Outcomes of Glucocorticoid Treatment in HBV-Associated Acute-on-Chronic Liver Failure Patients: A Retrospective Observational Study

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ABSTRACT

Background: *Our study aimed to investigate the effects of glucocorticoid (GC) treatment on liver function, hospitalization length, and expenses, as well as 28-day mortality in patients suffered from hepatitis B virus (HBV)-associated acute-on-chronic liver failure (ACLF).*

Methods: *This is a retrospective study of 349 patients who were hospitalized with HBV-associated ACLF. Biochemical assay results of alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, total bilirubin (TBil) level, and creatinine (Cr) level both at admission and before discharge were recorded. GC and antivirus treatment condition, hospitalization length and expenses, as well as 28-day status were also recorded.*

Results: *Among 349 patients with HBV-associated ACLF, GC treatment did not benefit in liver function outcomes, and even ended in higher ALT and TBil levels comparing to patients treated without GC. However, patients treated with GC might have lower 28-day mortality. Similar results were shown in patients with or without antivirus treatment. In addition, GC treatment could not shorten hospitalization length and could increase the expenses.*

Conclusion: *Using GC in HBV-associated ACLF patients could not improve their liver function, but might reduce the risk of death, no matter the patient had had antivirus treatment or not. In addition, GC treatment could not shorten hospitalization length and could increase the expenses in HBV-associated ACLF patients.*

Keywords: *Glucocorticoid, hepatitis B virus, liver failure, liver function*

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is such a fatal liver disease that results in almost 257 million infected people around the world, particularly the infection is endemic in the Asia-Pacific regions like China.[1] The HBV-related diseases range from an inactive HBV carrier state to progressive disease that possibly further evolves into cirrhosis and even a relevant series of complications.[2]

Treatment with either last generation nucleotide analogs (NAs) or pegylated interferon-alpha (pegIFN-α) could suppress serum viral load.[3] However, the commonly emerging problem of flare or deterioration of hepatitis in chronic HBV infected patients may cause acute-on-chronic liver failure (ACLF).[4] The concept of ACLF was introduced by Jalan and Williams in 2002.[5] The American Study Association for the Liver Diseases or European Study Association for the Liver Diseases have officially called ACLF as an acute worsen disease following with a pre-existing chronic liver disease, usually associated with a precipitating event and result in a 3 months increase of mortality which is owing to multifunctional exhaustion.[5]

Once the disease develops into the stage of ACLF, the prognosis will be extremely difficult.[6] Immune responses of the body to HBV are 2-sided. Except for defensing body, an immune response might develop into an overly aggressive state and cause fulminant HBV infection.[7] Along with ACLF progresses, the inflammatory responses in the focal area and consequent cellular immune disorder could lead to multifunctional exhaustion.[4]

Glucocorticoid (GC) has been used in treating chronic HBV infection with ACLF because of its anti-inflammatory effects.[4] The rationale for GC treatment in ACLF can be briefly described as alleviating hepatic inflammatory reaction and the following systematic pro-inflammatory responses throughout the body.[8] However, there is an

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ongoing debate about the benefit of GC treatment in such patients.[9] There is a significant risk of HBV activation using GC, which can be severe and potentially fatal in the context of immunosuppressive therapy.[10]

Thus, our study aimed to investigate the impacts of GC treatment on the function of the liver and outcome of health during hospitalization in patients with HBV-associated ACLF.

MATERIALS AND METHODS

Study Population

This retrospective observational study was approved by the Ethics Committee of The Second Xiangya Hospital of Central South University. We have obtained consent from all the participants to participate and publish the study. We also anonymize and de-identify statistics of the whole data before analysis. The medical records of patients hospitalized in the Department of Infectious Diseases, The Second Xiangya Hospital of Central South University, were carefully recorded who was hospitalized with HBV infection with ACLF during the time from January 2008 to December. Cases about other types of hepatitis virus infection were excluded.

