HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2018 July 23.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2017 January ; 15(1): 113–122. doi:10.1016/j.cgh.2016.06.008.

HBV-associated Acute Liver Failure after Immunosuppression and Risk of Death

Constantine J. Karvellas, MD, SM[#1], **Filipe S. Cardoso, MD, MSc**[#2], **Michelle Gottfried, MSc**[3], **K. Rajender Reddy, MD**[4], **A. James Hanje, MD**[5], **Daniel Ganger, MD**[6], and **William M. Lee, MD**[7] **US Acute Liver Failure Study Group**

[1.]Divisions of Hepatology and Critical Care Medicine, University of Alberta, Edmonton, Canada.

[2.]Division of Gastroenterology, Professor Doutor Fernando Fonseca Hospital, Amadora, Portugal. Liver Intensive Therapy Unit, King's College Hospital, London, UK.

[3.]Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina, USA.

[4.]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, USA.

[5.]Division of Gastroenterology and Hepatology, the Ohio State University, Columbus, USA.

[6.]Division of Gastroenterology and Hepatology, Northwestern University, Chicago, USA.

[7.]Division of Digestive and Liver Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

[#] These authors contributed equally to this work.

Abstract

Background & Aims: Acute liver failure (ALF) due to hepatitis B virus (HBV) infection can occur after immunosuppressive treatment and be fatal, although it might be preventable. We aimed to characterize the causes, clinical course, and short-term outcomes of HBV-associated ALF after

Corresponding author/reprints: Constantine J. Karvellas MD SM FRCPC, Assistant Professor of Medicine, Division of Gastroenterology (Liver Unit), Division of Critical Care Medicine, University of Alberta, 1–40 Zeidler Ledcor Building, Edmonton, Alberta T6G-2X8, Phone: (780) 248-1555, Fax: (780) 492-5643, dean.karvellas@ualberta.ca.

Author Contributions

CJK: Conceived the study concept and design, performed analysis and interpretation of the data, drafted the final manuscript with critical revision of important intellectual content

FSC: Drafted the initial manuscript, performed analysis and interpretation of the data, peformed critical revision of important intellectual content

MG: Performed statistical analysis and interpretation of data

KRR, AJH, DG: Critically revised the manuscript for important intellectual content

WML: Supervisor of entire US Acute Liver Failure Study Group (U-01 Grant). Assisted in developing study design, performed analysis and interpretation of data, critically revised the final manuscript for important intellectual content.

Disclosures/Conflict of interest:

All authors (CK, FSC, MG, KRR, AJH, DG, WML) have no personal or funding conflicts of interest.

Format: This paper followed the STROBE guideline for reporting cohort studies (BMJ 2007): See Supplementary File #1.

immune suppressive therapy, compared to patients with HBV-associated ALF without immunosuppression (controls).

Methods: We performed a retrospective multi-center study of 156 consecutive patients diagnosed with HBV-associated ALF (22 with a solid or blood malignancy) enrolled in the Acute Liver Failure Study Group registry from January 1998 through April 2015. We collected data on results of serologic and hepatic biochemistry analyses, grade of hepatic encephalopathy, model for end-stage liver disease (MELD) score, and King's College criteria. We also collected data on clinical features, medical therapies, and complications in the first 7 days following study enrollment. Logistic regression was used to identify factors associated with transplant-free survival 21 days in HBV-associated ALF (the primary outcome).

Results: Among patients with HBV-associated ALF, 28 cases (18%) occurred after immunosuppressive therapy (15 patients received systemic corticosteroids and 21 received chemotherapy); and 128 cases did not (controls, 82%). Significantly greater proportions of patients with Hepatitis B-associated ALF after immunosuppression were non-white, and had anemia or thrombocytopenic than controls (P<.02 for all). The serologic profile of HBV infection, severity of liver failure (based on MELD score), and complications (hepatic encephalopathy or need for mechanical ventilation, vasopressors, or renal replacement therapy) were similar between the groups (P>.17 for all). Significantly smaller proportions of patients with ALF after immunosuppression than controls survived for 21 days (42.9% vs 62.5% of controls; P=.0096). Factors associated with 21 day transplant-free survival (c-statistic = 0.866) were increased MELD score (odds ratio, 0.894 per increment), requirement for mechanical ventilation (odds ratio, 0.111), and immunosuppressive therapy (odds ratio, 0.274).

Conclusion: Within a cohort study of HBV-associated ALF patients, 18% had received immunosuppressive therapy. Significantly smaller proportions of HBV-associated ALF patients after immunosuppression survive beyond 21 days than patients with HBV-associated ALF who did not receive immunosuppression. Patients undergoing chemotherapy should be screened for HBV infection and given appropriate anti-viral therapies to reduce preventable mortality.

Keywords

Acute liver failure; Hepatitis B; Chemotherapy; Immunosuppression

INTRODUCTION

Acute liver failure (ALF) is a rare disease associated with high short-term morbidity and mortality [1]. In the United States (US), hepatitis B (HBV)-associated ALF represents about 7% of all ALF events [2]. It may develop following acute or reactivation of chronic HBV infection. Amongst causes of reactivation, the use of ***immunosuppressive agents,*** mostly to treat autoimmune diseases or cancer, have been recognized as an increasingly important issue [3, 4] In a recent American Gastroenterological Association technical review, patients who were HbsAg/anti-HBc positive had a reactivation rate of up to 30% if receiving anthracycline based chemotherapy while those who received b-cell depleting agents (rituximab) achieved reactivation rates as high as 60%[5] These patients are potentially at risk for ALF, and furthermore, given their own comorbidities, they may have contra-indications

that could preclude liver transplantation (LT). Fortunately, the risk of reactivation of chronic HBV infection in this context may be mitigated with appropriate antiviral prophylaxis [6, 7]

Studies have suggested that HBV-associated ALF due to immunosuppression treatment may have a specific pathophysiology, as it has been noted that these patients frequently display specific HBV surface antigen (HBsAg) mutations that may enhance the virus' capability of evading the immune system response[8, 9]. Other mechanisms that have been postulated include loss of immune control of viral replication via inhibition of gamma interferons, upregulated cytotoxic T-cell mediated hepatocyte necrosis, and B-cell depletion [7, 10, 11]. The outcomes of patients with HBV-associated ALF due to immunosuppression have been poorly studied[9].

