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## Liver Transplantation for Acute Liver Injury in Asians is More Likely due to Herbal and Dietary Supplements

Varun Kesar<sup>1</sup>, Lindsey Channen<sup>1</sup>, Masood Umair<sup>1</sup>, Priya Grewal<sup>1</sup>, Jawad Ahmad<sup>1</sup>, Nitzan C. Roth<sup>2</sup>, Joseph A. Odin<sup>1</sup>

<sup>1</sup>Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY,

<sup>2</sup>Division of Hepatology and Sandra Atlas Bass Center for Liver Diseases, Donald and Barbara School of Medicine at Hofstra/Northwell, Long Island, NY

### Abstract

Drug induced liver injury (DILI) due to medications and herbal and dietary supplements (HDS) is a major cause of acute liver injury leading to liver transplantation (LT). This study used United Network for Organ Sharing LT data to analyze severe HDS induced acute liver injury in the United States.

By convention, patients with acute DILI are listed as “Acute Hepatic Necrosis” (AHN) under the subheading “AHN: Drug Other Specify”. All patients waitlisted from 1994 to 2020 were divided into 3 subgroups: “HDS DILI”, “Non-HDS DILI”, and “AHN: unknown drug. Analyses were performed to identify epidemiologic differences between HDS DILI and Non-HDS DILI patients. Sub-analysis was performed for transplanted patients, including longitudinal changes.

Of 1875 patients waitlisted for LT, 736 (39.2%) underwent LT. The proportion of Asian patients in the HDS DILI group was significantly higher compared to the non-HDS DILI group (17.4% v. 3.8%,  $p < 0.001$ ). Excluding acetaminophen cases, the proportion of Black patients in the HDS DILI v. non-HDS group was significantly lower (8.7% v. 25.3%,  $p < 0.001$ ). Waitlisted HDS DILI patients were significantly older (median age 38 y for HDS DILI vs 31 y for non-HDS DILI,  $p=0.03$ ). Lastly, the number of patients requiring LT due to HDS DILI increased significantly over time with more than 70 % of cases occurring in the last 10 years (2010–2020) compared to the prior 15 years (1994–2009) ( $P_{\text{trend}}=0.001$ ).

**Conclusion:** Ethnicity may help in identifying the cause of severe acute DILI, a growing problem as more patients experiment with HDS.

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Corresponding author: Varun Kesar, M.D., Gastroenterology Fellow, Division of Gastroenterology, Virginia Tech Carilion School of Medicine-Carilion Clinic Roanoke, VA 24016, 3 Riverside Circle Roanoke, VA 24016, Cell: 631-565-4502, Fax: 212 731 7340, varundk18@gmail.com.

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Disclosures:

The authors have no conflict of interest to disclose.

## Keywords

Acute hepatic necrosis; Liver Transplantation; Drug Induced Liver Injury; Herbal and Dietary Supplement; Organ Procurement database

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## Background:

Drug induced liver injury (DILI) due to medications and herbal and dietary supplements (HDS) is the leading cause of severe acute liver injury in the United States and Western Europe (1,2). Amongst medications, acetaminophen is by far the most common cause of severe acute liver injury, whereas no single HDS product stands out in the same way. HDS include a large spectrum of agents used for a variety of medicinal and nutritional purposes including weight loss, bodybuilding, anxiety and depression, cardiovascular health, and pain management among others (3). There is no standard classification of HDS, which include vitamins, minerals, elements, herbal and botanical remedies, multi-ingredient compounds, and non-prescription anabolic steroids.

Americans are increasingly turning to complementary treatments such as HDS in addition to or instead of traditional medications. Data from the National Health Interview Surveys reveals that approximately 18% of American population used non-vitamin and non-mineral dietary supplements (4). Another study using data from the National Health and Nutrition Examination Survey reported that 52% of the US adults used supplements in 2011–2012 (5). HDS are readily available over the counter, do not require prescriptions from providers, and are not rigorously regulated by the Food and Drug Administration FDA (6). HDS use is not completely benign. Of HDS users, 4% reported experiencing an adverse event related to HDS consumption (7).

Increased use of HDS over time may lead to greater adverse hepatic events from mild to severe acute liver injury and possibly liver transplantation. Indeed, the US Drug-Induced Liver Injury Network (US-DILIN) reported the incidence of HDS DILI in their cohort increased significantly from 7% of collected non-acetaminophen DILI cases in 2004–2005 to 20% in 2013–2014, nearly a three-fold increase (8). Acute liver injury study groups across multiple Asian and European countries have reported that 20–40% of acute liver injury cases due to DILI are related to HDS use (9). Additionally, HDS related DILI in the US-DILIN cohort was significantly more likely to lead to death or liver transplantation (LT) compared to DILI from other medications (8). Also, in the US-DILIN cohort, Asian ethnicity was associated with an increased risk of death or liver transplantation (10). In the US Acute Liver Failure Study Group (ALFSG) cohort, both Blacks and Asians were overrepresented amongst those with severe liver injury related to DILI (11); no breakdown was provided with regard to DILI induction by HDS versus medications. These limited multi-site cohorts may not be representative of the national demographic and longitudinal patterns of severe liver injury due to DILI and specifically HDS consumption.