Records of Clinical Data

General information, such as gender, age, body mass index (BMI), and the diagnosis was recorded. Biochemical assay results of alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, total bilirubin (TBil) level, and creatinine (Cr) level both at admission and before discharge were recorded. The hospitalization length and expenses, as well as 28-day status, were also recorded, which was categorized into improved, deteriorated, and mortality.

Data Categorization

According to the treatment condition of GC, the cohort was divided into the GC group and none-GC group. In addition, to further exclude the impacts of the antivirus treatment, all cases were also divided according to the antivirus treatment condition and then compared.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 20.0 (IBM Corp.; Armonk, NY, USA) statistics software was used to analyze the data. All data were evaluated by medians (quartiles). Mann–Whitney–Wilcoxon test was applied on 2 independent variables. Pearson chi-square test was applied to analyze categorical variables. $P < .05$ was considered statistically significant in all statistical operations.

RESULTS

General Information and Serum Biochemical Levels of All Cases at Admission

A total of 349 cases were enrolled, including 311 males and 38 females, aging from 15 to 81, with median age of 39 (31;45) years (Table 1). There were 194 cases (55.6%) in the none-GC group and 155 cases (44.4%) in the GC group, which comprised 130 cases (37.2%) of Methylprednisolone treatment and 18 cases (5.2%) of Prednisone treatment (Figure 1). There were no significant statistical differences between the none-GC group and GC group in gender, age, BMI, or serum levels of ALT, AST, TBil, Cr at admission (all $P > .05$).

Outcomes of All Cases Treated With or Without GC

For all cases, there were no significant differences on levels of AST or Cr between the none-GC group and GC group (both $P > .05$) (Table 2 and Figure 2). Whereas, both ALT and TBil levels in the GC group were remarkably higher than the none-GC group (both $P < .05$), indicating that GC treatment could be related to worse liver function.

Moreover, there were lower rates of improved patients and higher rates of deteriorated patients in the GC group (both $P < .05$). However, the mortality rate was evidently higher in the none-GC group ($P < .05$). These results obviously suggested that GC treatment could not improve the 28-day status of ACLF patients, but might be able to decrease the risk of death.

Besides, no significant differences were shown in the hospitalization length between the none-GC group and GC group ($P > .05$). However, the hospitalization expenses in the GC group were obviously higher than those in the none-GC group ($P < .05$).

MAIN POINTS

- *Using GC in HBV-associated ACLF patients could not improve their liver function.*
- *Might reduce the risk of death, no matter the patient had had antivirus treatment or not.*
- *GC treatment could not shorten hospitalization length and could increase the expenses in HBV-associated ACLF patients.*

Table 1. General Information and Serum Biochemical Levels of All Cases at Admission

	None-GC* Group [Medium (Quartiles)]	GC Group [Medium (Quartiles)]	Total [Medium (Quartiles)]	*P**
Number	194	155	349	
Gender (male/female)	178/16	133/22	311/38	.085
Age (years)	38 (31;45)	40 (30;46)	39 (31;45)	.367
BMI	23.4 (20.2;25.2)	23.8 (20.2;26.3)	23.4 (20.2;25.2)	.615
ALT* (U/L)	429.4 (151.6;1055.9)	452.4 (147.8;1241.0)	450.3 (150.7;1092.3)	.304
AST* (U/L)	198.6 (92.0;502.9)	242.9 (93.9;654.0)	205.0 (92.7;557.1)	.221
TBil* (μmol/L)	283.6 (148.0;484.5)	347.5 (231.7;489.5)	317.0 (194.7;488.1)	.050
Cr* (μmol/L)	68.3 (61.4;80.8)	71.3 (58.1;87.9)	70.2 (60.2;81.9)	.652

*ALT, alanine aminotransferase level in serum at admission.
*AST, aspartate aminotransferase level in serum at admission.
*TBil, total bilirubin level in serum at admission.
*Cr, creatinine level in serum at admission.
*GC, glucocorticoid treatment.
**P* value: Pearson chi-square test was applied to compare gender. Mann–Whitney–Wilcoxon test was applied to compare other parameters. All $P > .05$.

