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Eight fold increase in the dietary supplement related liver failure leading to transplant waitlisting over the last quarter century in the US

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Abbreviations:

ALF, acute liver failure

APAP, acetaminophen

DIALF, drug induced acute liver failure

DILI, drug-induced liver injury

HDS, herbal or dietary supplement

MELD, model for endstage liver disease

PELD, pediatric model for endstage liver disease

LT, liver transplantation

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Abstract

Introduction: We investigated the trends in listing and outcomes of drug induced acute liver failure (DIALF) over the last quarter century in the United States using the United Network for Organ Sharing (UNOS) database.

Methods: We examined waitlisted patients in the UNOS database between 1995 and 2020 with a diagnosis of DIALF, and assessed trends in etiologies, demographic and clinical characteristics, and outcomes over 3 periods, 1995-2003, 2004-2012 and 2013-2020. Patients with DIALF and cirrhosis were classified as drug induced acute on chronic liver failure (DI-ACLF). Implicated agents including acetaminophen (APAP) and herbal or dietary supplements (HDS) were ascertained.

Results: There were 2146 individuals with DIALF during the study period. The observed demographic trends between the earliest and latest period included fewer pediatric patients (19% to 13%), but with increasing male gender in non-APAP DIALF (32% to 41%), and increased racial diversity in APAP DIALF. Antimicrobials remained the most common non-APAP agents across all periods, but antiepileptics, propylthiouracil and mushroom poisoning decreased, while HDS markedly increased from 2.9% to 24.1% of all non-APAP DIALF. The overall 5-year post liver transplant (LT) patient survival improved significantly over the 3 periods (69.9% to 77.4% to 83.3%) and was evident for both APAP and non-APAP DIALF.

Discussion: Over the last quarter century, there has been an eight-fold increase in HDS related liver failure necessitating waitlisting for liver transplantation in the US. There are other important temporal trends during the study period, including improved survival following LT among both APAP and non-APAP DIALF. (Word Count 249)

Introduction

Drug-induced liver injury (DILI) may be severe enough to lead to acute liver failure (ALF) and death. In such cases drug-induced acute liver failure (DIALF) requires lifesaving liver transplantation (LT). Prior studies on *LT for DIALF* using the United Network for Organ Sharing (UNOS) data spanning

1990-2006 indicated that 12-15% of LT for ALF was related to DIALF, with children (age<18) accounting for 14% of cases. Gender differences were noted where LT was predominantly in females (76%) (particularly with APAP and antimicrobial agents) [1, 2]. The most common agents were APAP, antituberculosis agents, antiepileptics and propylthiouracil [1, 2]. Racial differences included predominance of APAP injury in Caucasian (53%) vs. Black (25%) patients, in contrast to non-APAP agents, 47% vs. 75%, respectively. One-year post-LT patient and graft survival were 77% and 71% respectively, and antiepileptic-related DIALF in pediatric age and renal dysfunction were independently associated with poor survival [1, 2]. Trends in waitlist outcomes for DIALF and more recent post-LT outcomes in the UNOS database have not been examined.

In addition to the impact on patient morbidity and mortality, DILI is the leading cause for drug-withdrawal from the market or restriction of use and significantly impacts safe drug development [3]. This is epitomized by troglitazone which was approved in 1997, but subsequently recognized as a cause of life-threatening DILI with drug withdrawal in 2000 and wide publication of DILI risk in 2003 [4]. Increasing attention to post-marketing DILI and evolving regulatory oversight over the last 2 decades [5], is reflected in the Food and Drug Administrations (FDA) guidance for industry. This 2009 FDA guidance for pre-marketing clinical evaluation of DILI may impact the risk and incidence of life-threatening DILI [6]. Additionally, cultural changes in attitudes toward herbal or dietary supplements (HDS) and their increasing widespread use) [7], may also impact the epidemiology and outcomes of DIALF and even drug-induced acute-on-chronic liver failure [8, 9]. There is increasing interest in DILI occurring in patients with pre-existing chronic liver disease, with implications for drug development, since they represent an at-risk group for poor outcomes [10, 11]. Drug-induced liver injury precipitated 10% of acute-on-chronic liver failure in Asian populations and was associated with poor transplant-free survival [9].

In this study we sought to examine *waitlisting* for DIALF in the UNOS database and its outcomes over the last 26 years. In addition to describing demographic factors, we examined changes in the most common agents or classes of agents associated with DIALF. We examined the potential impact of drug approvals by the FDA on waitlisting for associated DIALF over this time period. Finally, we examined the characteristics and waitlist outcomes in patients with DILI and cirrhosis in comparison with those listed for DIALF.

Methods

All patients waitlisted for LT in the UNOS database between 1995 until 2020 were reviewed, with the current UNOS diagnosis codes at waitlisting being consistently used since 1995 (old diagnostic codes were in use up to 2014). Primary and secondary diagnosis codes and diagnosis text for waitlisting were examined for drug-induced liver injury. In the primary analysis patients were classified as having DIALF when listed with a diagnosis code of acute hepatic necrosis secondary to drug or acute hepatic necrosis due to other with a secondary code or text diagnosis of DILI. In the analysis of DIALF we excluded patients with; (i) any other diagnosis codes (ii) prior LT (iii) reported liver injury from total parenteral nutrition (iv) no listed agent or agent class and (v) previous liver transplant.

