elevation of liver enzyme with PT activity less than 80% n=469
Non-hepatitis n=141
Hepatitis n=328 (including 76 patients who exceed 20% of JHEPM)
Acute liver injury n=171
Acute on chronic liver failure n=31
Steroid pulse therapy after onset of coma n=5
Acute liver failure Late-onset hepatic failure n=121
Without steroid pulse therapy n=77
With steroid pulse therapy n=44

Figure 2

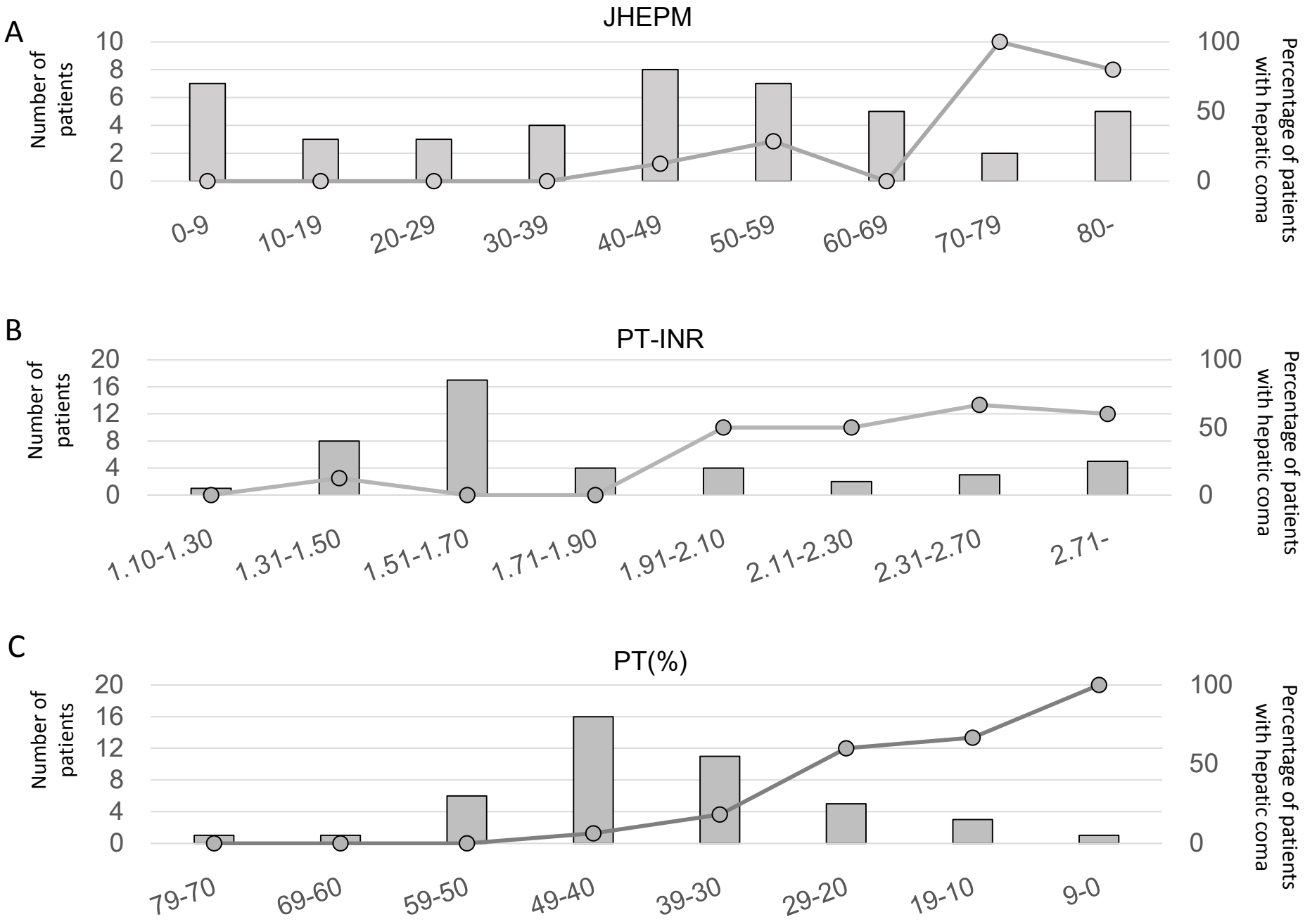
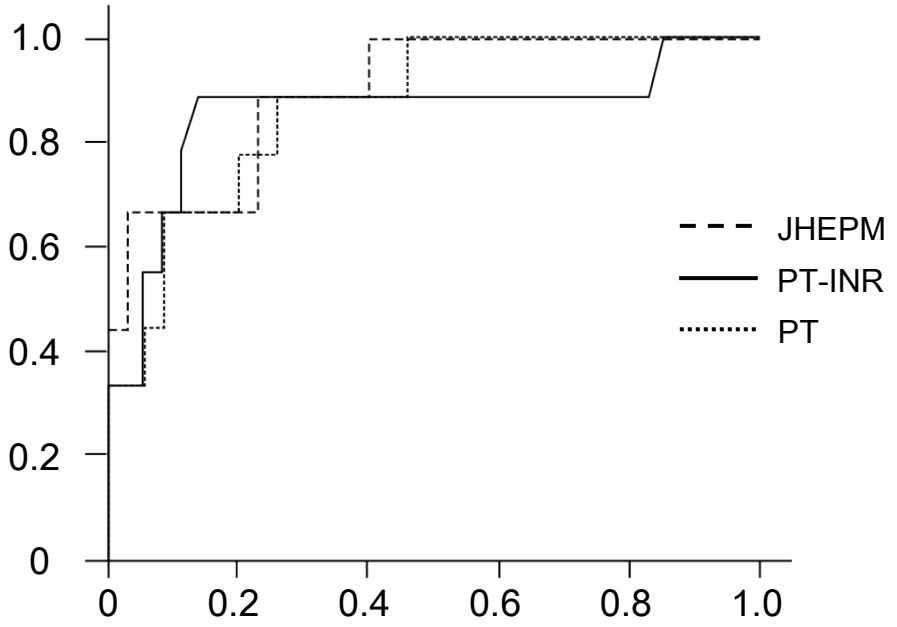

