Model for End-stage Liver Disease with additional criteria to predict short-term mortality in severe flares of chronic hepatitis B

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Abbreviations:
HBV, hepatitis B virus
AFOCHB, acute flare of chronic hepatitis B
CHB, chronic hepatitis B
HBeAg, hepatitis B e-antigen
ACLF, acute on chronic liver failure
MELD, Model for end stage liver disease
TIPSS, transjugular intrahepatic portosystemic shunt
AUROC, area under receiver operating characteristic

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PPV, positive predictive value
NPV, negative predictive value

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Abstract

Background & Aims: The prognosis in severe acute flares of chronic hepatitis B (AFOCHB) is often unclear. The current study aimed to establish the predictive value using the MELD score for short-term mortality for severe AFOCHB. Approach & Results: Patients with severe AFOCHB with bilirubin >50 umol/l, ALT >10x upper limit of normal, and INR >1.5 were included. All patients were commenced on entecavir and/or tenofovir. Laboratory results and MELD scores were pooled to calculate mortality at four time points (day 7, 14, 21, and 28). A total of 240 patients were included. Median HBV DNA was 7.77 log IU/mL (range, 4.11-10.06), and 49 (20.4%) were HBeAg-positive. The 7, 14, 21, and 28-day survival was 96.7%, 88.5%, 79.5%, and 72.8% respectively. Using pooled results derived from 4,201 blood samples, the AUROC for the MELD score to predict day 7, 14, 21, and 28 mortality was 0.909, 0.892, 0.883, and 0.871 respectively. For MELD ≤28, mortality at day 28 was low (<25%), compared to >50% mortality for MELD ≥32. For MELD 28 to 32, higher day-28 mortality was observed for 4 criteria: age ≥52 years, ALT >217 U/L, platelets <127, and abnormal baseline imaging (all $p<0.001$). In this MELD bracket, the 28-day mortality was 0%, 12.1%, 23.8%, 59.4%, and 78.8% for the presence of 0, 1, 2, 3, and 4 criteria respectively. Conclusions: MELD score at any time points can accurately predict the short-term mortality. Patients with MELD ≥28 should be worked up for liver transplantation, and those with MELD 28-32 with 3-4 at-risk criteria, or MELD ≥32 should be listed.

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Introduction

For patients chronically infected with hepatitis B virus (HBV), acute flares of chronic hepatitis B (AFOCHB) can be severe and fatal (1). In the natural history of chronic hepatitis B (CHB) infection, hepatitic flares can occur at various phases of infection (2). For patients with positive hepatitis B e-antigen (HBeAg), flares can occur during the HBeAg-positive CHB phase after the loss of immune tolerance. Even after HBeAg seroclearance, flares can also occur during the HBeAg-negative CHB phase. These phases are now referred as HBeAg positive chronic hepatitis and HBeAg negative chronic hepatitis respectively (3). Although treatment using nucleoside/nucleotide analogs can reduce the risk of AFOCHB, flares may occur in the context of non-compliance and also with the development of drug-resistant mutations (4). Less common causes of AFOCHB can be observed in immunocompromised hosts, and in those with reactivation of occult HBV infection during and after receiving immunosuppressive therapies (5, 6).

The phenomenon of AFOCHB is one of the leading causes of acute-on-chronic liver failure (ACLF) in Asia where CHB infection remains endemic (7). The precipitating factor is HBV reactivation or flare, leading to rapid deterioration of liver function, extra-hepatic organ failure, and high short-term mortality. Despite the use of highly potent antiviral therapy, patients with severe AFOCHB may still succumb without liver transplantation. The decision on whether to proceed to transplantation is often a difficult one, as there is a component of reversibility for those with ACLF. The conundrum exists because the window of opportunity for transplantation may be very narrow, especially in the presence of hepatic encephalopathy. On the other hand, there is always the concern about performing liver transplantation unnecessarily on patients who might otherwise make a full recovery.

To date, there is no consensus as to whom and when to transplant for those with severe AFOCHB who present with liver decompensation. Moreover, significant heterogeneity exists with the current definitions of ACLF, likely contributed by the fact that the primary liver disease profile differs between the East and West (8-10). Many factors have been shown to have prognostic significance in AFOCHB, including prothrombin time, INR, creatinine,

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sodium, albumin, HBV DNA, HBeAg status, and the presence of cirrhosis, hepatic encephalopathy, and hepatorenal syndrome (11-15).

The Model for End Stage Liver Disease (MELD) score, originally derived to estimate the 3 months survival in patients undergoing transjugular intrahepatic portosystemic shunt (TIPSS) procedure, has had variable results in predicting outcomes for patients with severe AFOCHB (16, 17). However, these studies were based on using the MELD at presentation, or at fixed time points during the hospitalization. In the current study, the predictive value of using the MELD score for short-term mortality was determined in patients presenting with severe AFOCHB using pooled results from the entire admission, with the development of a score-based prognostic model.

Patients and methods

Patients admitted with AFOCHB to the gastroenterology and liver transplant wards at Queen Mary Hospital, Hong Kong, between the period of January 2005 and September 2018, were included in the study if they fulfilled the criteria mentioned below. These included patients referred from other regional hospitals for further management and consideration for liver transplantation. The inclusion criteria include evidence of AFOCHB as defined by ALT ≥10x upper limit of normal, with HBV DNA ≥4 logs IU/mL, together with evidence of CHB infection, as documented by clinical history or known HBsAg positivity for 6 months or more. Patients included also had to have evidence of liver decompensation, as evident by a bilirubin ≥50 umol/L in combination with INR ≥1.5. These basic criteria were selected because they were easy to implement, and circumvents the various different criteria for ACLF. Therefore, the study included patients who presented with severe AFOCHB regardless of whether they had evidence of extrahepatic organ impairment. Patients with other causes of acute hepatitis flares, including hepatitis A, hepatitis E, co-infection with hepatitis C, and drug-induced liver injury, were excluded in the current study. The inclusion and exclusion criteria are summarized in table 1.