To exclude the effects of antivirus treatment, all cases were categorized into the antivirus-treated group and the non-antivirus-treated group as below.

Outcomes of Antivirus-Treated Patients With or Without GC Treatment

Among all cases, 284 (81.4%) of them had been given antivirus treatment, including 262 males and 22 females, aging from 15 to 81, with a median age of 40 (32;46) (Figure 1). At admission, no significant differences were observed between the none-GC group and GC group in serum levels of ALT, AST, TBil, or Cr (all $P > .05$) (Table 3). After hospitalization, no significant differences in AST, TBil, or Cr outcomes were observed between the none-GC group and GC group (all $P > .05$). Whereas, ALT levels in the GC group were distinctly higher than the none-GC group ($P < .05$), indicating that GC treatment could be related to worse liver function.

Moreover, although there were no significant differences in the rates of improved patients ($P > .05$), the rates of deteriorated patients were higher in the GC group ($P < .05$). However, the mortality rate was higher in the none-GC group ($P < .05$). These results demonstrated

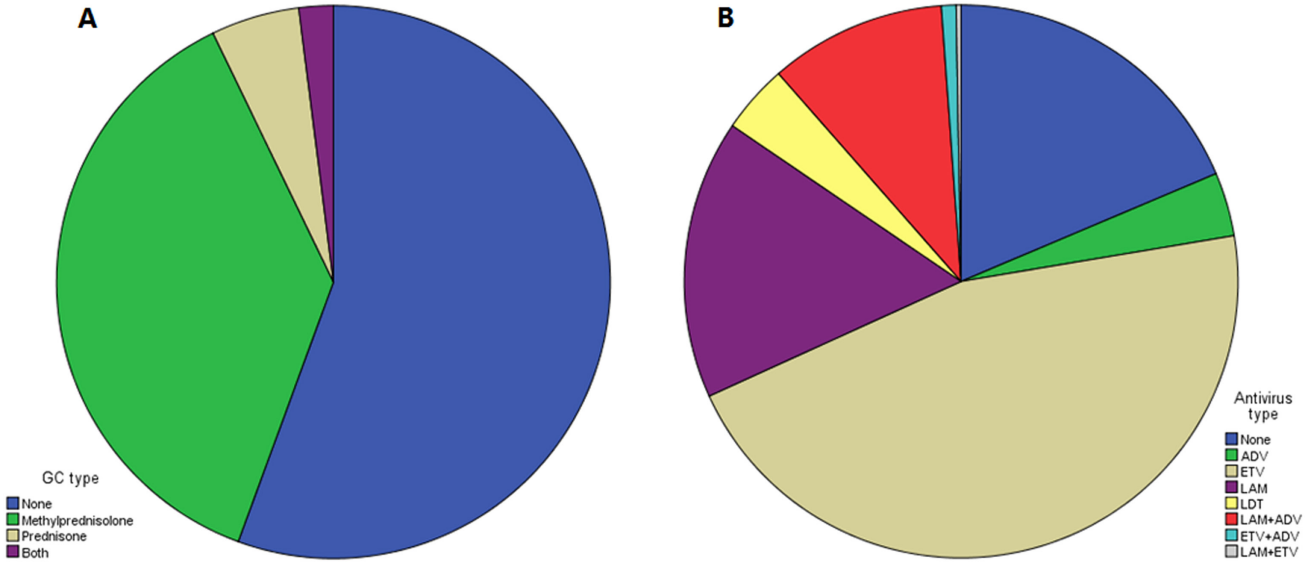

Figure 1. Pie charts of glucocorticoid (GC) treatment types and antivirus treatment types. (A) GC treatment types. (B) Antivirus treatment types. ADV, adefovir dipivoxil; ETV, entecavir; LAM, lamivudine; LD, telbivudine.