Taking into account the increasing burden of all immunosuppressive treatments for the health-care systems worldwide, this study aimed to evaluate the following

- The proportion of HBV-associated ALF patients in a large North American cohort due to immunosuppression (US ALFSG)
- Determine if there is an association between immunosuppression/chemotherapy (exposure) with decreased transplant-free (TFS) (and overall) survival in 156 HBV-associated ALF patients from the US ALFSG registry
- Determine if the presence of immunosuppression is associated with worse TFS to HBV-associated ALF controls after adjusting for other significant covariates (multivariable logistic regression)

METHODS

Design, setting, participants,

We performed a retrospective cohort study of all adjudicated HBV-associated ALF patients within the US ALF Study Group (US-ALFSG) prospective registry between January 1998 and April 2015. Patients not fulfilling criteria for ALF (see operational definitions) or with unknown primary outcome data were excluded. All participating sites were tertiary academic liver transplant referral centers [12]. This study's protocol has been approved by the institutional review boards or health research ethics boards of all enrolling US-ALFSG sites (see acknowledgements). Informed consent was obtained from next of kin for all patients as subjects were unable to provide consent (hepatic encephalopathy ~ HE). All research procedures were conducted according to the principles of the Declaration of Helsinki[13].

Data collection

Patients were enrolled prospectively into a database (coordinating center at University of Texas Southwestern Medical Center) where demographic, clinical, and outcome data on ALF patients were recorded. Baseline clinical data on HBV-associated ALF patients included serological testing, hepatic panel biochemistry, hepatic encephalopathy grade (West Haven criteria) on admission, Model for End-stage Liver Disease (MELD) score, King's College criteria fulfillment (admission), serological profile of HBV and hepatitis D virus (HDV) (admission and on history if available), history of human immunodeficiency virus

(HIV) and previous use of immunosuppressive treatments. Clinical data, medical therapies and complications in the first 7 days post- study enrollment were recorded. Data retrieved on outcomes at 21 days post-study enrollment TFS, LT, and overall survival.

Operational definitions: Inclusion criteria

ALF was defined according to the following criteria: a) HE of any degree, b) evidence of coagulopathy with international normalized ratio (INR) ≥ 1.5, c) acute illness onset <26 weeks, and d) no evidence of cirrhosis[14]. Patients were considered to have HBV-associated ALF when serological testing for HBsAg and/or IgM anti-HBc were positive[2]. HBV-associated ALF due to immunosuppression was defined in the setting of clinical or serological evidence of HBV-associated ALF (reactivation) and a history of immunosuppressive treatment[9]. The MELD score is described elsewhere, has been applied previously to predict outcomes of ALF patients[15–17]. The King's College criteria (KCC) have been widely used for prognostication in ALF and to determine which patients will most likely benefit from emergent LT[18]. The non-acetaminophen-induced ALF criteria were used in this analysis[19].

Outcomes

The exposure of interest in the study was exposure to chemotherapy or immunosuppression. The primary outcome was defined as **TFS** at 21 days post-study enrollment as this was thought to better depict the clinical course of Hepatitis B-associated ALF after immunosuppression, given that it does not take into account the effect of LT. Secondary outcomes were LT rate and overall survival at 21 days post study enrollment.

Statistical analysis

Categorical variables were presented as proportions while comparisons were performed using the Chi-square or Fisher's exact test where appropriate (< 5 cases). Continuous variables are presented as medians with inter-quartile ranges (IQR). Univariate comparisons were performed using the Kruskall-Wallis test. Statistical significance was defined as a p value < 0.05 for all comparisons. Multivariate analysis was performed with logistic regression. Covariates initially considered for modeling were chosen based on clinical relevance or a p<0.10 on univariate comparisons. Collinearity was determined and avoided where appropriate. Final model performance was assessed by c-statistic. All statistical analysis were done using SAS-STAT software, Version 9.4 (SAS Institute Inc., Cary, North Carolina, US).

RESULTS

Baseline characteristics of HBV-ALF patients

A total of 156 consecutive patients with HBV-associated ALF were identified in the US-ALFSG registry for the period of time considered. There were 28 (17.9%) patients with Hepatitis B-associated ALF after immunosuppression and 128 (82.1%) were HBV-associated ALF controls. Of the 28 Hepatitis B-associated ALF after immunosuppression, complete listing of HBV serologies, diagnoses (e.g. malignancy) and immunosuppressant therapy (chemotherapy, corticosteroids, etc.) are listed in Table 1. Within this subgroup, 15

patients received systemic corticosteroids as part of therapy, while 21 patients received chemotherapy. Twenty two patients had solid or blood malignancy.

Table 2 summarizes the baseline characteristics of all patients with HBV-associated ALF included stratified by group: HBV-associated ALF after immunosuppressive therapy vs. controls. Immunosuppressed patients were significantly older (51.5 vs. 41.0 years, P = 0.0014), more often non-white and non-African-American (50.0% vs. 14.1%, P = 0.0001) and had lower levels of platelets (118 vs. 165 $\times 10^9$/L, P <0.0001) at admission in comparison to controls. Significantly more patients in the Immunosuppressed group were previously identified (prior to the index hospital admission, available in 53 patients) as being HBsAg positive (64.3% vs. 15.4%, P = 0.0005). HBV serological profile (see Table 2) for the index hospital admission was similar between groups (P >0.17 for all comparisons) with the exception that significantly less HBV-associated ALF after immunosuppressive therapy patients were Anti-HBc IgM positive (42.9% vs. 51.6%, p < 0.0001).