All patients were commenced on oral nucleos(t)ide analog therapy once HBV infection was established, with over 95% started within one week of presentation. The majority were

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treated with entecavir monotherapy (77%), with the remaining patients treated with tenofovir monotherapy (7%) and other oral regimens (16%).

Patients with evidence of severe flares as characterized by coagulopathy and/or hepatic encephalopathy would be assessed for potential liver transplantation. Assessment for living-donor liver transplantation was also commenced in parallel for those with available donors. The decision to proceed to transplantation was made largely on the development of hepatic encephalopathy together with worsening laboratory parameters. For patients undergoing liver transplantation, no donor organs were obtained from executed prisoners or other institutionalized persons.

This is a retrospective review of a prospectively collected database. Laboratory data was collected at the time of admission to hospital until date of discharge or death/liver transplantation. This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong Western Cluster (UW-19-420). The MELD score was calculated using the following formula: 9.57 x ln(creatinine(mg/dL)) + 3.78 x ln(bilirubin(mg/dL)) + 11.2 x ln(INR) + 6.43. The laboratory results and MELD scores were pooled together to derive the predictive value of the MELD for day 7, 14, 21, and 28 mortality for the entire cohort for each individual time point. For patients who underwent liver transplantation, the pooled data was used only if they were still alive at those specific time points, and censored thereafter.

Statistical analyses

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). Chi-square test was used for categorical variables, and Fisher's exact test when appropriate. The Mann-Whitney test was used to compare the median for two continuous variables with skewed distribution, and the Kruskal-Wallis test used for 3 or more independent continuous variables. Multivariate analysis using bivariate model was used to determine significant factors in determining outcome at day 7, 14, 21 and 28. The area under receiver operating characteristic (AUROC) curve was used to determine the accuracy of different scores in predicting outcome. The optimal cut-off values were obtained by maximizing the Youden's

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index. Diagnostic accuracy was expressed as the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A P value of <0.05 was considered statistically significant.

Results

A total of 240 patients were included in the study, with a median age of 52 years (range, 21-81), of which 192 (80%) were male. The baseline parameters at the time of study inclusion are summarized in table 2. Patients who recovered without transplantation when compared to those who underwent transplant or who died, had higher albumin (35 vs 34 g/L respectively, p=0.015), with lower MELD score (21 vs 26 respectively, p<0.001), and lower incidence of ascites (12.7% vs 39.0% respectively, p<0.001). After multivariate analysis, both MELD score and presence of ascites remained significant factors. The ALT, HBeAg status, and the viral load at baseline were not significant in predicting recovery or transplant/death (Table 3).

Survival

Patients undergoing liver transplantation were censored at the time of transplant, but were included in the survival calculations. The 7, 14, 21, and 28-day survival was 96.7%, 88.5%, 79.5%, and 72.8% respectively. Using the parameters at the time of admission to predict mortality at 28 days, the AUROC for MELD, CLIF-OF, and CLIF-ACLF was 0.874, 0.837. and 0.783 respectively (see supplementary figure 2).

The longitudinal bloods results of patients from time of study entry to improvement beyond the inclusion criteria, liver transplant, or death was pooled together. In total, there were 4,021 samples representing different time-points of the admission. These were randomized to a training (n=2019) and validation (n=2002) set using a random computer number generator for each sample.

The AUROC for bilirubin, ALT, creatinine, INR, and MELD score was calculated to predict survival at the four time-points. In the training group, the AUROC for the MELD score to predict day 7, 14, 21, and 28 mortality was 0.909, 0.892, 0.883, and 0.871 respectively at any

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time during an admission, which was consistently higher than using bilirubin (0.722, 0.733, 0.743, and 0,739 respectively), INR (0.819, 0.827, 0.821, and 0.808 respectively), creatinine (0.826, 0.722, 0.696, and 0.683 respectively), or ALT (0.602, 0.541, 0.522, and 0.516 respectively) alone (see figure 1A-D). This is comparable to the validation group, where the AUROC for MELD score to predict day 7, 14, 21, and 28-day mortality was 0.913, 893, 0.877, and 0.875 respectively. In the training set, the optimal cut-off for MELD to predict day 7, 14, 21, and 28 mortality was 32, 29, 28, and 28 respectively. The sensitivity, specificity, positive predictive value, and negative predictive value in the training and validation groups are shown in table 4.

After stratifying patients by the presence or absence of any cirrhotic features on imaging (shrunken liver, nodular outline, splenomegaly, or ascites), the AUROC for predicting 28-day mortality was comparable between the overall, non-cirrhotic, and cirrhotic group for the training group (0.871, 0.834, and 0.873 respectively) and the validation group (0.875, 0.849, and 0.869 respectively).

A mortality-risk table was derived using the pooled blood samples in the training set to predict mortality at day 7,14, 21, and 28, as shown in figure 2A. Using the validation group, an 89.3% concordance rate was obtained. All of the discrepancies occurred at the fringes of the mortality cut-offs, lying within 15% of the predicted mortality rate. A transplant-free survival was also derived from the training set to predict transplant-free survival at day 7, 14, 21, and 28, as shown in figure 2B. For patients with MELD score <27, the transplant-free survival at day 28 was greater than 75%. The actual mortality percentages and transplant-free survival rates for the validation groups are shown in supplementary fig 1..