A
JHEPM
Number of patients
Percentage of patients with hepatic coma
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-
B
PT-INR
1.10-1.30
1.31-1.50
1.51-1.70
1.71-1.90
1.91-2.10
2.11-2.30
2.31-2.70
2.71-
C
PT(%)
79-70
69-60
59-50
49-40
39-30
29-20
19-10
9-0

Figure 3



	AUROC	Youden index	Cut-off	Sensitivity	Specificity	PPV	NPV
JHEPM	0.898	0.660	53.6	0.89	0.77	0.50	0.96
PT-INR	0.857	0.746	1.96	0.89	0.86	0.62	0.97
PT	0.873	0.632	39.4	0.89	0.71	0.47	0.96

Figure 4

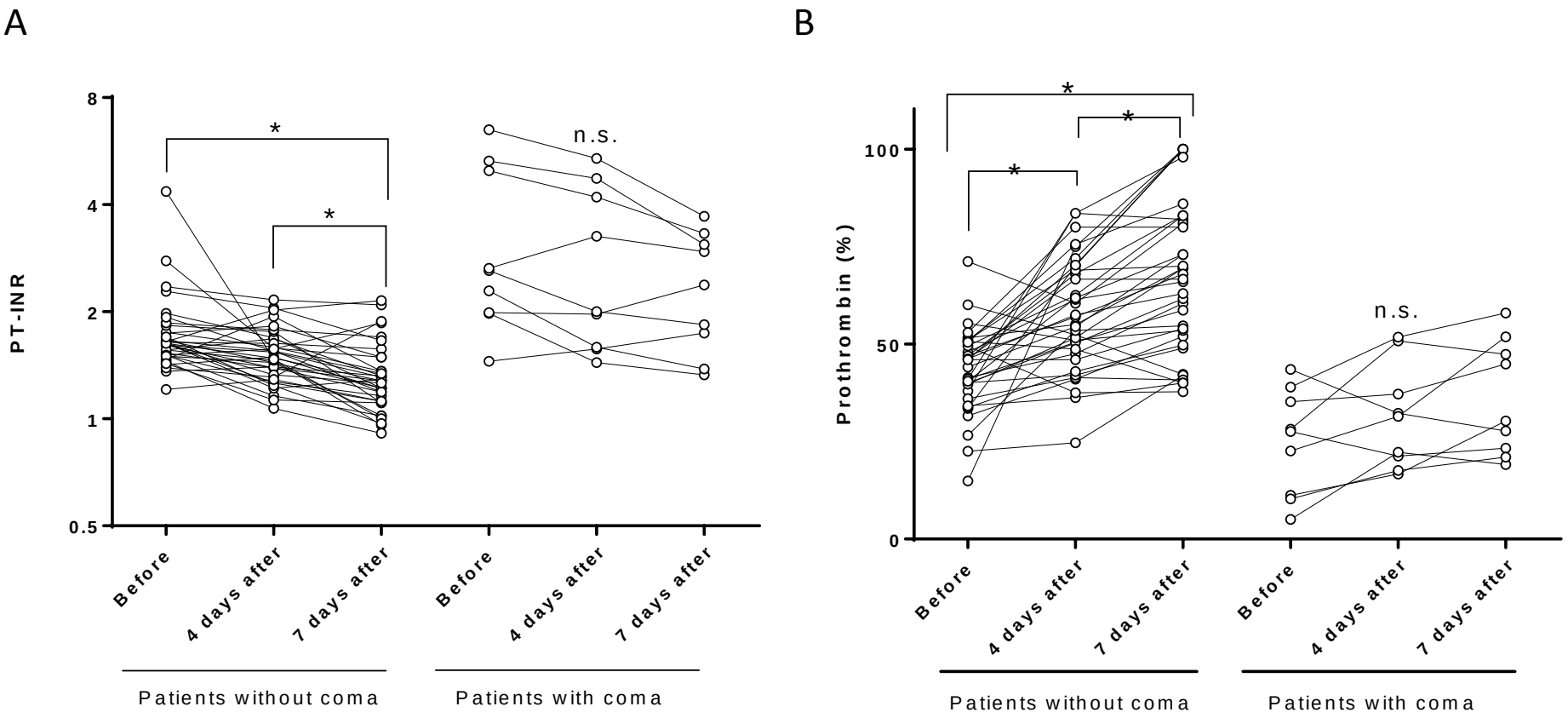
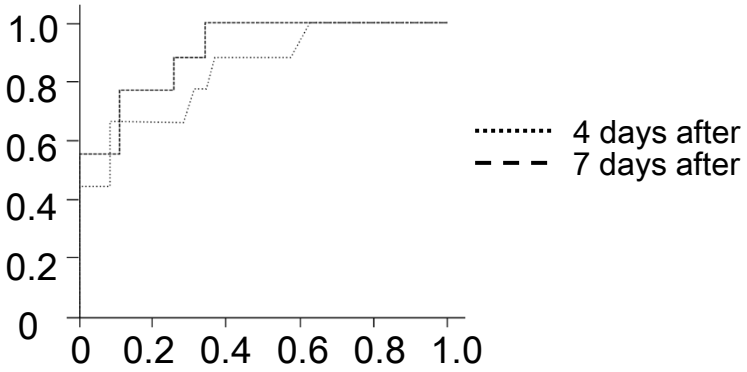

A
B
PT-INR
8
4
2
1
0.5
*
*
n.s.
Before
4 days after
7 days after
Before
4 days after
7 days after
Patients without coma
Patients with coma
Prothrombin (%)
100
50
0
*
*
*
n.s.
Before
4 days after
7 days after
Before
4 days after
7 days after
Patients without coma
Patients with coma