Table 2. Outcomes of All ACLF Patients Treated With or Without GC

	None-GC* Group	GC Group	Total	*P**
Serum biochemical levels before discharge [medium (quartiles)]				
ALT* (U/L)	74.7 (48.7;164.2)	98.0 (54.7;232.5)	85.9 (50.8;184.4)	.008**
AST* (U/L)	60.7 (43.2;92.6)	71.1 (48.8;115.4)	67.7 (42.3;101.0)	.057
TBil* (μmol/L)	92.7 (49.4;188.8)	101.7 (58.0;366.1)	98.1 (52.7;305.6)	.024**
Cr* (μmol/L)	67.2 (59.9;79.0)	69.0 (53.8;99.9)	68.6 (54.9;84.4)	.666
28-day status [Case number (percentage)]				
Improved*	151 (77.8%)	104 (67.1%)	255 (73.1%)	.029**
Deteriorated*	21 (10.8%)	45 (29.0%)	66 (18.9%)	<.001**
Mortality*	22 (11.3%)	6 (3.9%)	28 (8.0%)	.016**
Total	194 (100%)	155 (100%)	349 (100%)	
Hospitalization information [medium (quartiles)]				
Length (day)	21.0 (13.8;37.0)	19.0 (10.0;34.0)	20.0 (12.0;35.5)	.082
Expenses (yuan)	19057.0 (12550.0;39894.5)	33673.5 (18263.5;65177.8)	25658.0 (14615.0;53127.5)	<.001**

*ALT, alanine aminotransferase level in serum before discharge.
*AST, aspartate aminotransferase level in serum before discharge.
*TBil, total bilirubin level in serum before discharge.
*Cr, creatinine level in serum before discharge.
*Improved, the number of patients discharged with improved status.
*Deteriorated, the number of patients discharged with deteriorated status.
*Mortality, the number of patients who died during hospitalization.
*GC, glucocorticoid treatment.
**P* value, Mann–Whitney–Wilcoxon test was applied to compare biochemical levels. Pearson chi-square test was applied to compare status on discharge. $P < .05$ was labeled with **.

that GC treatment could not improve the 28-day status of antivirus-treated patients, but might be able to reduce the risk of death.

Outcomes of Non-Antivirus-Treated Patients With or Without GC Treatment

Among all cases, 65 (18.6%) of them had not been given antivirus treatment, including 49 males and 16 females, aging from 19 to 77, with a median age of 36 (28;45) (Figure 1). At admission, there were no significant differences between the none-GC group and GC group in serum levels of ALT, AST, or Cr (All $P > .05$) (Table 4). However, TBil was significantly higher in the GC group ($P < .05$).

After hospitalization, no significant differences in Cr outcomes were found between the none-GC group and GC group ($P > .05$). Whereas, the levels of ALT, AST, and TBil in the GC group were all significantly higher than the none-GC group (all $P < .05$), indicating that GC treatment could be related to worse liver function.

Moreover, there were lower rates of improved patients and higher rates of deteriorated patients in the GC group (both $P < .05$). However, there were no obvious differences in mortality rates between the 2 groups ($P < .05$). These results suggested that GC treatment could not improve the 28-day status of none-antivirus treated patients.

DISCUSSION

Our study showed that patients treated with GC did not benefit in liver function outcomes, and even ended in higher ALT and TBil levels comparing to patients treated without GC among 349 patients with HBV-associated ACLF. However, patients treated with GC might have lower 28-day mortality. Similar results were shown in patients with or without antivirus treatment. In addition, GC treatment could not shorten hospitalization length and could increase the expenses.