For patients with MELD ≤28, the mortality up to 28 days was relatively low (less than 25%). At the other spectrum, a MELD score of ≥32 was associated with >50% mortality at day 28. Beyond a MELD score of 28, there is a more dramatic rise in mortality. Further subgroup analyses were performed for MELD scores of 28 to 32 to better stratify those in the “grey zone” for short-term survival.

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Four criteria were identified in this MELD bracket in the training set which were significantly associated with short term mortality, including older age, higher ALT level, lower baseline platelets, and abnormal baseline imaging (either ultrasound or CT) as define by cirrhosis (coarse nodular or shrunken liver), and/or ascites and/or splenomegaly. There was a significantly higher median age (55 vs 51 years, p<0.001) and ALT level (670 vs 159 U/L, p<0.001), and lower median baseline platelet levels (120 vs 140 $x10^9$/L, p=0.010) for those who died within 28 days compared to those who survived. The baseline HBV DNA levels were not significantly different between the two groups (1.5 vs 1.1 $x10^8$ IU/ml, p=0.356). The AUROC for predicting day-28 mortality for age, ALT, and baseline platelets was 0.712, 0.662, and 0.586 respectively, with optimal cutoff values of 52 years, 217 U/L, and 127 $x10^9$/L respectively. Significantly higher mortality at day 28 was observed for those with age ≥52 vs <52 years (45.9% vs 19.0% respectively, p<0.001), ALT ≥217 vs <217 U/L (48.4% vs 18.1% respectively, p<0.001), platelets <127 vs ≥127 (49.0% vs 22.8% respectively, p<0.001), and with abnormal baseline imaging (56.3% vs 15.9%, p<0.001). These results are shown in figure 3A. There was a gradient of increasing mortality rates in this MELD bracket with each additional criteria present. In the absence of any criteria, the mortality at 28 days was 0%, compared to 12.1 %, 23.8%, 59.4% and 78.8% in the presence of each additional criteria (p<0.001, figure 3B). In the validation set, using the same criteria, the 28-day mortality rate from 0 to 4 criteria was 0%, 18.3%, 29.6%, 47.2%, and 73.3% respectively in the presence of each incremental criteria, without significant differences between training and validation group (p=0.29, p=0.45, p=0.13, and p=0.58 respectively). A proposed algorithm for stratifying and managing severe AFOCHB using a MELD-based system is shown in figure 4.

Discussion

Despite the use of potent antiviral therapy, AFOCHB resulting in liver decompensation remains a difficult scenario for clinical management. It has already been demonstrated that despite the use of effective antiviral therapy, the immediate short-term outcome is not likely to be significantly altered (18). This is also reflected in the current study, whereby a biphasic pattern of survival is observed, with the overwhelming majority of mortality occurring within the first 60 days (supplementary figure 3). Unlike patients with acute hepatitis B

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infection, those with AFOCHB already have pre-existing underlying chronic liver disease. The severity of liver failure is dependent on two major factors, namely the severity of the hepatitic flare, and the severity of the pre-existing underlying liver disease (19). For instance, those with mild flares may still decompensate with underlying cirrhosis, and those without significant fibrosis may decompensate with a severe flare.

The difficulty in managing these patients is in deciding whether liver transplantation is indicated and at what time should it be decided. This special condition should not be strictly guided by the King's criteria for acute liver failure. This is compounded by the fact that the window of opportunity to work up the patient for liver transplantation is often narrow. On the other hand, there is also a potential risk that patients may be transplanted unnecessarily. Although the CLIF-SOFA models can predict higher mortality with addition organ failure, it has limited usage when determining whether the patients require transplantation or not, because any additional extra-hepatic organ failure such as hemodynamic instability, or respiratory failure, would usually preclude the patient for transplantation. It is in fact those patients with liver-related organ failure only that remains the primary focus as these remains eligible for transplantation.

Currently, various definitions for ACLF exist. However, these are often not specific to predict outcomes. For AFOCHB who satisfy the criteria for ACLF, the prognosis is generally poor. A model to predict unfavorable outcome accurately is of paramount importance, especially when liver transplantation is available as a treatment option. The current study has demonstrated the MELD score to be highly predictive of short-term mortality in AFOCHB patients, and can be used to determine whether the patient is likely to require liver transplantation. By pooling all longitudinal results together, and calculating the mortality at each individual time points relative to that sample, the mortality at any given time point can be estimated using a MELD-based system. This is important as the prognosis of the patient may vary significantly during the course of admission due to the dynamic nature of AFOCHB. A MELD of <28 was shown to be associated with low risk of short-term mortality of <10% and 25% at day 14 and 28 respectively. In contrast, patients with a MELD of 32 or greater had a mortality of over 50% at day 28. Although there is a sharp rise in mortality for those

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with MELD 28 or above, patients with MELD 28 to 32 represents the greatest uncertainty, where 28-day mortality approaches 50%, with a similar proportion who may also recover. However, those who eventually recover will gradually lower their MELD score, thus re-categorizing their risk according to their new MELD score and out of the zone of uncertainty. Similarly, those who do not recover will have an increase in MELD with subsequent shift into the higher risk zone, indicating the definitive need for liver transplantation. It is unclear whether these patients with ACLF do worse than patients with chronic decompensation given the same MELD score, however, those with decompensation usually will have significantly lower MELD scores.