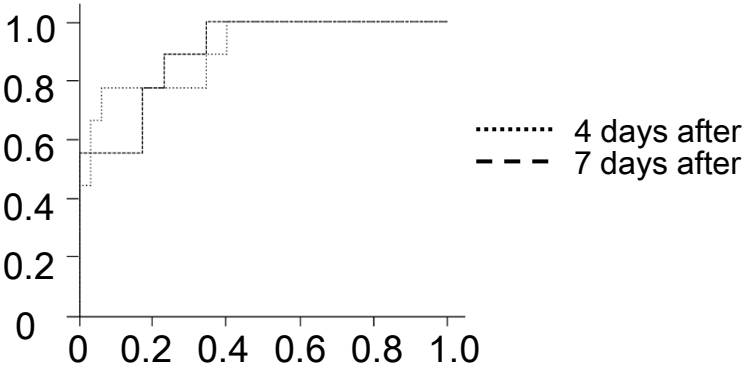
Figure 5

A



	AUROC	Youden index	Cut-off	Sensitivity	Specificity	PPV	NPV
4 days after	0.843	0.581	1.96	0.67	0.91	0.67	0.91
7 days after	0.908	0.663	1.72	0.78	0.89	0.64	0.94

B



	AUROC	Youden index	Cut-off	Sensitivity	Specificity	PPV	NPV
4 days after	0.905	0.721	37.4	0.78	0.94	0.78	0.94
7 days after	0.898	0.660	52.0	0.78	0.74	0.37	0.92

