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A Decline in Status 1 listings: The impact of ALF etiology and ICU care

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Abbreviations

AIH	Autoimmune hepatitis
ALF	Acute liver failure
ALFSG	Acute Liver Failure study group
APAP	Acetaminophen
DILI	Drug induced liver injury
HAV	Hepatitis A virus
LT	Liver Transplantation
MELD	Model for end stage liver disease

Words= 1, 083

In the current issue, the outcomes of adult patients with acute liver failure (ALF) in the United States listed as status 1 for liver transplantation (LT) between 2002 and 2016 are presented (1). Key findings include 1) Black patients with ALF had higher MELD scores and a lower likelihood of spontaneous recovery compared to whites with a larger proportion undergoing LT and 2) black patients had a lower 1 year survival after transplantation. These provocative findings confirm prior reports that waitlist mortality and post-LT outcomes vary by race and that the number of adults with ALF being referred for LT appears to have declined (2,3)

Liver transplantation for acute liver failure

ALF is a rare clinical syndrome defined by the sudden onset of coagulopathy and mental status changes in a patient without known prior liver disease. Patients with ALF are at high risk for dying and currently account for ~ 3% of the liver transplants in the United States. The Acute Liver Failure Study Group (ALFSG) is a multicenter NIH network that has been prospectively studying the etiologies and outcomes of ALF since 1998 (2). The ALFSG has demonstrated that patients with acetaminophen (APAP) overdose

and hepatitis A (HAV) related ALF have a much greater likelihood of transplant- free survival compared to patients with idiosyncratic drug induced liver injury (DILI) and autoimmune hepatitis (AIH) (**Table 1**) (2). Furthermore, the proportion of ALFSG patients being listed as well as undergoing emergency LT have significantly declined in the US between 2002 and 2016 (2) **(Figure 1**). Whether these trends are due to more rapid diagnosis and treatment with effective therapies such as N-acetylcysteine for APAP and non-APAP etiologies or less frequent use of blood products and mechanical ventilation is unclear. In addition, FDA regulatory actions to reduce the amount of APAP in narcotic analgesic congeners and over the counter formulations may be having a favorable impact but APAP hepatotoxicity remains the leading cause of ALF in the US. An alternative explanation for the observed decline in status 1 listings could be improved categorization of patients as true ALF cases versus acute on chronic liver failure. Although 40% of the Status 1 patients were coded as "Unknown" etiology by UNOS, it is unlikely that these patients truly had indeterminate ALF in light of recent studies that use formal causality assessment (4). Therefore, there is no convincing evidence that the etiologies nor incidence of ALF have substantially changed in the past 20 years in the US. However, it remains plausible that the medical management of these critically ill patients is globally improving with fewer requiring transplant listing and undergoing LT (2).

Waitlist outcomes among Status 1 patients

Although the proportion of ALF patients listed as status 1 has significantly declined over the past 15 years, black patients remain overrepresented compared to other racial groups. Furthermore, black ALF patients had a greater likelihood of dying or deteriorating prior to LT on univariate analysis but not when taking into the account the competing risk of transplant. The greater need for LT in black ALF patients may, in part, be driven by their greater likelihood of having a diagnosis of DILI, AIH or HBV that are all associated with a lower rate of spontaneous recovery compared to APAP overdose that predominates among white ALF patients. In support of this, white ALF patients were also more likely to be removed from the waiting list due to clinical improvement.

The higher rate of LT amongst black ALF patients may also be related to racial differences in the likelihood of developing and presenting with severe DILI and AIH. In support of this, the ALFSG showed that blacks were significantly more likely to present with idiosyncratic DILI compared to whites (24.4% vs 14.9%, p = 0.009) (5). Recent European studies have also demonstrated that black patients with AIH present with more severe liver injury and are more likely to require transplant or die during follow-up (6). Prospective studies of idiosyncratic DILI have also suggested that black patients are more likely to

have poorer clinical outcomes including higher short-term mortality compared to whites (7,8). The reason for the poorer outcomes when controlling for disease etiology are unknown but could be mediated by genetic or immunological factors.

Post-transplant Outcomes in Status 1 ALF patients

The 1-year survival of ALF transplant recipients significantly differed by patient race (79.6% black vs 82.8% white and 89.3% Asian, p= 0.02). The superior outcomes amongst Asian ALF LT recipients are similar to prior studies demonstrating better outcomes in Asians with chronic HBV undergoing LT compared to other groups (9). Although the median time to LT was similar across all racial groups at 2 days, the presence and severity of cerebral edema and infections at the time of LT were not available for analysis. Furthermore, other donor factors (age, cold ischemia, A, B, O compatibility) and recipient factors (age, use of induction immunosuppression) that may have impacted outcomes were also not available to review (10).

Prior studies have demonstrated lower 1-year survival amongst black patients with cirrhosis undergoing LT compared to whites (11). Interestingly, donor-recipient race matching may be particularly important for black LT recipients with hepatocellular carcinoma and cirrhosis as has been shown for black kidney, lung and heart transplant recipients (12, 13). However, it is unlikely that matching by donor race will be feasible under the emergency circumstances encountered in status 1 ALF patients. Nonetheless, if an immunological basis for the differences in outcomes is demonstrated, immunosuppression protocols could be adapted in future race mismatched Status 1 ALF transplant recipients.