To better stratify outcome for patients with MELD 28 to 32, other independent criteria including age ≥52 years, ALT ≥217 U/L, baseline platelet levels <127 $x10^9$/L, and the presence of cirrhosis/splenomegaly/ascites on imaging characteristics can be used to determine the likelihood of needing liver transplantation. In the absence of any of these at-risk criteria, there was no mortality at 28 days despite a MELD of 28-32. The presence of single at-risk criteria was associated with 14.1% mortality at 28-day, with additional criteria associated with an increment in mortality. These criteria provide better stratification for those with MELD in this uncertain bracket, until the time the patient improves or deteriorates, with subsequent shift towards a more definitive MELD score. A proposed pathway suggests that those with MELD ≥28 should undergo liver transplant assessment, those with MELD 28-32 and 2 or more at-risk criteria and those with MELD ≥32 should be listed (figure 4). Although the AUROC for using MELD to predict short term survival was comparable between those and without cirrhotic features on imaging, it appears that stratification for cirrhosis was most useful for MELD scores in the grey zone in stratifying patients with higher risk of mortality.

Interestingly, HBV-specific markers such as HBV DNA was not associated with higher mortality, whereas previous studies have shown increase mortality for those with decompensated cirrhosis. However, the results for chronic decompensated cirrhosis may be different to the current study where patients are largely non-cirrhotic, but with a severe immune-mediated inflammatory response from the acute flare leading to liver failure. This

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process may already be irreversible for a proportion where antiviral therapy and HBV DNA suppression may not actually improve survival in the immediate short term (18). However, antiviral therapy is nevertheless essential and is likely to be beneficial for longer term survival. Furthermore, the absolute decline in HBV DNA level, rather than the baseline HBV DNA, may be a more important predictor of survival (20). Despite the potential association between higher mortality with entecavir secondary to lactic acidosis in patients with liver decompensation, this was not observed in the current study, or in a previous study of entecavir-treated patients treated with entecavir with severe flares whom were subsequently transplanted (21, 22). This is likely because the doses of nucleos(t)ide analogue were reduced accordingly to the creatinine clearance of the patients in the current study. Even though HBV markers not being part of the model, it is not recommended to use this model for non-HBV ACLF, because the disease course and pathogenesis differs significantly. Although MELD would still be predictive of survival, the specific cut-offs would probably be different. However, to answer this question definitively, a validation study of non-HBV ACLF would be required.

There were several limitations of the study. Firstly, validation was performed internally, and ideally should be follow-up with external validation. Secondly, the study included patients who eventually underwent liver transplantation. As the timing of liver transplant is subjected to availability of graft, it may not reflect the true timing of an unfavorable outcome. Therefore, patients were censored at the time of transplant. However, these patients were not excluded because their MELD scores up to the point of transplantation contribute important survival data. As a consequence, mortality may have been underestimated rather than overestimated. However, we have also included the transplant free survival, which grouped both death and LT as a significant event. Thirdly, the majority of patients had flares as part of the natural history of CHB infection, with a smaller proportion due to cessation of antiviral therapy. Only a handful (≤5) had reactivation as a result of chemotherapy for underlying malignancy. A recent study demonstrated poorer outcome for this group (23). In our cohort, none of these patients recovered spontaneously, with 3 undergoing living donor LT and 2 patients succumbing. Fourthly, hepatitis D virus (HDV) was not checked. However, HDV is rare in our locality, although in areas where

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infection is more common it should be excluded. Finally, those with HBV DNA $<10^4$ IU/mL were excluded, which may have excluded those with resolving flares. However, those with low HBV DNA are more likely to have other causes other than HBV flare as a cause of their ALT elevations, such as herbal medicine intake.

In conclusion, severe AFOCHB with liver decompensation can be associated with high rates of mortality and liver transplantation despite antiviral therapy. The MELD score at any time points can accurately predict the short-term mortality, determine the urgency of liver transplantation workup, and ultimately, the need for transplantation. Patients with MELD ≥28 should be worked up for liver transplantation, and those with MELD 28-32 with 3-4 at-risk criteria, or MELD >32 should be listed.

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Figure legends

Figure 1. AUROC of bilirubin, ALT, creatinine, INR, and MELD in predicting (A) Day-7 mortality, (B) Day-14 mortality, (C) Day-21 mortality, and (D) Day -28 mortality

Figure 2. (A) MELD-based predictor of short-term mortality in severe acute flares of chronic hepatitis B, (B) MELD-based predictor of transplant-free survival in severe acute flares of chronic hepatitis B

Figure 3. (A) 28-day mortality stratified by age, ALT level, platelet levels, and imaging findings for MELD 28-32, (B) 28-day mortality according to number of at-risk criteria for MELD 28-32

Figure 4. Proposed algorithm for severe acute flares of chronic hepatitis B patients presenting with decompensation

Table 1. Study inclusion and exclusion criteria

Inclusion criteria

- Age 18 years or older
- Evidence of acute flare of chronic hepatitis B
    - Chronic hepatitis B infection
        - Known/documented history of infection and/or
        - Hepatitis B surface antigen positivity ≥6 months
    - ALT ≥10x upper limit of normal
    - HBV DNA ≥4 logs IU/mL
- Evidence of liver decompensation
    - Bilirubin ≥50 mmol/L
    - INR ≥1.5

Exclusion criteria

- Hepatitis from other causes
    - Acute hepatitis A
    - Acute hepatitis E
    - Drug-induced liver injury

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Table 2. Baseline patient characteristics and laboratory data, and outcome