We examined trends in patient demographics, implicated agents, waitlist and liver transplant outcomes over 3 periods spanning approximately similar intervals, 1995-2003, 2004-2012 and 2013-2020. Demographic factors assessed included patient age, adult vs pediatric, gender, and race and ethnicity. Transplant registrant or recipient clinical factors assessed included measures of total bilirubin, INR, serum sodium, albumin and creatinine, critical care measures at listing or LT (mechanical ventilation, vasopressors or renal replacement therapy if listed). Outcomes examined included LT, death or waitlist removal for being too sick for LT, and delisting for improvement. Post-LT patient and graft survival were also described.

The analysis of agents included examination of APAP and non-APAP causes of ALF, and description of the most common non-APAP classes and the most common non-APAP agents associated with listing for DIALF over time. For consistency with prior studies, we included mushroom (amanita phyllodes) related DIALF, even though it is not a drug or supplement per se [1, 2]. HDS were identified by a combination of text search using the terms “herb” “supplement” “tea” “weight” “energy” and by manual review of the text fields by the lead author.

To compliment these analyses, we determined the year of FDA approval for all named agents. We identified cases of waitlisting for DIALF related to agents approved during the study period (1995-2020). We determined the interval from the year of FDA approval to the year of waitlisting for DIALF for each agent. This allowed us to describe the number of waitlisted patients with DIALF due to those implicated agents within 5 and 10 years of their approval.

Finally, we examined the characteristics and outcomes of patients with DILI (diagnosis codes or documentation as used above), in addition to cirrhosis diagnosis codes as determined by diagnosis codes or related text documentation. We compared clinical characteristics, waitlist and post LT outcomes in patients with DILI and cirrhosis vs. DIALF.

Descriptive analyses were performed using Chi-square test for categorical variables and with parametric and non-parametric methods for normally and non-normally distributed continuous variables as appropriate. Survival rates were described using Kaplan Meier Curves and survival tables, and comparisons using log-rank testing. Analyses were performed using IBM SPSS Statistics for Window, version 26 (IBM Corp., Armonk, NY, USA), and Stata Statistical Software: Release 15 (Statacorp LLC, College Station, Tx) with p-value <0.05 as the threshold for significance.

Results

Between 1995 and 2020, 267,615 patients were waitlisted for LT in the UNOS database. Among them, 2382 were listed for DIALF, but 238 were excluded (unspecified agent or class). As a result, 2146 patients with DIALF with a defined implicated agent or drug class were included in this analysis. The proportion of all waitlisted patients with DIALF was 0.9% during 1995-2003, 1% during 20014-2012, but decreased to 0.5% during 2013-2020 (p<0.001). Among 159,589 patients undergoing LT during the study period, 874 had DIALF, representing 0.6% of LT in 1995-2003, 0.7% in 2004-2012 and 0.4% in 2013-2020 (p<0.001). The mean age was 34±15, 285 (13.7%) were children (age<18), and 1,609 (75%) were female.

Patient demographics and clinical characteristics

Clinical and demographic characteristics among patients with DIALF over the study period are described in **Table 1**. The mean age at listing increased over time. The proportion of children decreased in non-APAP (19% to 9%) and APAP-DIALF (19% to 15%). While the majority of patients were female, the proportion of males with non-APAP DIALF increased (32% to 41%), and with APAP-DIALF decreased (25% to 20%). There were fewer Caucasians and Blacks, and more Asians and Hispanics in 2013-2020 compared with earlier time periods. The racial and ethnic differences were attributed to changes relating to APAP-DIALF (Whites decreased from 76% to 67%, with increase in Blacks, 10% to 12%, Asians 8% to14% and Hispanics 8% to 14% (p<0.001)). The

distribution of race and ethnicity was not statistically different over the three periods in non-APAP-DIALF. Medical insurance also changed over time, most notably an increase in Medicaid and decrease in private pay. This was observed in both APAP and non-APAP DIALF, though it was most pronounced in APAP-DIALF (Medicaid in 30.5% and private insurance in 52.8% in 2013-2020). The frequency of private and Medicaid insurance also differed in Whites (66.1% and 16.7%), Blacks (46.2% and 33.3%), Asians (46.7% and 30%) and Hispanics (47.2% and 29%), respectively (p-value < 0.001) during the study. Over the 3 time periods, Medicaid insurance increased significantly in Asian (from 17.9% to 41.7%, p-value = 0.02) and Hispanic patients (from 16.7% to 41.1%, p-value = 0.01). It also increased in Black (from 29.3% to 46.2%, p-value=0.14) and White patients (from 15.3% to 20%, p-value = 0.07).