HBV does not cause a measurable innate immune reaction in the infected liver.[11] The pathological development is not cytopathic, but immunomediated. The clinical outcome of HBV infection is based on the interplay between host immune response and HBV replication.[12-15] Once ACLF occurs, immune changes in the inflammatory process are similar to severe sepsis.[16]

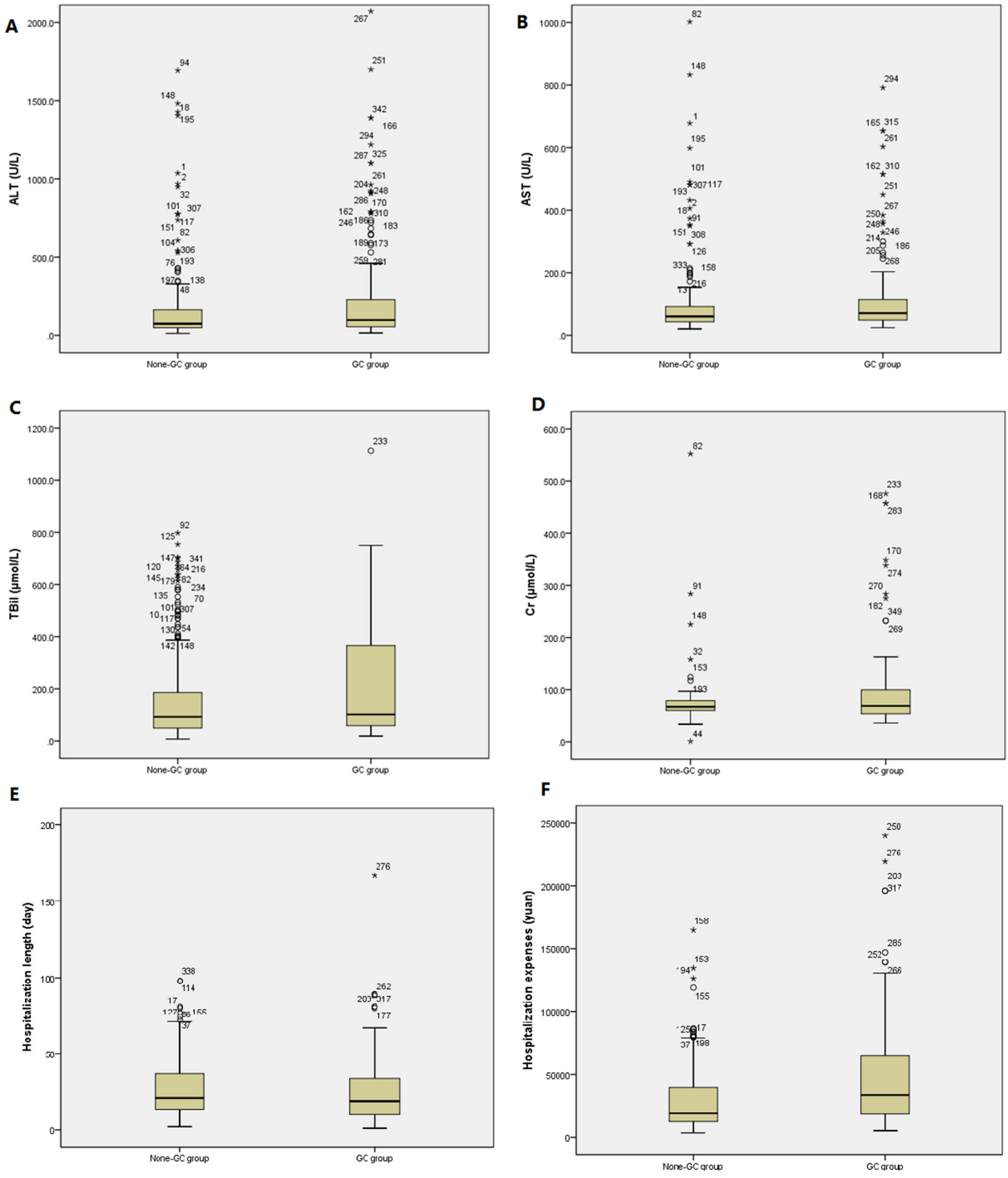

Figure 2. Box plots of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), creatinine (Cr) levels before discharge and hospitalization length and expenses. (A) Box plots of ALT levels before discharge. (B) Box plots of AST levels before discharge. (C) Box plots of TBil levels before discharge. (D) Box plots of Cr levels before discharge. (E) Box plots of hospitalization length. (F) Box plots of hospitalization expenses.