Overall and TFS at 21 days following hospital admission for all HBV-associated ALF patients in the overall cohort were 59.0% and 34.9%, respectively. On unadjusted (crude) analysis, HBV-associated ALF after immunosuppressive therapy patients had significantly decreased overall 21-day survival (42.9% vs. 62.5%, P = 0.0096) compared with controls. There was evidence of decreased unadjusted TFS at 21 days for immunosuppressed patients (21.4% vs. 38.0%, P = 0.097), although this was not statistically significant. The proportion of HBV-associated ALF patients in the overall cohort who were listed for and who received LT during the 21-day study period were 46.4% and 33.3% (72.3% of the waitlisted patients), respectively. Rates of listing and receipt of LT were similar between groups (Table 2, P >0.4 for both comparisons). Of the 7 HBV-associated ALF after immunosuppressive therapy patients who underwent LT, 3 patients were treated with chemotherapy for breast cancer, 2 for lymphoma, one patients had been treated with steroids for Guillane Barre syndrome and one with steroids for autoimmune hemolytic anemia (Table 1).

Transplant-free survival at 21 days post-study enrollment

Amongst the 156 patients with HBV-associated ALF initially included, 149 (95.5%) had available data on the primary outcome and were therefore considered for this analysis. Table 3 summarizes the baseline characteristics of these patients stratified by outcome at 21 days post- study enrollment: TFS vs. LT or death. Fifty-two (34.9%) patients spontaneously survived and 97 (65.1%) patients either underwent LT or died.

TFS patients had significantly lower INR (2.2 vs. 3.9) and MELD score (30.1 vs. 40.7, p <0.0001 for both) at admission than deceased/transplanted HBV-ALF patients. TFS patients had fewer extra-hepatic organ failures during the first seven days post-study enrollment, including grade III-IV HE (35.5% vs. 78.9%, P <0.0001), need for mechanical ventilation (21.6% vs. 67.0%, P <0.0001), vasopressor support (10.0% vs. 32.0%, P = 0.014), and renal replacement therapy (2.0% vs. 23.7%, P = 0.0008). TFS patients fulfilled KCC significantly less often (20.4% vs. 46.2%, P = 0.0026).

Multivariable analysis: Independent associations with 21-day transplant free survival

After performing logistic regression analysis, the best final model for spontaneous survival at 21 days post-study enrollment for all patients with HBV-associated ALF included 3 independent covariates (see Table 4). These were MELD (adjusted odds ratio (aOR) per unit increment = 0.894), mechanical ventilation (aOR = 0.111), and **immunosuppression (aOR = 0.274)** that were independently associated with primary outcome. The model performed well with a c-statistic of 0.866.

DISCUSSION

Key results and comparison with literature

Using a large North American cohort of HBV-associated ALF patients, we found that HBV-associated ALF after immunosuppressive therapy accounted for approximately one fifth of overall HBV-ALF cases enrolled in the ALFSG registry. This analysis demonstrated that immunosuppressed patients significantly differed from the other patients with HBV-associated ALF in being older, more often non-white and non-African-American, and were more frequently anemic and thrombocytopenic. Cytopenias may be related to these patients' underlying conditions (auto-immune diseases or cancer) as well as immunosuppressive treatments resulting in bone marrow toxicity [20, 21]. The HBV serological profiles for the index hospital admission were similar between immunosuppressed patients and controls with the exception of Anti-HBc IgM (higher in HBV-ALF controls). A recent study dedicated to evaluating differences in the HBV serological profile between new onset and reactivation-related HBV-associated ALF (all causes considered) demonstrated that high IgM anti-HBc titers and low HBV viral loads were characteristic of the new onset (acute hepatitis B) subgroup, whereas the opposite was true for the reactivation-related subgroup[9]. In our study we did not find a significant difference in the HBV viral loads between patients with HBV-associated ALF due to immunosuppression and controls and we did not have data on the IgM anti-HBc titers available. Nevertheless, while features of the HBV serological profile may be a surrogate for the immune response to the virus and help to distinguish between newly-onset and reactivation-related HBV-associated ALF [9], it remains unclear whether they have a direct prognostic value.

In terms of outcomes, we showed that HBV-associated ALF overall frequently showed a poor short-term prognosis, with only about one third of patients spontaneously surviving at 21 days post-study enrollment. Approximately one third of all patients underwent LT during this period. It has been previously reported elsewhere that patients with HBV-associated ALF demonstrate worse outcomes than other ALF etiologies [22, 23].

Despite severity of organ dysfunction being similar, patients with HBV-associated ALF after immunosuppressive therapy had significantly worse (unadjusted) overall 21-day survival compared with controls. Given that the LT rate was similar between both groups (5 patients that received LT had known treated malignancy), we sought to determine which covariates most influenced TFS at 21 days post- study enrollment for the entire cohort. In the univariate (unadjusted) analysis, we showed that the overall characteristics of the TFS group at 21 days post-study enrollment differed from patients who underwent LT or died in demonstrating

less severe organ failures (requirement for mechanical ventilation, vasopressors, or renal replacement therapy), lower MELD scores and less frequently demonstrating high grade (III-IV) hepatic encephalopathy. These findings are in keeping with previous reports stating that the prognosis of patients with ALF largely depends on the severity of organ failures that ensues [24, 25]

In the adjusted analysis, we found 3 factors that were independently associated with TFS at 21 days post-hospital admission for patients with HBV-associated ALF: MELD, mechanical ventilation, and receipt of immunosuppressive therapy. Of note, the prognostic ability of this model was deemed robust as c-statistic was 0.866. The predictive value of MELD and mechanical ventilation quantified in the final model reinforces the argument that the severity of hepatic failure (INR and bilirubin as part of MELD) and extra-hepatic organ failures, namely renal (creatinine as part of MELD), respiratory and neurological (mechanical ventilation may have been needed both for respiratory failure per se or due to coma) failures, are likely crucial for the short-term prognosis of patients with HBV-associated ALF. Two recent publications have emphasized the good prognostic ability of MELD in the setting of non-acetaminophen ALF[16, 26]