Supplemental Figure

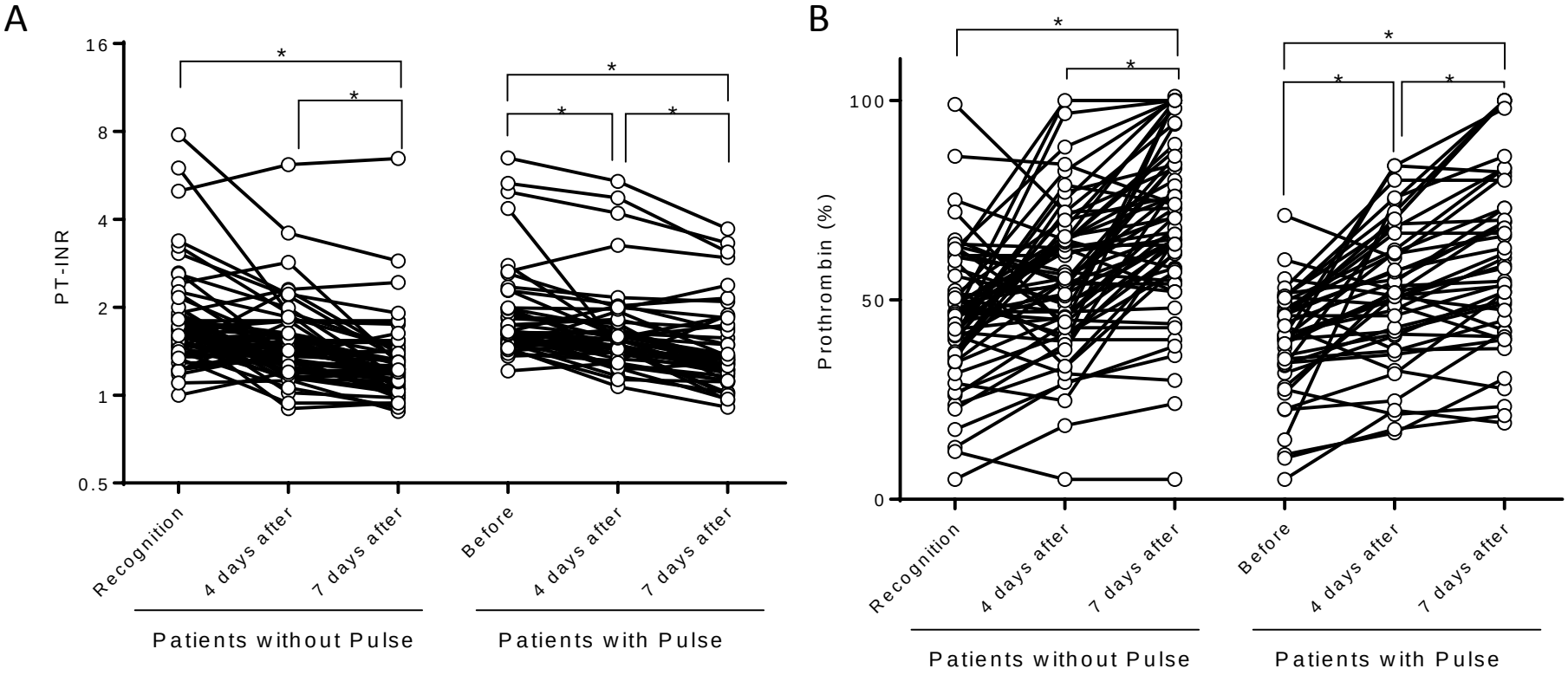


Table 1. Etiologies and prognosis of acute liver failure (ALF) and late-onset hepatic failure (LOHF) in 44 patients

	Acute liver failure			LOHF
	Without coma	With coma		
		Acute type	Subacute type	
Number of subjects	35	1	7	1
F:M	26:9	0:1	3:4	1:0
Etiology				
HBV acute infection	2	0	1	0
Carrier	3	0	2	0
De novo	0	0	2	0
Other viral infections	3	0	0	0
Autoimmune	10	1	0	0
DILI	6	0	1	0
Undetermined	11	0	1	1
Outcome				
Survival	33	0	1	0
Dead	2	0	5	1
Liver transplantation	0	1	1	0

Abbreviations: acute liver failure, ALF; Drug-induced liver injury, DILI; hepatitis B virus, HBV; late onset hepatic failure, LOHF

Table 2. Laboratory data for patients treated by high-dose corticosteroid therapy with acute liver failure with and without coma

		Without coma (n = 35)	With coma (n = 9)	
WBC	/mL	5605±1903	6058 ± 1602	
Cre	mg/dL	0.61 ± 0.23	0.92 ± 0.52	
TBil	mg/dL	12.0 ± 7.9	18.0 ± 7.8	
AST	IU/L	1350 ± 1434	1068 ± 834	
ALT	IU/L	1566 ± 1550	1301 ± 982	
PT	%	43.4 ± 10.6	24.7 ± 13.6	*
PT-INR		1.75 ± 0.27	3.31± 0.89	*
JHEPM		36.6 ± 22.6	72.3 ± 16.3	*

*: $p<0.05$