Although the mean creatinine at listing was lower in the most recent period, the proportion of patients on renal replacement therapy at listing was higher. Despite this, the mean listing MELD/PELD was numerically similar over the 3 periods. The etiology of DIALF differed during the 3 periods, with a peak in APAP-DIALF in 2004-2012 (78.4% of all DIALF), followed by a decrease in the 2013-2020 (70.4% of all DIALF). The average number of non-APAP DIALF waitlistings per year decreased (26.6, 22.2 and 18.1) over the 3 study periods, respectively.

Implicated agents

Antimicrobials were the most commonly implicated class/agent during all 3 periods, but represented a proportionally higher subset of non-APAP DIALF in 2013-2020 (**Table 1**). In contrast, we observed decreases in antiepileptic, mushroom, and propylthiouracil DIALF over each study period, with only 1 listing for mushroom DIALF and no propylthiouracil DIALF in 2013-2020. Propylthiouracil and antiepileptics were associated with the highest proportion of children with DIALF (35% and 30.2%, respectively). Children represented 13.9% of patients with APAP, 10% with antimicrobials, and 10.1% of all other etiologies of DIALF. There was a significant increase in the HDS related DIALF over time, with HDS implicated in approximately one quarter of all non-APAP DIALF in 2013-2020. During 1995-2003, HDS related DIALF accounted for 2.9% of all DIALF whereas this has increased to 24.1% by 2013-2020 **(Table 1)**. We compared demographic and clinical factors over time in patients with HDS related DIALF. The mean age was 42 in all periods but an increasing proportion of

males was observed over time (from none to 49%). There was also increased racial diversity with relative decrease in Whites (71% to 40%) and increase in Blacks (none to 17%) Asians (None to 20%) and Hispanics (none to 20%). There were no differences in medical insurance, MELD or 90-day mortality or delisting for severity of illness. The most frequent transplant region was region 5, accounting for 26 (43%) of 61 cases of HDS related DIALF, with 21 of those patients listed in the state of California.

The non-APAP agents or classes of implicated agents are listed in **Table 2.** Antimicrobials, antiepileptics and HDS were the most frequent agent classes. Among antimicrobials, antituberculosis agents were the most frequent (isoniazid), while previously not reported agents included azithromycin and terbinafine [1, 2]. Fluoroquinolones were associated with 9 cases of DIALF (levofloxacin 4, trovafloxacin 3, moxifloxacin 2). Other notable agents included the anti-tumor necrosis factor agent, infliximab with 9 cases and troglitazone with 5 cases of DIALF. While HDS were increasingly associated with DIALF in 2013-2020, the specific HDS products/supplements were not consistently documented (**Table 3)**. The most common HDS or their intent of action included, weight loss supplements, Oxylite Pro, Hydroxycut, green tea extract and muscle building supplements. Herbal teas and supplements targeting weight loss were common HDS agents during the three periods examined, with additional cases of green tea extract and muscle building supplements in the most recent period.

Drug approval for marketing by the US FDA and DIALF

During 1995-2020, the FDA approved 25 agents which were implicated in 45 instances of waitlisting for associated DIALF during the same period. These included 38 cases due to 26 agents approved in 1995-2003, 7 cases due to 6 cases approved in 2004-2012 and no agents approved in 2013-2020 (**Table 4**). Only one drug (efavirenz/lamivudine/tenofovir), approved in 2004-2012, was associated with more than one case of waitlisting for DIALF. The majority of DIALF waitlistings were observed within 10 years of FDA approval (27 cases due to 14 agents approved in 1995-2003 and 6 cases due to 5 agents approved in 2004-2012). Three agents that were approved in 1995-2003 were discontinued during the same period due to hepatotoxicity (Bromfenac, Troglitazone and Trovafloxacin).

Drug-induced liver injury with underlying cirrhosis

During 1995-2020, 507 waitlisted patients had a diagnosis of cirrhosis and drug-induced liver injury. Among them 309 were reported to have drug-induced cirrhosis rather than other forms of cirrhosis with DILI and were excluded from the subgroup of DILI and cirrhosis. The underlying liver conditions in 198 patients with DILI and cirrhosis included alcohol-related in 66 (3 with hepatitis C), non-alcoholic fatty liver disease in 35, autoimmune hepatitis in 24, hepatitis C in 22, cryptogenic disease in 12, hepatitis B in 9, primary sclerosing cholangitis in 5, primary biliary cirrhosis in 1, other conditions in 9 and unspecified in 15 patients. Compared with DIALF, patients with DILI and cirrhosis were older, more frequently male, with non-APAP drug injury (**Table 5**). The most common non-APAP agents implicated in DILI and cirrhosis included methotrexate, antimicrobials and HDS, among others, while the offending agent was unknown in 37 cases (**Supplemental Table 1**). Patients with DILI and cirrhosis were more jaundiced at listing but had lower MELD/PELD scores compared with patients with DIALF, driven by significantly higher INR in patients with DIALF. Patients with DILI and cirrhosis were listed as status 1, 2, or 3 in 15%, 6% and 10% of cases respectively, and by MELD/PELD in 69% of cases. Whereas patients with DIALF were listed as status 1, 2, or 3 in 84%, 2% and 2% of cases respectively, and by MELD/PELD in 12% of cases. Few waitlisted patients with DILI and cirrhosis were delisted for improvement compared to DIALF, and they were more likely to undergo LT after listing.