We demonstrated that receipt of immunosuppression was independently associated with lower spontaneous survival at 21 days in HBV-associated ALF. Potential explanations for this include a higher rate of prior/underlying liver disease correlating with chronic hepatitis B infection. While pre-hospital admission serology was known in only 53 patients, a higher percentage of immunosuppressed patients demonstrated a prior history of being HBsAg positive (9/14 ~ 64.3% vs. 6/39 ~ 15.4%, p=0.0005). This could potentially suggest that immunosuppressed patients had less hepatic reserve despite similar hepatic synthetic parameters at presentation. These patients may have other reasons that predispose them to reactivation. In a recent study, 76% of patients with immune suppression-related reactivation of a chronic HBV infection carried HBsAg mutations localized in the immune-active HBsAg regions[8]. These HBVsAg mutations are thought to potentiate the virus' ability to evade the immune system which might be deleterious by possibly contributing to the development of ALF. Finally, immunosuppressive therapy, particularly cytotoxic cancer chemotherapy could potentially also interfere with hepatic regeneration.

According to our findings, HBV-associated ALF after immunosuppressive therapy has a poor prognosis emphasizing once more that clinicians need to initiate appropriate screening and preventive strategies prior to use of chemo- or immunotherapies, particularly in high risk populations (prolonged steroids > 4 weeks/anthracycline/anti-CD 20 use)[5]. Medical societies worldwide have produced guidelines on the theme and, despite some differences as to which patients should be prioritized for screening for HBV infection, they all agree that patients at high risk for immunosuppression-related reactivation of chronic HBV infection should be screened before starting immunosuppressive treatments[24, 27]. In a recent metaanalysis, Paul and colleagues demonstrated that prophylaxis significantly reduced rates of reactivation (OR 0.12) and HBV-related hepatitis (OR 0.18)[6]. Institutional protocols such as this may represent a decisive step forward in the prevention of IMX-HBV-ALF.

Limitations

This study has limitations that warrant consideration. First, as this was a cohort from North America, a region known to be non-endemic for HBV infection, our findings may be difficult to generalize to endemic areas of HBV infection. We also did not have complete data on prior HBsAg status (chronic carrier status) nor data on Anti-HBc IgM titers. Second, supportive therapeutic approaches to ALF and criteria for LT not only have been evolving over time but also may be center dependent although a centre effect could not be identified on multivariable analysis (P= 0.6, data not shown). Third, although this was a large multicenter cohort where patients were prospectively enrolled into the registry, the retrospective nature of this study analysis implies that we can only comment on associations between covariates examined and not causation. Finally, rates of transplant in immunosuppressed patients were likely impacted by the fact that the majority of patients had underlying malignancy which could have precluded listing for LT. Nonetheless, this analysis was based on the largest Northern American cohort of HBV-associated ALF patients. In being a rare but potentially devastating disease, findings determined in the analysis raise an important public health issue.

Conclusion

In conclusion, HBV-associated ALF due to immunosuppression/chemotherapy represents approximately one fifth of all HBV-associated ALF patients in the US ALFSG registry. Only one fifth of immunosuppressed patients were alive at 21 days post-hospital admission in the absence of LT. Independent factors associated with TFS for patients in HBV-associated ALF were MELD, mechanical ventilation, and use of immunosuppression/chemotherapy. Taking into account the poor prognosis of patients with HBV-associated ALF due to immunosuppression and possible contra-indications for LT, this represents a significant public health issue where preventive strategies need to be reinforced.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Members and institutions participating in the Acute Liver Failure Study Group 1998–2015 are as follows: W.M. Lee, M.D. (Principal Investigator); Anne M. Larson, M.D., Iris Liou, M.D., University of Washington, Seattle, WA; Oren Fix, M.D., Swedish Medical Center, Seattle, WA; Michael Schilsky, M.D., Yale University, New Haven, CT; Timothy McCashland, M.D., University of Nebraska, Omaha, NE; J. Eileen Hay, M.B.B.S., Mayo Clinic, Rochester, MN; Natalie Murray, M.D., Baylor University Medical Center, Dallas, TX; A. Obaid S. Shaikh, M.D., University of Pittsburgh, Pittsburgh, PA; Andres Blei, M.D., Northwestern University, Chicago, IL (deceased), Daniel Ganger, M.D., Northwestern University, Chicago, IL; Atif Zaman, M.D., University of Oregon, Portland, OR; Steven H.B. Han, M.D., University of California, Los Angeles, CA; Robert Fontana, M.D., University of Michigan, Ann Arbor, MI; Brendan McGuire, M.D., University of Alabama, Birmingham, AL; Raymond T Chung, M.D., Massachusetts General Hospital, Boston, MA; Alastair Smith, M.B., Ch.B., Duke University Medical Center, Durham, NC; Robert Brown, M.D., Cornell/Columbia University, New York, NY; Jeffrey Crippin, M.D., Washington University, St Louis, MO; Edwin Harrison, Mayo Clinic, Scottsdale, AZ; Adrian Reuben, M.B.B.S., Medical University of South Carolina, Charleston, SC; Santiago Munoz, M.D., Albert Einstein Medical Center, Philadelphia, PA; Rajender Reddy, M.D., University of Pennsylvania, Philadelphia, PA; R. Todd Stravitz, M.D., Virginia Commonwealth University, Richmond, VA; Lorenzo Rossaro, M.D., University of California Davis, Sacramento, CA; Raj Satyanarayana, M.D., Mayo Clinic, Jacksonville, FL; and Tarek Hassanein, M.D., University of California, San Diego, CA; Constantine J. Karvellas MD, University of Alberta, Edmonton, AB; Jodi Olson MD, University of Kansas, Kansas City, KA; Ram Subramanian MD, Emory, Atlanta, GA; James Hanje MD, Ohio State

University, Columbus,OH. The University of Texas Southwestern Administrative Group included Grace Samuel, Ezmina Lalani, Carla Pezzia, and Corron Sanders, Ph.D., Nahid Attar, Linda S. Hynan, Ph.D., and the Medical University of South Carolina Data Coordination Unit included Valerie Durkalski, Ph.D., Wenle Zhao, Ph.D., Jaime Speiser, Catherine Dillon, Holly Battenhouse and Michelle Gottfried

Financial support: The study was sponsored by NIH grant U-01 58369 (from NIDDK).