Parameter	Value
Total number	240
Age (years)	52 (21-81)
Male sex	192 (80.0 %)
Alcohol use (≥20g/day)	12 (5.0%)
Laboratory	
Bilirubin (umol/L)	193 (51-719)
ALT (U/L)	1989 (502-11443)
Albumin (g/L)	34 (16-46)
Creatinine (umol/L)	73 (36-848)
INR	2 .1 (1.5 – 8.0)
Platelet ($x10^9$/L)	125 (12-327)
MELD score	24 (15-42)
Viral	
HBeAg positivity	49 (20.4%)
HBV DNA (log IU/ml)	7.77 (4.11 – 10.06)
Imaging*	
Liver cirrhosis	70 (32.0%)
Splenomegaly	54 (24.7%)
Ascites	71 (32.4%)
Outcome	
Discharged	64 (26.7%)
Transplanted	121 (50.4%)
Death	55 (22.9%)

* 219 (91.3%) had imaging (ultrasound or CT scan) at the time of admission

Continuous variables are expressed in median (range)

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Table 3. Baseline factors and clinical outcomes

	Clinical outcome				
Parameter	Recover	Transplant	Death	P value*	P value**
Sex (male)	76.2%	82.6%	78.6%	0.557	0.379
Age (years)	50	49	58	<0.001	0.138
Alcohol use (≥20g/d)	5%	4.3%	7.7%	0.690	0.920
Bilirubin (mmol/mL)	143	191	286	<0.001	<0.001
ALT (U/L)	1951	1923	2040	0.657	0.367
Albumin (g/L)	35	34	33	0.006	0.015
Creatinine (umol/l)	71	77	73	0.087	0.054
INR	1.8	2.2	2.6	<0.001	<0.001
MELD score	21	25	28	<0.001	<0.001
Platelets ($x10^9$/L)	126	129	120	0.548	0.781
HBeAg positive	22.2%	22.8%	16.4%	0.610	0.802
HBV DNA (log IU/mL)	7.56	7.84	7.80	0.891	0.632
Liver cirrhosis	21.8%	35.4%	35.3%	0.176	0.062
Splenomegaly	21.8%	23.0%	31.4%	0.440	0.572
Ascites	12.7%	38.1%	41.2%	0.001	<0.001

* Comparison between recover vs liver transplant vs death

** Comparisons between recover vs liver transplant and death

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Table 4. Optimal cut-offs for predicting Day 7, 14, 21, and 28 mortality

Mortality	Day 7	Day 14	Day 21	Day 28
Optimal MELD cut-off	32	29	28	28
Training set				
AUROC	0.909	0.892	0.883	0.871
Sensitivity	78.8%	80.9%	82.6%	77.2%
Specificity	87.0%	79.9%	77.1%	79.7%
Positive predictive value	36.2%	47.1%	53.1%	61.1%
Negative predictive value	97.8%	95.0%	93.4%	90.1%
Validation set				
AUROC	0.913	0.893	0.877	0.875
Sensitivity	77.1%	81.0%	81.5%	78.3%
Specificity	88.4%	79.2%	78.5%	82.6%
Positive predictive value	36.1%	44.8%	54.7%	66.1%
Negative predictive value	97.9%	95.2%	93.0%	89.8%

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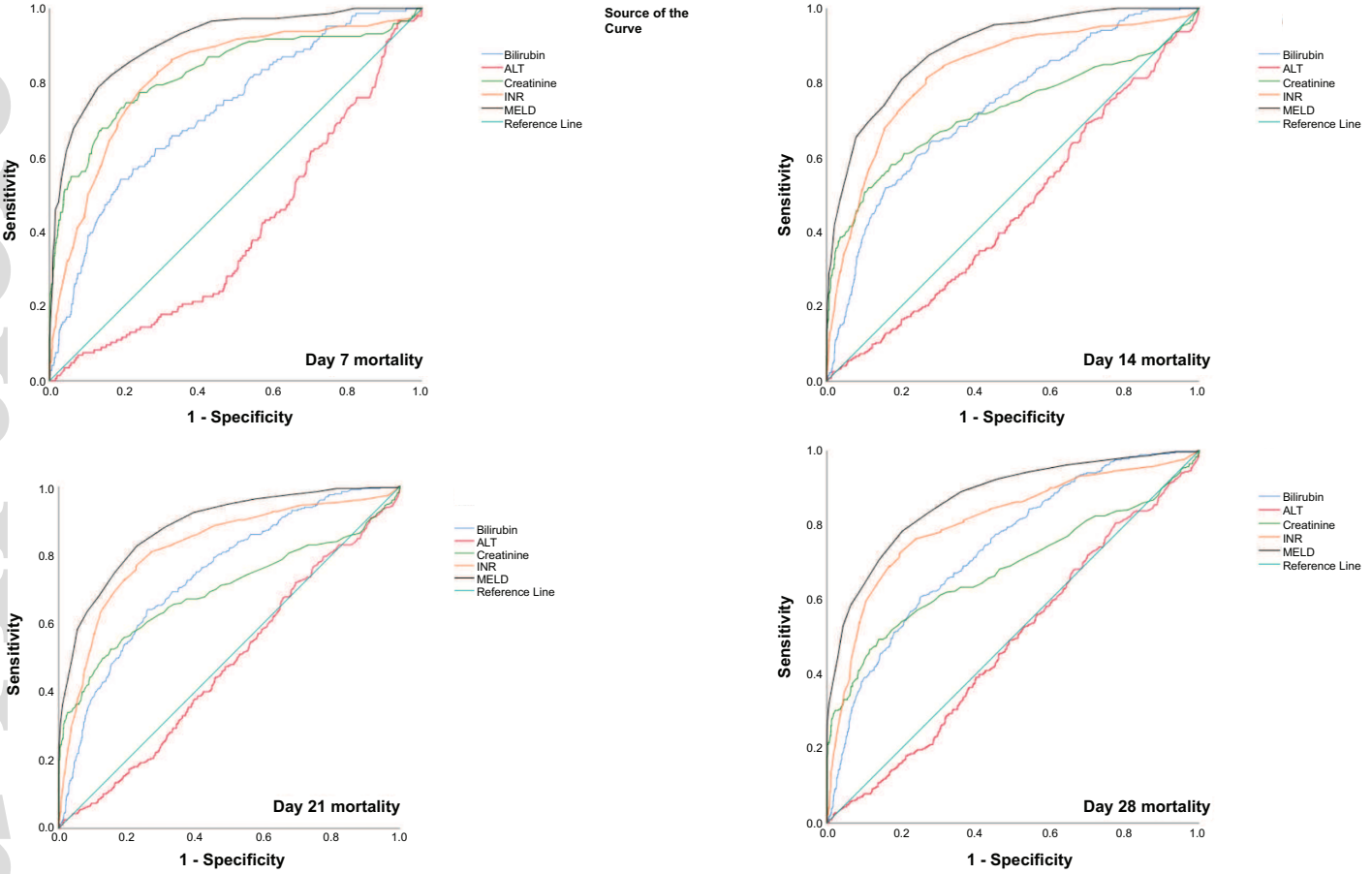