Outcomes while waitlisted

The proportion of patients undergoing LT increased after 2003 but remained stable since then. The proportion of patients delisted for improvement was stable throughout the study period (**Table 1**). The proportion with waitlist mortality was similar for APAP (21.5%) and non-APAP (19.7%) DIALF during the study period, although a higher proportion of delisting for improvement was observed in APAP (42.2%) vs. non-APAP (13.5%) DIALF, respectively. A higher proportion of APAP-DIALF waitlistings resulted in LT over the 3 study periods (56.9%, 67% and 70.3%) relative to non-APAP DIALF (23.1%, 37.1% and 34%) respectively. There were no notable changes related to LT region over time. Ninety-day mortality and delisting for disease severity improved over time. The waitlisting outcomes were similar when examining only 1806 patients with DIALF listed as status 1 or 1A. There

was a trend for increased waitlist mortality in patients with DILI and cirrhosis compared to DIALF (**Supplemental Figure 1-A**).

Post-transplant outcomes

Overall post-LT patient and graft survival improved over the three study periods (**Figure 1-A and B).** There were no differences in post-LT patient survival in APAP vs. non-APAP DIALF at 1 (81.8% vs. 81.4%) and 5 (69.9% vs. 71.7%) years, (p=0.5). Patient and graft survival improved over time for both APAP and non-APAP DIALF. The findings were similar when examining only 741 patients with DIALF and listed as status 1 or 1A. For reference to other LT indications, we examined post LT survival in patients with DIALF in relation to 118,991 patients undergoing LT for cirrhosis without DILI or ALF during the study period. While 1- and 5-year post LT patient survival was lower between 1995 and 2003 for patients with DIALF (76.7% and 63.5%) compared to cirrhosis alone (87.3% and 73.9%), respectively, (P-value = 0.003), survival was similar for both LT indications between 2013-2020 (**Supplemental Figure 2**).

Antimicrobial, HDS and antiepileptics were associated with 60 or more waitlistings for DIALF. One and 5-year post-LT patient survival was lower with antiepileptics (79.5% and 65.5%) compared to antimicrobials (90.7% and 81.2%) (p=0.03) and HDS (88.5% and 80.4%), (p=0.08). One and 5-year post-LT patient survival were similar in patients with DIALF (86.1% and 76.7%) compared with patients with DILI and cirrhosis (83.8% and 73.1%) respectively, (p=0.9) (**Supplemental Figure 1-B**).

Discussion

In this examination of waitlisted patients in UNOS with DIALF over a 26-year period, we observed; (i) significant changes in offending agents or classes of agents, (ii) decreased waitlisting for DIALF attributed to newly FDA approved agents, (iii) improvements in post-LT survival and (iv) provide novel description of waitlisting for DILI and cirrhosis in the United States.

There were demographic changes as well over time, with a small increase in mean age with fewer children, and an increased proportion of males with non-APAP DIALF. There was increasing racial diversity in APAP-DIALF with fewer Caucasians and more Asians and Hispanics in 2013-2020. The increase in Medicaid insurance in patients waitlisted for DIALF during the study period, combined with higher rates of Medicaid insurance in Blacks, Asians and Hispanics, may reflect the impact of Medicaid expansion over the last decade. While Medicaid expansion has been examined in relation to hepatitis C treatment rates and waitlisting outcomes in cirrhosis [12, 13], the present study suggests a potentially important impact on access to transplant services among non-White patients with DIALF.

Among the implicated agents in DIALF, APAP was consistently the most the common agent, with a peak of waitlisting for related DIALF during 2004-2012, but a decrease in waitlistings in 2013-2020. The reasons for these variations are unclear. Rates of APAP overdose increased from 2007 to 2018 in the UK [14] and from 2007-2017 in Australia [15]. Rates of APAP-related adverse events in the US increased between 1998 and 2009 but were decreasing by 2012, though liver-specific and longer-term data are lacking [16]. Variability in administration of N-acetylcysteine for APAP hepatotoxicity and intensive care management for ALF have led to suggested standardized prescribing tools and an intensive care management toolbox [17, 18]. Therefore, it is possible that improved emergent and intensive care of APAP overdoses may have led to a lower proportion of patients with APAP hepatotoxicity requiring LT.

While antimicrobials were the most common non-APAP class during all periods. However, there were notably fewer antiepileptic, mushroom, and propylthiouracil cases in 2013-2020. During the same period HDS accounted for approximately one quarter of all non-APAP cases, contrasting sharply with prior experience [1, 2]. These findings are concordant with those of the multicenter Drug-induced Liver Injury Network study where the most common non-APAP agents implicated in DILI were antimicrobials (45%) and HDS (16%) [11].