List of Abbreviations

ALF	Acute Liver Failure
ALFSG	Acute Liver Failure Study Group
Anti-HBc (IgM)	Anti-Hepatitis B core antibody (IgM if indicated)
HBsAg	Hepatitis B Surface antigen
HBV	Hepatitis B
HE	Hepatic Encephalopathy
ICU	Intensive Care Unit
INR	International normalized ratio
IQR	Interquartile range
KCC	King's College Criteria
LT	Liver transplantation
MELD	Model for End-stage Liver Disease
OR	Odds Ratio
TFS	Transplant-free survival

REFERENCES

1Fontana RJ, Ellerbe C, Durkalski VE. Two-year outcomes in initial survivors with acute liver failure: results from a prospective, multicentre study Liver Int. 2015; 35(2):370–80. [PubMed: 25039930]

2Teo EK, Ostapowicz G, Hussain M. Hepatitis B infection in patients with acute liver failure in the United States Hepatology. 2001; 33(4):972–6. [PubMed: 11283862]

3Hoofnagle JH. Reactivation of hepatitis B Hepatology. 2009; 49(5 Suppl):S156–65. [PubMed: 19399803]

4Reddy KR, Beavers KL, Hammond SP. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy Gastroenterology. 2015; 148(1):215–9. quiz e16–7. [PubMed: 25447850]

5Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy Gastroenterology. 2015; 148(1):221–44 e3. [PubMed: 25447852]

6Paul S, Saxena A, Terrin N. Hepatitis B Virus Reactivation and Prophylaxis During Solid Tumor Chemotherapy: A Systematic Review and Meta-analysis Ann Intern Med. 2016; 164(1):30–40. [PubMed: 26595058]

7Loomba R, Rowley A, Wesley R. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy Ann Intern Med. 2008; 148(7):519–28. [PubMed: 18378948]

8Salpini R, Colagrossi L, Bellocchi MC. Hepatitis B surface antigen genetic elements critical for immune escape correlate with hepatitis B virus reactivation upon immunosuppression Hepatology. 2015; 61(3):823–33. [PubMed: 25418031]

9Dao DY, Hynan LS, Yuan HJ. Two distinct subtypes of hepatitis B virus-related acute liver failure are separable by quantitative serum immunoglobulin M anti-hepatitis B core antibody and hepatitis B virus DNA levels Hepatology. 2012; 55(3):676–84. [PubMed: 21987355]

10Di Bisceglie AM, Lok AS, Martin P. 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):703–11. [PubMed: 25412906]

11Yang PL, Althage A, Chung J. Immune effectors required for hepatitis B virus clearance Proc Natl Acad Sci U S A. 2010; 107(2):798–802. [PubMed: 20080755]

12Ostapowicz G, Fontana RJ, Schiodt FV. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States Ann Intern Med. 2002; 137(12):947–54. [PubMed: 12484709]

13Association WM World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013; 310(20):2191–4. [PubMed: 24141714]

14Polson J, Lee WM. American Association for the Study of Liver D. AASLD position paper: the management of acute liver failure Hepatology. 2005; 41(5):1179–97. [PubMed: 15841455]

15Yantorno SE, Kremers WK, Ruf AE. MELD is superior to King's college and Clichy's criteria to assess prognosis in fulminant hepatic failure Liver Transpl. 2007; 13(6):822–8. [PubMed: 17539002]

16Speiser JL, Lee WM, Karvellas CJ. Predicting outcome on admission and postadmission for acetaminophen-induced acute liver failure using classification and regression tree models PLoS One. 2015; 10(4):e0122929. [PubMed: 25885260]

17Kamath PS, Wiesner RH, Malinchoc M. A model to predict survival in patients with end-stage liver disease Hepatology. 2001; 33(2):464–70. [PubMed: 11172350]

18O'Grady JG. Prognostication in acute liver failure: a tool or an anchor? Liver Transpl. 2007; 13(6): 786–7. [PubMed: 17538997]

19O'Grady JG, Alexander GJ, Hayllar KM. Early indicators of prognosis in fulminant hepatic failure Gastroenterology. 1989; 97(2):439–45. [PubMed: 2490426]

20Devitt KA, Lunde JH, Lewis MR. New onset pancytopenia in adults: a review of underlying pathologies and their associated clinical and laboratory findings Leuk Lymphoma. 2014; 55(5): 1099–105. [PubMed: 23829306]

21Strati P, Wierda W, Burger J. Myelosuppression after frontline fludarabine, cyclophosphamide, and rituximab in patients with chronic lymphocytic leukemia: analysis of persistent and new-onset cytopenia Cancer. 2013; 119(21):3805–11. [PubMed: 23943357]

22Bernal W, Lee WM, Wendon J. Acute liver failure: A curable disease by 2024? J Hepatol. 2015; 62(1 Suppl):S112–20. [PubMed: 25920080]

23Park SJ, Lim YS, Hwang S. Emergency adult-to-adult living-donor liver transplantation for acute liver failure in a hepatitis B virus endemic area Hepatology. 2010; 51(3):903–11. [PubMed: 20041403]

24Reddy KR, Ellerbe C, Schilsky M. Determinants of outcome among patients with acute liver failure listed for liver transplantation in the United States Liver Transpl. 2016; 22(4):505–15. [PubMed: 26421889]

25Urrunaga NH, Magder LS, Weir MR. Prevalence, Severity, and Impact of Renal Dysfunction in Acute Liver Failure on the US Liver Transplant Waiting List Dig Dis Sci. 2016; 61(1):309–16. [PubMed: 26386861]

26McPhail MJ, Farne H, Senvar N. Ability of King's College Criteria and Model for End-Stage Liver Disease Scores to Predict Mortality of Patients With Acute Liver Failure: A Meta-analysis Clin Gastroenterol Hepatol. 2016; 14(4):516–25 e5. [PubMed: 26499930]

27European Association For The Study Of The L EASL clinical practice guidelines: Management of chronic hepatitis B virus infection J Hepatol. 2012; 57(1):167–85. [PubMed: 22436845]

TABLE 1.