Abbreviations: alanine aminotransferase, ALT; albumin, Alb; aspartate transaminase, AST; creatinine, Cre; Japan hepatic encephalopathy prediction model, JHEPM; lactate dehydrogenase, LDH; prothrombin time , PT; prothrombin time-international normalized ratio, PT-INR; total bilirubin, TBil; white blood cell, WBC.

Supplemental Table. Laboratory data for 121 patients with acute liver failure or late-onset hepatic failure

		Without steroid pulse therapy (n=77)			With steroid pulse therapy (n=44)			
Age		51.4	±	38.8	56.9	±	27.6	
F:M		36	:	41	35	:	9	
Ascites (-/+)		71	:	6	32	:	12	*
Liver atrophy (-/+)		74	:	3	31	:	13	*
Hepatic coma (-/+)		69	:	8	35	:	9	
Etiology (AIH/Others)		4	:	73	11	:	33	*
WBC	/mL	7047	±	7637	6369	±	7633	
Cre	mg/dL	0.85	±	1.51	0.72	±	0.63	
TBil	mg/dL	7.0	±	13.7	10.2	±	13.6	
AST	IU/L	2578	±	8336	1402	±	2539	*
ALT	IU/L	2199	±	4730	1375	±	1808	*
LDH	IU/L	1548	±	5357	688	±	1112	*
PT	%	47.5	±	37.5	49.2	±	34.5	
PTINR		2.28	±	5.51	1.90	±	2.03	
JHEPM		23.0	±	43.7	30.5	±	47.8	

*: $p<0.05$

Abbreviations: autoimmune hepatitis, AIH; alanine aminotransferase, ALT; albumin, Alb; aspartate transaminase, AST; Japan hepatic encephalopathy prediction model, JHEPM; lactate dehydrogenase, LDH; prothrombin time , PT; prothrombin time-international normalized ratio, PT-INR; total bilirubin, TBil; white blood cell, WBC.