The rise of waitlisting for HDS related DIALF is not surprising given the widespread use of these agent [7], and an estimated incidence of HDS-DILI of 1.1 per 100,000 persons in the U.S. [19]. This examination of UNOS data demonstrated demographic changes from predominantly white females before 2003 to gender, race and ethnically diverse in 2013-2020. The geographic concentration of cases in region 5 and the state of California may reflect cultural attitudes to HDS use and may help target education initiatives on the dangers of HDS. Only few HDS agents were listed by name, but

common themes were products aimed at weight loss and physical enhancement, which warrant specific scrutiny and questioning in suspected cases of DILI or DIALF. Outcomes of waitlisting and LT for HDS DIALF did not differ from those of the broader cohort.

Among patients with DIALF due to highly active antiretroviral therapy, the most commonly implicated agent was efavirenz (exclusively in 1 case and in combination therapy in 2 cases). We speculate that it was the likely culprit among the combination therapy cases.

The annual rate of waitlisting for non-APAP DIALF decreased over the study period. Again, the reasons for this are not fully discerned from the data on hand. The observation of decreased DIALF due FDA approval of agents during the specified study period (predominantly within 10 years of agent approval) explains this to a point. Furthermore, it provides indirect evidence for the benefits resulting from FDA regulatory guidance and industry attention to DILI risk in drug development [6]. Unfortunately, there are no population data that shed light on trends in the incidence and severity of DILI on a national level.

The improvement in post-LT survival of the study period was striking, and was observed for both APAP and non-APAP DIALF, and was similar to that of patients undergoing for LT without DILI or ALF. The increased post LT mortality for DIALF due to antiepileptics was notable [2], and has been previously described although the reasons for this remain unclear. The decreased waitlisting for DIALF due to antiepileptics and in pediatric patients could have contributed to improved post LT survival, although the small number of those patients would have had limited impact. It is possible that the peri and post-operative intensive care management of patients with severe multisystem dysfunction improved for patients waitlisted for and undergoing LT for DIALF.

Finally, the description DILI and cirrhosis here was novel within the UNOS database. While a subset of patients with DILI and cirrhosis may have acute-on-chronic liver failure, this was hard to assess in the UNOS dataset. As expected in patients with underlying cirrhosis were older and more frequently males and more likely to be listed according to MELD/PELD rather than status 1. Non-APAP agents were more commonly implicated in DILI and cirrhosis. Notably few patients with DILI and cirrhosis improved on the waitlist, however, they did not have higher waitlist mortality and were more likely to

go on to receive LT, with comparable post-LT outcomes to LT for DIALF. DILI with cirrhosis was not associated with increased waitlist or post-LT mortality, suggesting that these patients are not evidently disadvantaged on the waitlist compared to DIALF.

There are a number of important limitations to this study. It is prone to coding errors of diagnostic codes, missing details for diagnosis, data was not available for all clinical parameters examined, and the implicated agents were not consistently identified by name. In addition, the diagnosis of DILI lacks a gold standard definition and adjudication of the specifid agents is based on clinical opinion in the course of care. This could lead to potential incorrect diagnoses and erroneous implication of agents. Furthermore, manual review of text fields to identify implicated agents could lead to errors in agent classification. The strengths of the study include the standardized data format used by UNOS, the size and longitudinal nature of the cohort, and the broad applicability of the data to LT centers in the United States. The study highlights changing etiology in DIALF, with increasing impact of HDS DILI. It indicates improving post LT survival in both APAP and non-APAP DIALF. Finally, the study lends novel insight into the burden and outcomes of DILI and cirrhosis on the waitlist in the United States.

Figure Legends

Figure 1 A and B. The Kaplan Meier curves depicting post-liver transplant patient (**1A**) and graft (**1B**) survival in patients undergoing liver transplantation for drug-induced acute liver failure in 1995-2003 (black line), 2004-2012 (green line) and 2013-2020 (blue line).

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Table 1. Clinical and demographic characteristics, and outcomes in patients waitlisted for liver transplantation between 1995 and 2020 for drug-induced acute liver failure. Data are shown as mean ± standard deviation or number(percentage).