Clinical, serological and outcome characteristics of 28 patients with Hepatitis B Acute Liver Failure due to reactivation from immunosuppression/chemotherapy

Case	Medications	Diagnosis	Cancer	Chemo	Anti-CD20/33	Steroids	+HBs Ag	Prior +HBsAg	+Anti-HBc	+HBV DNA	Listed for LT	Received LT	Spontaneous Survivor?
1	Prednisone	Autoimmune (CREST syndrome)	NO	NO	NO	YES	NO	·	YES	YES	NO	NO	NO
2	Chemotherapy (specific drugs not specified)	Non-Hodgkin's Lymphoma	YES	YES	Unknown	Unknown	YES	·	·	·	NO	NO	YES
3	Chemotherapy (specific drugs not specified)	Non-Hodgkin's Lymphoma	YES	YES	Unknown	Unknown	YES	·	YES	YES	YES	**YES**	NO
4	Chemotherapy (specific drugs not specified)	Breast Cancer	YES	YES	Unknown	Unknown	YES	·	YES	·	YES	**YES**	NO
5	Prednisone, tacrolimus	Stem Cell Transplant for AML, GVHD	NO	NO	NO	YES	YES	·	YES	YES	NO	NO	YES
6	Gemtuzimab	Acute myelogenous leukemia	YES	YES	YES	NO	YES	·	YES	YES	NO	NO	NO
7	Prednisone	Chronic lung disease	NO	NO	NO	YES	YES	·	YES	·	YES	NO	NO
8	CHOP	Non-Hodgkin's Lymphoma	YES	YES	NO	YES	YES	·	·	YES	YES	NO	NO
9	Methylprednisone	Autoimmune disorder	NO	NO	NO	YES	YES	·	YES	·	YES	NO	NO
10	Prednisone, mycophenolate mofetil, IVIg	Guillane Barre	NO	YES	NO	YES	YES	·	YES	YES	YES	**YES**	NO
11	Prednisone	CLL/hemolytic anemia	YES	NO	NO	YES	YES	·	YES	YES	NO	NO	NO
12	Hydroxyu rea	Chronic lymphocytic leukemia	YES	YES	NO	NO	YES	·	YES	NO	YES	NO	YES
13	Bleomycin	Metastatic testicular cancer	YES	YES	NO	NO	YES	·	YES	YES	NO	NO	YES
14	Paclitaxel, bevacizumab, prednisone	Breast Cancer	YES	YES	NO	YES	·	·	·	YES	NO	NO	YES
15	Steroids (specific drugs not specified)	Autoimmune hemolytic anemia	NO	NO	NO	YES	NO	YES	YES	YES	YES	**YES**	NO
16	Chemotherapy (specific drugs not specified)	Diffuse large b-cell lymphoma	YES	YES	Unknown	Unknown	YES	YES	YES	YES	NO	NO	NO
17	Docetaxel, doxorubicin, cyclophosphamide, trastuzumab, dexamethasone	Breast cancer	YES	YES	NO	YES	YES	YES	YES	YES	YES	**YES**	NO
18	**Rituximab**-CHOP	Diffuse large b-cell lymphoma	YES	YES	YES	YES	YES	YES	YES	YES	YES	**YES**	NO
19	Linalidomide, Bortezomib	Multiple myeloma	YES	YES	NO	NO	YES	NO	YES	YES	NO	NO	NO
20	Dexamethasone, doxorubicin, cyclophosphomide, paclitaxel	Breast Cancer	YES	YES	NO	YES	YES	YES	YES	YES	YES	**YES**	NO
21	Chemotherapy (specific drugs not specified)	CLL/lymphoma	YES	YES	Unknown	Unknown	YES	YES	YES	YES	NO	NO	NO
22	Bleomycin, etoposide, doxorubicin, prednisone, cyclophosphamide, vincristine, procarbazine	Non-Hodgkin's Lymphoma	YES	YES	NO	YES	YES	YES	YES	·	·	·	NO
23	Cisplatin, etopiside, bleomycin	Testicular cancer	YES	YES	NO	NO	YES	YES	YES	YES	NO	NO	NO
24	**Rituximab**-CHOP	Non-Hodgkin's Lymphoma	YES	YES	YES	YES	YES	NO	·	·	NO	NO	YES
25	**Rituximab**-CHOP, IVIg	Diffuse large b-cell lymphoma	YES	YES	YES	YES	YES	NO	YES	YES	·	·	NO
26	Chemotherapy (specific drugs not specified)	Chronic lymphocytic leukemia	YES	YES	Unknown	Unknown	YES	YES	YES	YES	NO	NO	NO
27	**Rituximab**	Chronic lymphocytic leukemia	YES	NO	YES	NO	NO	NO	·	YES	NO	NO	NO
28	Methotrexate, **rituximab**, temozolomide	CNS lymphoma	YES	YES	YES	NO	YES	NO	YES	·	NO	NO	NO

AML ~ Acute myelogenous Leukemia, Anti-HBc: hepatitis B virus core antibody. Anti-HBs: hepatitis B virus surface antibody, CHOP ~ cyclophosphamide, vincristine, doxorubicin, prednisone; CLL ~ Chronic Lymphocytic Leukemia, CNS ~ Central Nervous System, GVHD ~ Graft vs. host disease, HBsAg: hepatitis B virus surface antigen. HBV-DNA: hepatitis B virus deoxyribonucleic acid, IVIg ~ Intravenous immunoglobulin

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2018 July 23.