Table 3. Outcomes of Antivirus-Treated ACLF Patients With or Without GC Treatment

	None-GC* Group	GC Group	Total	*P**
Serum biochemical levels at admission [medium (quartiles)]				
ALT* (U/L)	352.9 (130.6;1028.6)	383.5 (141.7;1188.0)	367.8 (141.4;1059.3)	.183
AST* (U/L)	161.3 (88.0;475.2)	205.0 (89.5;626.9)	190.3 (89.5;490.8)	.178
TBil* (μmol/L)	338.4 (190.5;503.4)	336.6 (231.7;489.5)	337.5 (214.2;491.9)	.716
Cr* (μmol/L)	69.6 (61.4;81.5)	70.7 (58.9;84.0)	70.2 (60.2;81.9)	.982
Serum biochemical levels before discharge [medium (quartiles)]				
ALT (U/L)	71.7 (43.4;161.5)	96.0 (51.0;194.0)	81.4 (47.6;165.5)	.030**
AST (U/L)	67.9 (46.0;93.4)	67.9 (48.1;97.9)	67.9 (46.5;97.0)	.780
TBil (μmol/L)	100.0 (54.4;263.0)	97.7 (54.3;346.3)	97.9 (54.3;320.0)	.625
Cr (μmol/L)	66.1 (60.1;79.0)	69.0 (53.7;90.4)	68.1 (55.3;83.9)	.564
28-day status [Case number (percentage)]				
Improved*	108 (74.5%)	101 (72.7%)	209 (73.6%)	.788
Deteriorated*	19 (13.1%)	34 (24.5%)	53 (18.7%)	.015**
Mortality*	18 (12.4%)	4 (2.9%)	22 (7.7%)	.003**
Total	145 (100%)	139 (100%)	284 (100%)	

*ALT, alanine aminotransferase level in serum before discharge.
*AST, aspartate aminotransferase level in serum before discharge.
*TBil, total bilirubin level in serum before discharge.
*Cr, creatinine level in serum before discharge.
*Improved, the number of patients discharged with improved status.
*Deteriorated, the number of patients discharged with deteriorated status.
*Mortality, the number of patients who died during hospitalization.
*GC, glucocorticoid treatment.
**P* value, Mann–Whitney–Wilcoxon test was applied to compare biochemical levels. Pearson chi-square test was applied to compare status on discharge. $P < .05$ was labeled with **.

Whether we should use GC in ACLF patients is still controversial.[9] Few relevant studies have provided powerful evidence about the favorable effect of GC treatment on survival.[17-19] Zhao et al. reported that there was a close relation between GC treatment and restoration of myeloid dendritic cells that increase survival.[20] Chen et al. reported GC treatment had no benefit on survival in such patients.[21] Whereas, results of our study demonstrated that no matter the patient had had antivirus treatment or not, using GC for patients with HBV-associated ACLF had no benefit in promoting liver function or short-term health status.

However, the results of our study suggested that using GC might decrease the risk of death in HBV-associated ACLF patients. The reason might be explained as that infectious complication are both the main precipitants eliciting ACLF and the major cause of death from ACLF. These patients are susceptible to microbial challenges, which is termed as immuneparesis.[8] Thus even though GC treatment could not promote liver function or short-term health status, it might still be needed in critical patients.