	1995-2003 (n= 720)	**2004-2012 (n= 927)**	**2013-2020 (n= 499)**	**p-value**
Age	32±16	34±14	35±16	0.004
Pediatric	131 (18.8)	89 (9.9)	65 (13.5)	<0.001
Gender female	524 (72.8)	716 (77.2)	369 (73.9)	0.1
Race				
Caucasian	484 (67.2)	673 (72.6)	300 (60.1)	
Black	99 (13.8)	111 (12)	78 (15.6)	0.001
Asian	78 (10.8)	90 (9.7)	71 (14.4)	
Hispanic ethnicity	84 (11.7)	91 (9.8)	73 (14.6)	0.03
Medical insurance				
Private	453 (63)	564 (60.8)	267 (53.35)	
Medicaid	126 (17.5)	180 (19.4)	143 (28.7)	
Medicare	41 (5.7)	48 (5.2)	40 (8)	<0.001
Other government	16 (2.2)	32 (3.5)	21 (4.2)	
Self-pay	55 (7.6)	69 (7.4)	16 (3.2)	
Unknown	28 (3.9)	34 (3.7)	12 (2.4)	
Body mass index (kg/m^2)	24.6±5.9	25.6±5.9	26.9±6.3	<0.001
Bilirubin (mg/dL)	9.4±10*	9.1±9.7	10.5±10.1	0.03
INR	5.8±6.8*	5.7±7	4.5±2.8	0.001
Creatinine (mg/dL)	2.5±2.5*	2.1±1.7	1.7±1.5	<0.001
Sodium meq/ml	139±6*	139±6	139±6	0.7
MELD or PELD	34.4±11.7*	35.5±9.5	34±8.4	0.01
Albumin (g/L)	2.9±0.6*	3±0.6	2.9±0.6	0.8
Renal replacement therapy	23 (11.2)*	117 (12.6)	91 (18.2)	0.006
Implicated agents				
APAP	481 (66.8)	727 (78.4)	354 (70.9)	<0.001
Most common non-APAP	(n=239)	(n=200)	(n=145)	
Antimicrobial	75 (31.4)	75 (37.5)	60 (41.1)	
Antiepileptic	36 (15.1)	19 (9.5)	8 (5.5)	

Mushroom	22 (9.2)	11 (5.5)	1 (0.7)	<0.001
Propylthiouracil	13 (5.4)	7 (3.5)	None	
Herbal/Dietary supplement	7 (2.9)	19 (9.5)	35 (24.1)	
NSAID	12 (5)	9 (4.5)	7 (4.8)	
Waitlisting outcomes				
Death or too sick	175 (24.3)	189 (20.4)	87 (17.4)	0.01
90-day waitlist mortality**	164 (22.8)	183 (19.7)	85 (17)	0.05
Improved	265 (36.8)	297 (32)	176 (35.3)	0.1
Liver transplantation	247 (34.4)	404 (43.6)	223 (44.7)	<0.001

Abbreviations: APAP, acetaminophen; HDS, herbal or dietary medicine; MELD, model for endstage liver disease; NSAID, non-steroidal anti-inflammatory; PELD; pediatric model for endstage liver disease

*Missing data, results shown for evaluable cases

**Waitlist removal due to death or delisting for being too sick to transplant within 90-days of waitlisting. P-value shown reflects Chi-square test

Table 2. The 584 non-acetaminophen agents or classes of agents implicated in DIALF between 1995-2020. Agents or classes of agents associated with 4 or more cases of waitlisting for related drug-induced acute liver failure are listed individually. Agents with 2 or fewer cases if DIALF are listed in the footnotes

Agent name or class	**Most common agents in class**	**Overall N=584**	**1995-2003 n=239**	**2004-2012 n=200**	**2013-2020 n=145**
Antimicrobials		**210**	**75**	**75**	**60**
	*Isoniazid**	*94*	*38*	*35*	*21*
	Sulfamethoxazole trimethoprim	*24*	*7*	*9*	*8*
	Nitrofurantoin	*13*	*6*	*5*	*2*
	Amoxicillin clavulanate	*10*	*3*	*2*	*5*
	Amoxicillin	*10*	*None*	*3*	*4*
	Minocycline	*6*	*2*	*2*	*2*
	Azithromycin	*5*	*2*	*2*	*1*
	Terbinafine	*5*	*1*	*2*	*2*
Antiepileptics		**63**	**36**	**19**	**8**
	Phenytoin	*33*	*21*	*12*	*None*
	Valproate	*21*	*10*	*5*	*6*
	Carbamazepine	*6*	*4*	*2*	*None*
HDS		**61**	**7**	**19**	**35**
Mushroom		**34**	**22**	**11**	**None**
NSAID		**28**	**12**	**9**	**7**
	Diclofenac	*7*	*2*	*5*	*None*
Propylthiouracil		**20**	**13**	**7**	**None**
Statins		**16**	**5**	**9**	**2**
	Simvastatin	*4*	*3*	*1*	*None*
	Simvastatin/ezetimibe	*3*	*None*	*3*	*None*

Disulfiram		**12**	**8**	**3**	**1**
Anesthetics		**12**	**10**	**2**	**None**
	Halothane	*4*	*3*	*1*	*None*
	Isoflurane	*4*	*4*	*None*	*None*
Antidepressants		**11**	**5**	**4**	**2**
	Nefazodone	*3*	*3*	*None*	*None*
	Duloxetine	*2*	*None*	*1*	*1*
	Paroxetine	*2*	*None*	*None*	*1*
Methotrexate		**10**	**7**	**2**	**1**
Anti-tumor necrosis factor		**10**	**None**	**8**	**2**
	Infliximab	*9*		*7*	*2*
HAART**		**8**	**2**	**3**	**3**
Iron		**6**	**1**	**2**	**3**
Antidiabetic		**6**	**6**	**None**	**None**
	Troglitazone	*5*	*5*	*None*	*None*
Sulfasalazine		**5**	**3**	**2**	**None**
Chlorzoxazone		**5**	**2**	**None**	**3**
Amiodarone		**5**	**1**	**2**	**2**
Antineoplastic		**5**	**2**	**1**	**2**
Methyldopa		**4**	**None**	**2**	**2**

Abbreviations. HAART, highly active antiretroviral therapy; HDS, herbal or dietary supplements; NSAIDs, non-steroidal anti-inflammatory drugs; NS, not specified.