TABLE 2.

Baseline characteristics of patients with Hepatitis B associated acute liver failure.

		HBV-associated ALF due to Immunosuppression (N = 28)		Controls (N = 128)	P
	N	N (%) or median (IQR)	N	N (%) or median (IQR)	
Age	28	51.5 (40.0–60.0)	128	41.0 (30.5–53.0)	0.0014
Sex (female)	28	12 (42.9%)	128	62 (48.4%)	0.59
Race	28		128		0.0001
White		10 (35.7%)		73 (57.0%)	
African-american		4 (14.3%)		37 (28.9%)	
Other		14 (50.0%)		18 (14.1%)	
Blood biochemistry (admission)					
Hemoglobin (g/dL)	27	11.0 (9.8–12.4)	124	12.1 (10.8–13.6)	0.019
White blood cells (10^9/L)	27	7.6 (5.4–12.3)	124	9.3 (7.1–12.3)	0.14
Platelets (10^9/L)	26	117.5 (70.0–152.0)	122	165.0 (125.0–226.0)	<0.0001
INR	27	3.2 (2.4–6.1)	121	2.8 (2.1–5.3)	0.37
Bilirubin (mg/dL)	27	19.2 (13.4–22.9)	125	18.4 (10.4–25.2)	0.80
ALT (IU/L)	26	1852.0 (701.0–2926.0)	125	1671.0 (670.0–3244.0)	0.95
Creatinine (mg/dL)	27	0.9 (0.6–1.1)	126	1.1 (0.7–2.0)	0.059
Lactate (mmol/L)	10	3.6 (2.3–5.2)	43	4.6 (2.6–6.3)	0.39
MELD (admission)	27	34.0 (28.6–43.9)	118	34.5 (28.1–42.7)	0.94
Hepatic encephalopathy * (first 7 days)					
Grade III/IV	20	14 (60.0%)	106	70 (66.0%)	0.92
King's College criteria ** (admission)	27	9 (33.3%)	121	43 (35.5%)	0.83
Organ support (first 7 days)					
Mechanical ventilation	28	12 (42.9%)	128	66 (51.6%)	0.40
Vasopressors	28	8 (28.6%)	128	29 (22.7%)	0.51
Renal replacement therapy	28	6 (21.4%)	128	18 (14.1%)	0.33
Hepatitis B serology (admission)					
Positive HBsAg	28	24 (85.7%)	127	108 (85.0%)	0.17
Prior positive HbsAg	14	9 (64.3%)	39	6 (15.4%)	0.0005
Positive Anti-HBc (total)	28	24 (85.7%)	128	123 (96.1%)	0.055
Positive Anti-HBc (IgM)	28	12 (42.9%)	125	107 (85.6%)	<0.0001
Positive Anti-HBs	27	6 (22.2%)	128	37 (28.9%)	0.12
Positive HBV-DNA	26	18 (69.2%)	122	78 (63.9%)	0.82
HBV-DNA (copies/mL)	10	188704 (61075–116569367)	28	110020 (307–1059273)	0.35
Positive Anti-HDV	28	1 (3.6%)	123	1 (0.8%)	0.48
Nucleoside therapy (admission)	28	12 (43%)	128	36 (28%)	0.17
Lamivudine		5		29	
Entecavir		2		5	
Tenofovir		5		2	
Adefovir		0		2	

		HBV-associated ALF due to Immunosuppression (N = 28)		Controls (N = 128)	P
N-acetyl-cysteine (first 7 days)	28	7 (25.0%)	128	39 (30.5%)	0.57
ICP therapies (first 7 days)					
ICP monitor	26	1 (3.9%)	119	13 (10.9%)	0.27
Mannitol	28	2 (7.1%)	128	17 (13.3%)	0.37
Hypertonic saline	28	0 (0.0%)	128	6 (4.7%)	0.24
Hypothermia	28	0 (0.0%)	128	3 (2.3%)	0.41
Complications (first 7 days)					
Seizures	28	0 (0.0%)	128	2 (1.6%)	0.50
Gastro-intestinal bleeding	28	1 (3.6%)	128	7 (5.5%)	0.68
Blood infection	28	1 (3.6%)	128	7 (5.5%)	0.68
Outcomes (first 21 days)					
Waitlisted for transplant	26	11 (42.3%)	127	60 (47.2%)	0.65
Transplanted	28	7 (25.0%)	128	45 (35.2%)	0.40
Overall survival	28	12 (42.9%)	128	80 (62.5%)	0.0096
Spontaneous survival	28	6 (21.4%)	121	46 (38.0%)	0.097
Cause of death ***	16		31		0.85
Hepatic failure		6 (37.5%)		9 (29.0%)	
Multiorgan failure		7 (43.8%)		11 (35.5%)	
Septic shock		1 (6.3%)		4 (12.9%)	
Neurological event		2 (12.5%)		5 (16.1%)	
Intraoperative		0 (0.0%)		1 (3.2%)	
Cardiac event		0 (0.0%)		1 (3.2%)	

N: frequency. IQR: interquartile range. INR: international normalized ratio. AST: aspartate aminotransferase. ALT: alanine aminotransferase. MELD: Model for End-stage Liver Disease. HBsAg: hepatitis B virus surface antigen. Anti-HBc: hepatitis B virus core antibody. Anti-HBs: hepatitis B virus surface antibody. HBV-DNA: hepatitis B virus deoxyribonucleic acid. Anti-HDV: hepatitis D virus antibody. ICP: intracranial pressure.

* Hepatic encephalopathy evaluated according to West-Haven criteria.

** King's College criteria for non-acetaminophen acute liver failure [10].

*** n=16 deaths in the IMX-HBV-ALF group and n=48 in the control group. Causes of death in 17 control patients were unavailable.