ALT, AST, and TBil are the main biochemical indexes of liver function.[22] Cr is the main biochemical index of kidney function. Our study demonstrated the cohort of HBV-associated ACLF patients without significant differences of gender, age, BMI, or serum levels of ALT, AST, TBil, Cr at admission, which avoided some bias, including the bias of general information, as well as the bias of liver and kidney function before GC treatment. In order to further avoid bias, all cases were grouped by whether they had received antivirus treatment.

Although new immunotherapies for HBV have been improved greatly during the last decades and show a promising future, ideal therapeutic strategies are still lacking.[23] To our knowledge, our study first shows the effects of GC treatment on HBV-associated ACLF patients with or without antivirus treatment. The results of our study could provide some references for clinical practice.

Table 4. Outcomes of Non-antivirus-Treated ACLF Patients With or Without GC Treatment

	None-GC* Group	GC Group	Total	*P**
Serum biochemical levels at admission [medium (quartiles)]				
ALT* (U/L)	976.6 (263.2;1206.0)	840.6 (652.0;1507.0)	968.0 (298.6;1324.8)	.345
AST* (U/L)	345.3 (123.2;666.0)	514.9 (203.2;825.9)	415.2 (147.2;732.5)	.170
TBil* (μmol/L)	247.1 (78.7;383.3)	418.2 (230.7;565.1)	267.7 (97.3;456.4)	.003**
Cr* (μmol/L)	68.3 (61.8;76.3)	80.3 (55.1;116.2)	70.3 (58.1;84.5)	.271
Serum biochemical levels before discharge [medium (quartiles)]				
ALT (U/L)	100.0 (54.9;215.9)	736.6 (179.9;1143.1)	114.3 (58.8;345.4)	<.001**
AST (U/L)	52.4 (38.1;82.3)	278.1 (92.7;653.7)	61.9 (40.2;185.7)	<.001**
TBil (μmol/L)	68.0 (35.8;114.9)	365.4 (168.8;472.1)	101.1 (44.0;222.4)	<.001**
Cr (μmol/L)	72.4 (52.4;283.8)	72.5 (54.9;116.2)	72.4 (54.8;116.2)	.769
28-day status [Case number (percentage)]				
Improved*	43 (87.8%)	3 (18.8%)	46 (70.8%)	<.001**
Deteriorated*	2 (4.1%)	11 (68.8%)	13 (20.0%)	<.001**
Mortality*	4 (8.2%)	2 (12.5%)	6 (9.2%)	.631
Total	49 (100%)	16 (100%)	65 (100%)	

*ALT, alanine aminotransferase level in serum before discharge.
*AST, aspartate aminotransferase level in serum before discharge.
*TBil, total bilirubin level in serum before discharge.
*Cr, creatinine level in serum before discharge.
*Improved, the number of patients discharged with improved status.
*Deteriorated, the number of patients discharged with deteriorated status.
*Mortality, the number of patients died during hospitalization.
*GC, glucocorticoid treatment.
**P* value, Mann–Whitney–Wilcoxon test was applied to compare biochemical levels. Pearson chi-square test was applied to compare status on discharge. $P < .05$ was labeled with **.

However, there are some limitations of the study. First, the GC and antivirus treatments were individualized. There was no unified dosage or time window. Second, this is a retrospective observational study. More prospective trials are needed.

CONCLUSION

Using GC in HBV-associated ACLF patients could not improve their liver function, but might reduce the risk of death, no matter the patient had had antivirus treatment or not. In addition, GC treatment could not shorten hospitalization length and could increase the expenses in HBV-associated ACLF patients.