Agents associated with 2 cases of DIALF included allopurinol, chloramphenicol, hydralazine, leflunomide, lisinopril, pemoline and zafirlukast

Agents associated with a single case of DIALF included antihypertensive (unspecified), azathioprine, butorphanol, carisoprodol, carbon tetrachloride, chemical (unspecified), clomiphene, diltiazem, ecstasy, ephedrine, hormone (unspecified), illicit drug (unspecified), isotretinoin, lamotrigine, levetiracetam/olanzapine, loratadine, losartan, mercaptopurine, methamphetamines, natalizumab, niacin, orlistat, paint exposure, plaquenil, prednisone, risperidone, salicylate, steroid, teriflunomide, tocilizumab, valsartan, vitamin A, 3 instances of unspecified agents, and 2 unspecified study drugs

* Isoniazid was also listed in 3 cases of combination antituberculosis treatment

** HAART therapy was specified as efavirenz and nevirapine in a case each, combination therapy of efavirenz/emtricitabine/tenofovir disoproxil fumarate in 2 cases and was unspecified in 4 cases,

Table 3. The implicated herbal and dietary supplements in waitlisted patients with DIALF during 1995-2020.

Herbal or dietary supplement	Overall N=61	1995-2003 n=7	2004-2012 n=19	2013-2020 n=35
Herbal agent unspecified	27	3	10	14
Weight loss	7	1	2	4
Herbal tea	5	1	2	2
Oxylite pro	4	None	None	4
Hydroxycut	3	None	2	1
Green tea extract	2	None	None	2
Muscle building	2	None	None	2
Banaba	1	None	1	None
Cleansing	1	None	None	1
Energy enhancer	1	None	None	1
Garcinia Cambogia	1	None	None	1
Kamdudha Ras / Mahamanjisthadi Kwath	1	None	1	None
Kava Kava	1	1	None	None
Khat	1	None	None	1
Lipolyze	1	None	1	None
Maca root	1	1	None	None
Nerve renew	1	None	None	1
Tesla	1	None	None	1

Table 4. Waitlisting by period of FDA approval of the agents implicated in drug-induced acute liver failure.

FDA approval among agents implicated in DIALF between 1995 and 2020				
FDA approval Period	**Drugs approved implicated in DIALF**	**Listings for associated DIALF**	**Listed within 5 years of approval**	**Listed within 10 years of approval**
1995-2003	26	38	15 (12 agents)	27 (14 agents)
2004-2012	6	7	3 (3 agents)	6 (5 agents)
2013-2020	None	None	None	None

Abbreviations: DIALF drug-induced acute liver failure; FDA, Food and Drug Administration; NA, not applicable.

Table 5. Clinical and demographic characteristics and outcomes in patients waitlisted for liver transplantation between 1995 and 2020 for drug-induced liver injury vs. drug-induced acute liver failure. Data are shown as mean ± standard deviation or number(percentage).

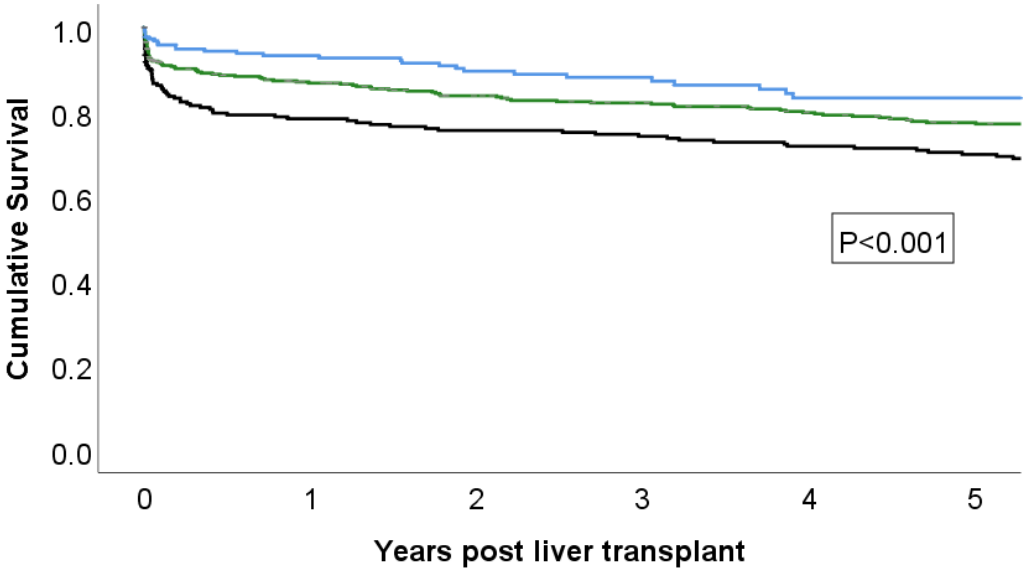
	Drug-Induced liver injury with cirrhosis (n= 198)	**Drug-induced acute liver failure (n= 2146)**	**p-value**
Age	49±14	34±15	<0.001
Pediatric	2 (1)	285 (13.7)	<0.001
Gender female	93 (47)	1609 (75)	<0.001
Race			
Caucasian	146 (74)	1457 (68)	
Black	19 (10)	288 (13)	0.5
Asian	19 (10)	240 (11)	
Hispanic ethnicity	19 (10)	248 (12)	0.4
Body mass index (kg/m^2)	28.6±6.1	25.6±6	<0.001
Bilirubin (mg/dL)	14.1±13.7	9.6±9.9	<0.001
INR	2.6±2	5.4±6	<0.001
Creatinine (mg/dL)	1.8±1.6	2±1.7	0.06
Sodium meq/ml	136±5.3	139±6	<0.001
MELD or PELD	27.2±12.2	34.9±9.4	<0.001
Albumin (g/L)	3±0.6	3±0.6	0.8
Renal replacement therapy*	12 (7.6)	231 (14.2)	0.02
Implicated agents			
APAP	52 (32)**	1562 (73)	<0.001
Non-APAP	(n=109)**	(n=532)	
Antimicrobial	19 (17)	210 (39)	
Antiepileptic	2 (2)	63 (13)	
Mushroom	None	34 (6)	
Propylthiouracil	None	20 (4)	
Herbal/Dietary supplement	8 (7)	61 (11)	
NSAID	1 (1)	28 (5)	
Anti-tumor necrosis factor	2 (1)	10 (0.5)	
HAART	None	8 (0.4)	