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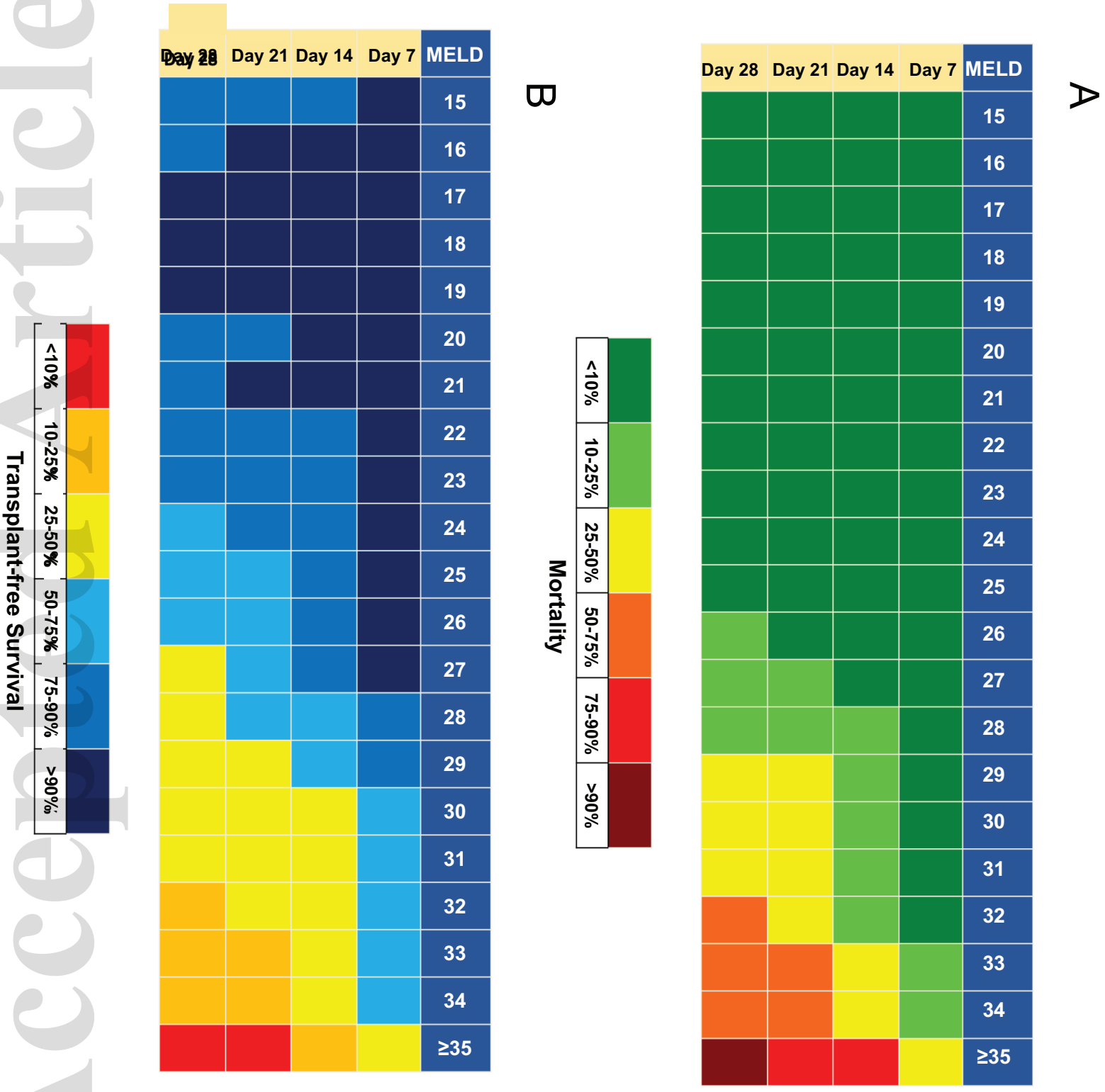