TABLE 3.

Transplant-free survival at 21 days post- hospital admission amongst patients with hepatitis B virus related-acute liver failure.

		Transplant free survival (N = 52)		Death or transplant (N = 97)	P
	N	N (%) or median (IQR)	N	N (%) or median (IQR)	
Age	52	45.0 (34.0–53.0)	97	42.0 (36.0–55.0)	0.72
Sex (female)	52	31 (59.6%)	97	43 (44.3%)	0.38
Race	52		97		0.77
White		27 (51.9%)		51 (52.6%)	
African-American		16 (30.7%)		25 (25.8%)	
Other		9 (17.7%)		21 (21.7%)	
Blood biochemistry (admission)					
Hemoglobin (g/dL)	49	11.9 (10.8–13.1)	95	11.6 (10.4–13.2)	0.95
White blood cells (10^9/L)	49	8.3 (5.9–11.8)	95	10.0 (7.4–13.8)	0.019
Platelets (10^9/L)	49	157.0 (120.0–218.0)	92	144.5 (115.0–206.0)	0.33
INR	49	2.2 (2.0–2.9)	91	3.9 (2.5–7.1)	<0.0001
Bilirubin (mg/dL)	50	18.1 (10.6–24.7)	94	19.4 (10.5–25.2)	0.61
ALT (IU/L)	50	1469.0 (697.0–2857.0)	93	1768.0 (634.0–3338.0)	0.66
Creatinine (mg/dL)	51	1.0 (0.7–1.7)	95	1.1 (0.8–2.1)	0.19
Phosphate (mg/dL)	41	3.0 (2.7–4.1)	82	3.0 (2.2–5.0)	0.76
pH	16	7.4 (7.4–7.5)	67	7.5 (7.4–7.5)	0.014
Lactate (mmol/L)	13	2.8 (2.2–5.2)	39	4.6 (2.8–6.3)	0.17
Ammonia (venous) μmol/L)	15	98.0 (65.0–108.0)	38	95.0 (58.0–169.0)	0.42
MELD (admission)	48	30.1 (25.5–35.3)	90	40.7 (32.0–46.7)	<0.0001
Hepatic encephalopathy * (first 7 days)					
Grade III/IV	31	11 (35.5%)	90	71 (78.9%)	<0.0001
King's College criteria** (admission)	49	10 (20.4%)	91	42 (46.2%)	0.0026
Organ support (first 7 days)					
Mechanical ventilation	51	11 (21.6%)	97	65 (67.0%)	<0.0001
Vasopressors	50	5 (10.0%)	97	31 (32.0%)	0.014
Renal replacement therapy	51	1 (2.0%)	97	23 (23.7%)	0.0008
Immunosuppression	52	6 (11.5%)	97	22 (22.7%)	0.097
Hepatitis B serology (admission)					
Positive HBsAg	51	42 (82.4%)	96	83 (86.5%)	0.71
Prior positive HBsAg	21	3 (14.3%)	29	11 (37.9%)	0.066
Positive Anti-HBc (total)	52	49 (94.2%)	97	92 (94.9%)	1.0
Positive Anti-HBc (IgM)	49	43 (87.8%)	95	69 (72.6%)	0.11
Positive Anti-HBs	51	19 (37.3%)	96	24 (25.0%)	0.17
Positive HBV DNA	50	37 (74.0%)	90	56 (62.2%)	0.34
HBV-DNA (copies/mL)	14	7286 (105–1112318)	21	286607 (61075–2690000)	0.13
Positive Anti-HDV	49	1 (2.0%)	94	1 (1.1%)	0.82
Nucleoside therapy (admission)	52	12 (23%)	97	35 (36%)	0.14

		Transplant free survival (N = 52)		Death or transplant (N = 97)	P
N-acetyl-cysteine (first 7 days)	51	15 (29.4%)	97	29 (29.9%)	0.99
ICP therapies (first 7 days)					
ICP monitor	50	2 (4.0%)	88	11 (12.5%)	0.10
Mannitol	51	3 (5.9%)	97	15 (16.5%)	0.061
Hypertonic saline	51	1 (2.0%)	97	5 (5.2%)	0.33
Hypothermia	51	1 (2.0%)	97	2 (2.1%)	0.95
Blood products (first 7 days)					
Fresh frozen plasma	51	4 (7.8%)	97	51 (52.6%)	<0.0001
Recombinant Vila factor	51	0 (0.0%)	97	2 (2.1%)	0.29
Platelets	51	1 (2.0%)	97	6 (6.2%)	0.24
Red-blood cells	50	2 (4.0%)	97	8 (8.3%)	0.33
Complications (first 7 days)					
Seizures	51	0 (0.0%)	97	2 (2.1%)	0.29
Gastro-intestinal bleeding	51	0 (0.0%)	97	8 (8.3%)	0.033
Blood infection	50	2 (4.0%)	97	6 (6.2%)	0.58
ARDS	51	1 (2.0%)	97	2 (2.1%)	0.95

*See Table 2 legend for abbreviations

Table 4.

Predictors of spontaneous survival at 21 days post- hospital admission amongst patients with Hepatitis B virus- associated acute liver failure.

	OR	Unadjusted 95% CI	P	OR	Adjusted 95% CI	P
MELD	0.878	0.833–0.926	<0.0001	0.894	0.842–0.949	0.0003
Mechanical ventilation	0.103	0.045–0.237	<0.0001	0.111	0.041–0.300	<0.0001
Immunosuppression	0.445	0.168–1.178	0.1031	0.274	0.082–0.923	0.0366

OR: odds-ratio. CI: confidence interval. MELD: Model for End-stage Liver Disease. IMX-HBV-ALF: immunosuppression-related hepatitis B virus-related acute liver failure.

Model's properties: N = 139; spontaneous survivors = 49 (35.3%); c-statistic = 0.866.