Statins	None	16 (0.7)	
Methotrexate	33 (17)	10 (0.5)	
Disulfiram	4 (2)	12 (0.6)	
Antineoplastic	3 (2)	5 (0.2)	<0.001
Azathioprine/mercaptopurine	2 (1)	2 (0.1)	
Antidiabetic	2 (1)	6 (0.3)	
Anti-depressants	1 (0.5)	12 (0.6)	
Illicit drug (unspecified)	7 (4)	3 (0.1)	
Chemical	10 (5)	3 (0.1)	
Anesthetics	None	12 (0.6)	
Other	15 (8)	69 (3)	
Waitlisting outcomes			
Death or too sick to transplant	52 (26)	451 (21)	0.09
90-day waitlist mortality**	35 (18)	432 (20)	0.4
Improved	16 (8)	738 (34)	<0.001
Liver transplantation	113 (57)	874 (41)	<0.001

Abbreviations: APAP, acetaminophen; HAART, highly active antiretroviral therapy; HDS, herbal and dietary medicine; MELD, model for endstage liver disease; NSAID, non-steroidal anti-inflammatory; PELD; pediatric model for endstage liver disease

*Missing data, results shown for evaluable cases

** Implicated agent unknown in 37 patients with drug-induced acute on chronic liver failure, proportions shown for evaluable cases



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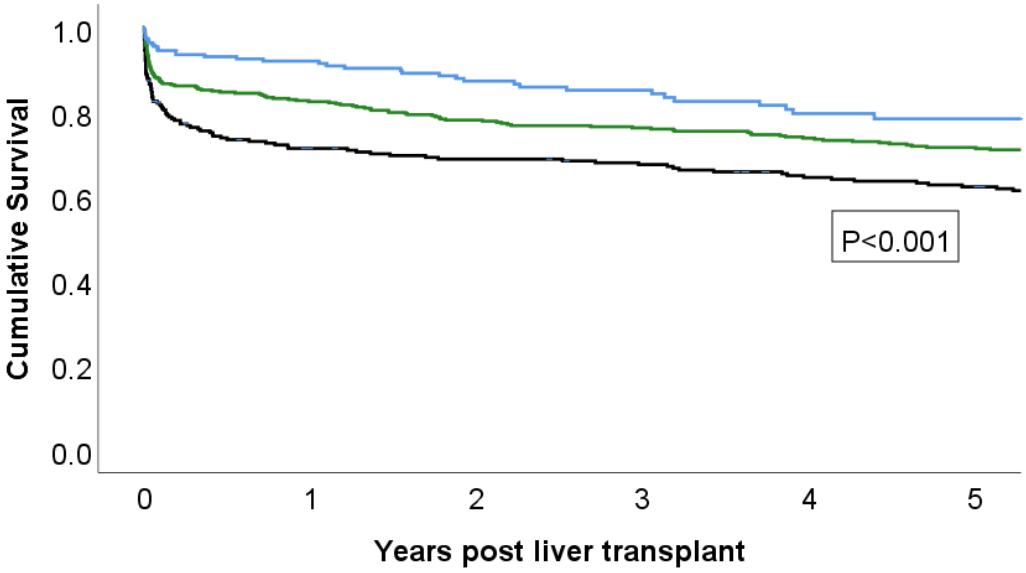

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