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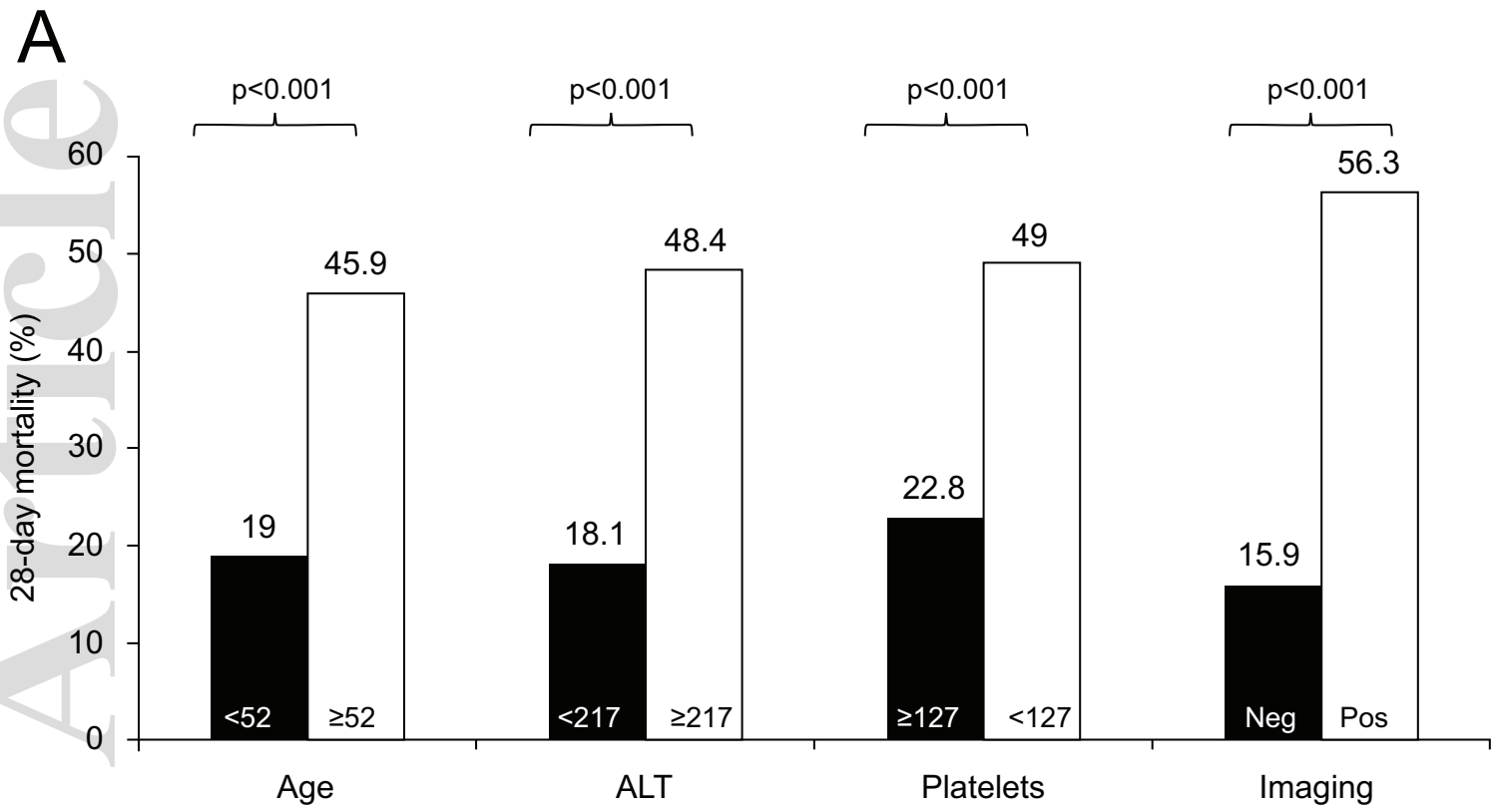