In closing, Nephew et al provide interesting and useful data regarding the incidence, etiologies and outcomes of a large cohort of critically ill patients with a rare disease (i.e. ALF) being cared for in over LT 100 programs around the country. The significant decline in the listing of ALF patients as status 1 is good news for the general population and the many patients with cirrhosis awaiting LT (2). The higher rate of transplantation amongst black patients is likely due to their greater likelihood of having a non-recoverable cause of ALF (i.e. DILI, AIH) rather than being due to other clinical management issues or biases. Although 1-year survival after LT varied by patient race and ethnicity, the current analyses did not take into account other potential confounders that may have influenced outcomes. Additional prospective studies are now needed to identify modifiable recipient or donor factors that could lead to further improvements in ALF patient outcomes across all racial groups.

Figure 1 Listing and receipt of liver transplantation in adult patients enrolled in the US ALFSG registry between 2002 and 2016. The proportion of ALF patients being listed and undergoing emergency LT both significantly declined over time ($p < 0.05$ by Cochron-Armitage test)

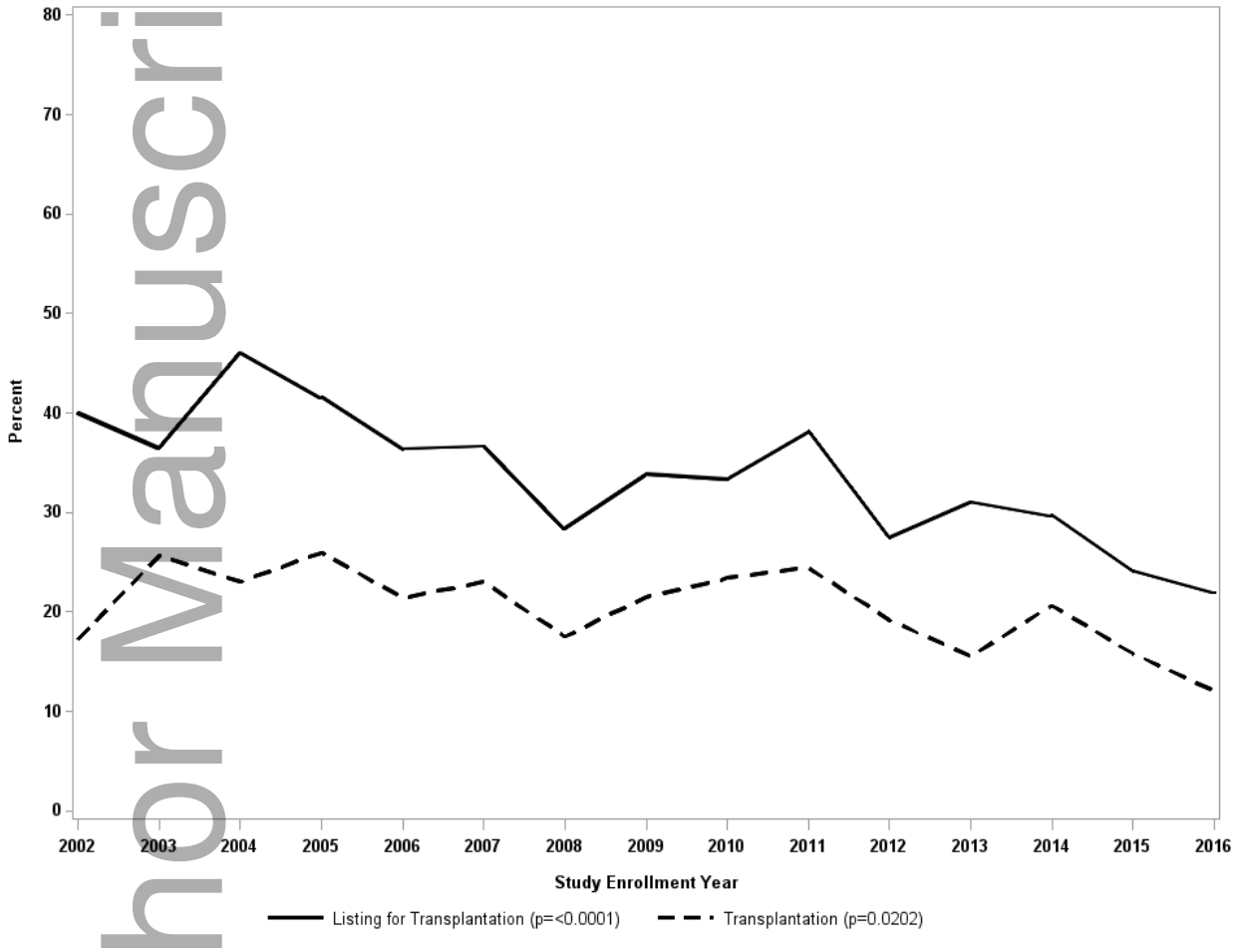

Table 1- Etiologies and outcomes in adult ALF patients

Etiology (%)	Recommended Treatment	Spontaneous survival
Favorable etiology		

Acetaminophen (50%)	N-acetylcysteine Nasogastric lavage and Activated charcoal *	70-80%
Ischemia (5-10%)	Pressors, fluids	50 -60%
Hepatitis A (1-3%)	? N-acetylcysteine	60-70%
Pregnancy (1-3%)	Emergent delivery	50-60%
Unfavorable etiology		
Idiosyncratic DILI (5-10%)	? N-acetylcysteine	20-30%
Indeterminate (5-10%)	? N-acetylcysteine	20-30%
Hepatitis B (1-3%)	Entecavir/ tenofovir ? N-acetylcysteine	20-30%
Autoimmune (5%)	Corticosteroids ? N-acetylcysteine	20-30%
Wilson's disease (< 1%)	? Chelation	< 5%

- *** for single time point ingestions < 12 hours**

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