Ethics Committee Approval: This study was approved by the Ethics Committee of The Second Xiangya Hospital of Central South University.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.L., Y.X., YF.J.; Design - Y.L.,Y.X.,; Supervision -Y.L.,; Resource -Y.L.,Y.X., YF.J.; Materials -Y.X., YF.J.; Data Collection and/or Processing -Y.L., Y.X., YF.J.; Analysis and/or Interpretation - Y.L., Y.X., YF.J.; Literature Search -Y.X., YF.J.; Writing -Y.L., Y.X.; Critical Reviews -Y.L.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386(10003):1546-1555. [CrossRef]
2. Idilman R. Management of special patient groups with hepatitis B virus infection: the EASL 2017 Clinical Practice Guidelines. Turk J Gastroenterol. 2017;28(6):518-521. [CrossRef]
3. Testoni B, Durantel D, Zoulim F. Novel targets for hepatitis B virus therapy. Liver Int. 2017;37(suppl 1):33-39. [CrossRef]

4. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1-98. [CrossRef]
5. Jalan R, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif. 2002;20(3):252-261. [CrossRef]
6. Mori N, Suzuki F, Kawamura Y, et al. Determinants of the clinical outcome of patients with severe acute exacerbation of chronic hepatitis B virus infection. J Gastroenterol. 2012;47(9):1022-1029. [CrossRef]
7. Trépo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet. 2014;384(9959):2053-2063. [CrossRef]
8. Bernsmeier C, Singanayagam A, Patel VC, Wendon J, Antoniades CG. Immunotherapy in the treatment and prevention of infection in acute-on-chronic liver failure. Immunotherapy. 2015;7(6):641-654. [CrossRef]
9. Fede G, Spadaro L, Tomaselli T, et al. Adrenocortical dysfunction in liver disease: a systematic review. Hepatology. 2012;55(4):1282-1291. [CrossRef]
10. Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? Hepatology. 2015;61(2):703-711. [CrossRef]
11. Guidotti LG, Isogawa M, Chisari FV. Host-virus interactions in hepatitis B virus infection. Curr Opin Immunol. 2015;36:61-66. [CrossRef]
12. Bertoletti A, Ferrari C. Innate and adaptive immune responses in chronic hepatitis B virus infections: towards restoration of immune control of viral infection. Gut. 2012;61(12):1754-1764. [CrossRef]
13. Bertoletti A, Maini MK, Ferrari C. The host-pathogen interaction during HBV infection: immunological controversies. Antivir Ther. 2010;15(suppl 3):15-24. [CrossRef]
14. Dandri M, Locarnini S. New insight in the pathobiology of hepatitis B virus infection. Gut. 2012;61(suppl 1):i6-i17. [CrossRef]
15. Vlachogiannakos J, Papatheodoridis GV. Hepatitis B: who and when to treat? Liver Int. 2018;38(suppl 1):71-78. [CrossRef]
16. Wasmuth HE, Kunz D, Yagmur E, et al. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. J Hepatol. 2005;42(2):195-201. [CrossRef]
17. Marik PE, Gayowski T, Starzl TE, Hepatic Cortisol Research and Adrenal Pathophysiology Study Group. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. Crit Care Med. 2005;33(6):1254-1259. [CrossRef]
18. Fernández J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. Hepatology. 2006;44(5):1288-1295. [CrossRef]
19. Arabi YM, Aljumah A, Dabbagh O, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. CMAJ. 2010;182(18):1971-1977. [CrossRef]
20. Zhao J, Zhang JY, Yu HW, et al. Improved survival ratios correlate with myeloid dendritic cell restoration in acute-on-chronic liver failure patients receiving methylprednisolone therapy. Cell Mol Immunol. 2012;9(5):417-422. [CrossRef]
21. Chen JF, Wang KW, Zhang SQ, et al. Dexamethasone in outcome of patients with hepatitis B virus-related acute-on-chronic liver failure. J Gastroenterol Hepatol. 2014;29(4):800-806. [CrossRef]
22. Tabak F, Yurdaydın C, Kaymakoğlu S, et al. Diagnosis, management and treatment of hepatitis B virus infection: Turkey 2017 Clinical Practice Guidelines. Turk J Gastroenterol. 2017;28(suppl 2):73-83. [CrossRef]
23. Golsaz-Shirazi F, Shokri F. Hepatitis B immunopathogenesis and immunotherapy. Immunotherapy. 2016;8(4):461-477. [CrossRef]