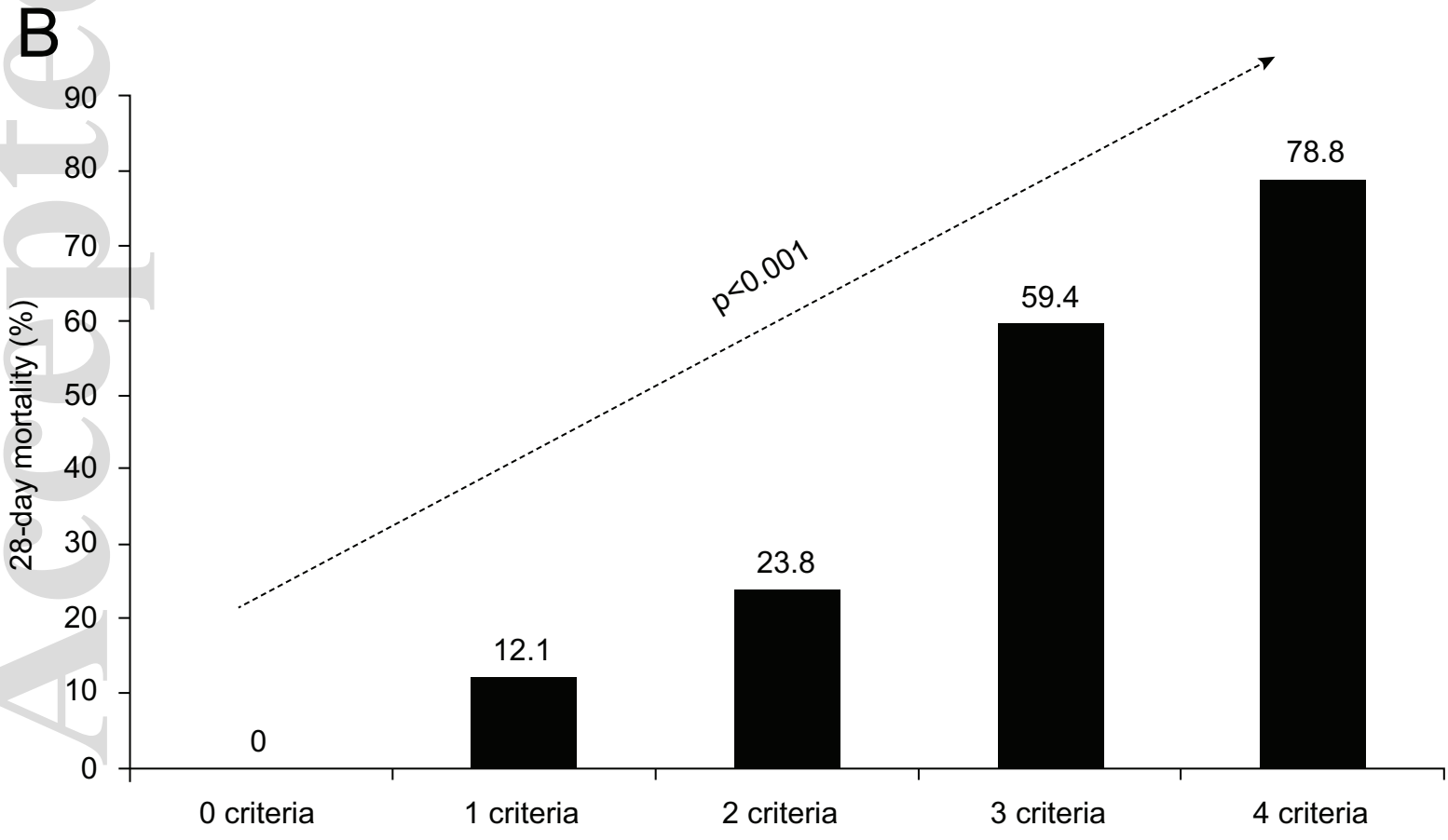

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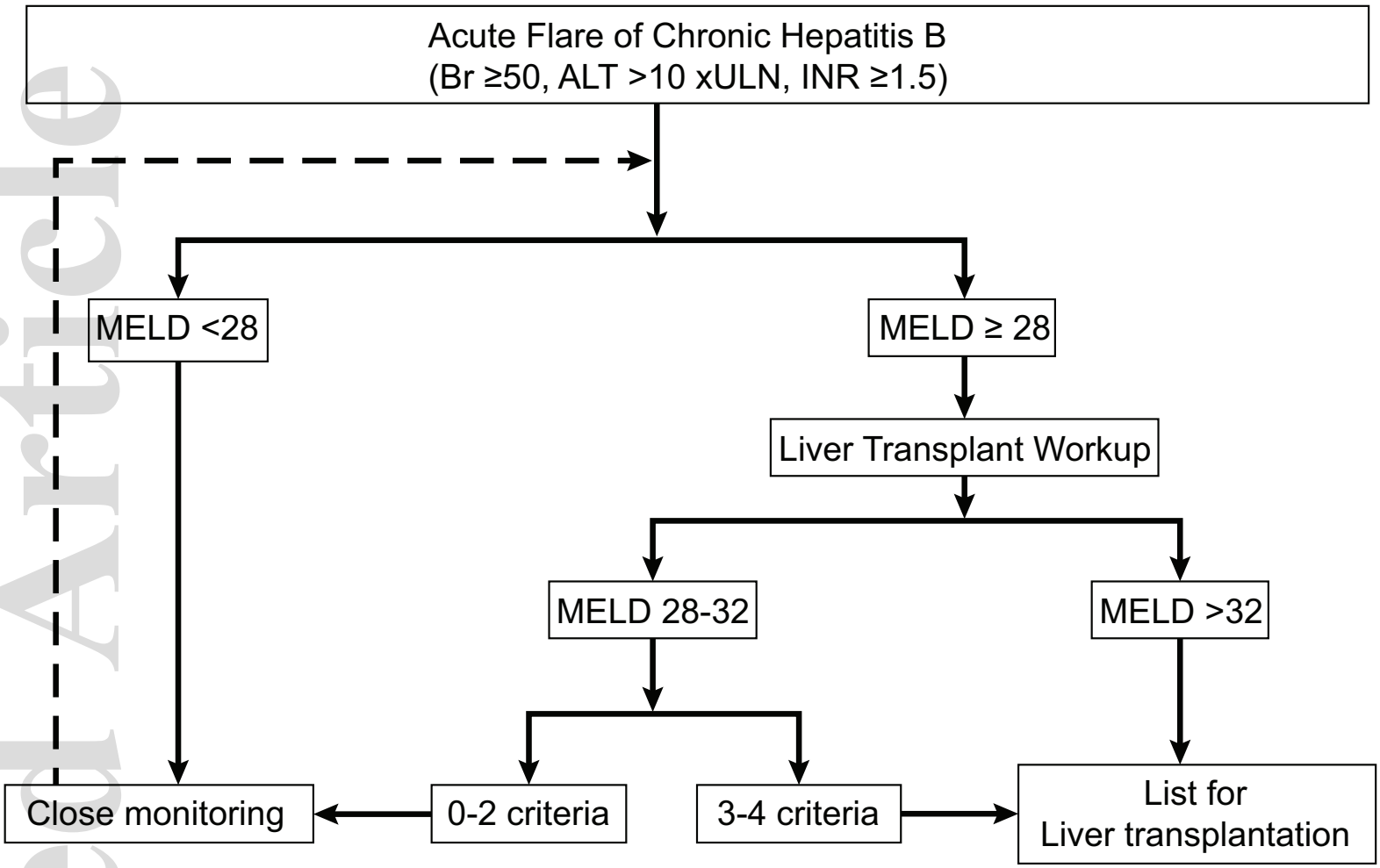

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