The United Network for Organ Sharing (UNOS) database provides information on all those waitlisted for liver transplantation in the United States. Earlier studies of acute liver failure cases in the UNOS database did not specifically examine HDS related cases nor ethnicity

(12, 13). This study utilizes the UNOS database to provide a broad, updated evaluation of the demographic and longitudinal trends of severe acute liver injury due to DILI.

## Methods:

Patients were identified by searching the UNOS database, which contains information regarding every organ donation and transplantation in the U.S. since October 1, 1987. There is no specific category for acute liver injury in the UNOS database. By convention, patients with drug induced acute liver injury are listed in the “Acute Hepatic Necrosis” (AHN) category under the subheading “AHN: Drug Other Specify”. We identified all patients who were waitlisted for LT for a diagnosis of “AHN” between January 1, 1994 and December 31, 2020. We chose the calendar year 1994 as our starting point for data collection as there was no diagnosis code required for waitlisting prior to it. We excluded patients with AHN due to a non-DILI etiology or due to DILI but with no specific agent implicated. Patients with AHN due to DILI were categorized as HDS DILI or non-HDS DILI. In some analyses, the acetaminophen (APAP) cases were excluded from comparisons between HDS and non-HDS-non-APAP cases. We collected data on the characteristics of patients including their sex, age, ethnicity, and education level. MELD score at listing and the time of transplantation was available since 2002. Ethnicity was assigned based on Organ procurement and transplantation network (OPTN) database categories: Asian, Black, Hispanic, White, American Indian/Alaska Native, Pacific Islanders and Multiracial. Given the small number of patients in the latter three ethnicities, they were combined into “other ethnicities”, leaving 5 categories for comparison purposes. Ethnicity was mostly self-declared. Education is collected in OPTN database as follows: primary school, high school, college/some technical university, associate degree or post graduate degree. For simplicity, we divided the education categories into any education after high school vs no education beyond high school. One year transplant free survival of patients post transplantation was calculated and compared between groups.

Subgroup comparisons were also performed specifically on the waitlisted patients who ultimately underwent LT. Rurality was added to the comparisons for between transplanted patients until 2014 (supplementary file). Patients’ zip codes were used to determine whether they resided in rural or non-rural areas using U.S. Census Bureau official definitions. The U.S. Census Bureau defines rural as what is not urban—that is, after defining individual urban areas, rural is what is left. Urbanized areas are areas with 50,000 or more people. Urban clusters are areas with at least 2,500 but fewer than 50,000 people. We used US census data from 2010 and along with their zip codes to define urban and rural populations (14–16).

## Statistical analysis:

We compared the characteristics of patients waitlisted and transplanted due to AHN from HDS versus non-HDS DILI, both including and excluding patients with DILI due to acetaminophen. Comparisons between groups were performed using chi-square tests or Fisher exact tests for categorical variables and non-parametric Kruskal-Wallis rank-sum tests for continuous variables. Associations between ethnicity and having HDS as the cause

of DILI-related AHN were calculated with univariate and multivariate logistic regression models. Multivariate models included age, sex, ethnicity, and calendar year. Trends by waitlist and transplantation year in the proportions of patients with HDS DILI among all DILI were calculated using univariate logistic regression models. All significance tests and resulting p values were two-sided with an alpha level of 0.05. Statistical analyses were performed using STATA SE 16 (Stata Corp LLC).

## Results:

### Categorization of AHN groups

Of 2446 patients waitlisted for LT within the UNOS “AHN” diagnostic category in the 26-year period studied, 1,875 had DILI with a specific agent implicated: 69 (3.7%) due to HDS and 1806 (96.3%) due to non-HDS DILI (Fig.1). The implicated HDS agents included herbal products, muscle building products, vitamins/minerals, and other dietary supplements (Fig. 2). Herbal products were the most common implicated agent in both those waitlisted and the transplanted subgroup. Use of body building supplements was marginally higher in those transplanted than in the waitlisted HDS group as a whole (32% v. 22%) (Fig. 2). The specific products that show up multiple times in the three main categories are: Oxyelite pro, Iron, and vitamin A. Acetaminophen (APAP) cases accounted for 1,371 (75.91%) of the non-HDS cases. The top 5 most common categories for non-apap non-HDS DILI includes: anti-tuberculosis drugs, antibiotics, anti-epileptics, anti-neoplastic agents and non-steroidal anti-inflammatory drugs. The top 5 implicated specific causes for non-APAP, non-HDS DILI includes: Isoniazid, Phenytoin, Propylthiouracil, Valproic acid and Trimethoprim/sulfamethoxazole (Table 1). All commonly known as causes of idiosyncratic liver injury (17). Of the HDS DILI cases, 59.4% underwent LT and only 38.5% of the non-HDS DILI cases had LT, though this increases to 61.8% if APAP cases are excluded.

### Demographics of HDS DILI versus non-HDS DILI cases

The overall distribution of our study patients when categorized by race/ethnicity was 68.8% White, 13.6% Black, 10.5% Hispanic, 4.3% Asian, and 2.8% other, which is similar to the 2010 US Census data (72% White, 13% Black, 16% Hispanic, 5.6% Asian, 7% Other) (16). While those with Asian ethnicity made up only 5.6% of the total US population (16) they accounted for 17.1% of all cases of LT due to HDS DILI in our study. This large difference in proportions was not seen for the other ethnic or demographic groups studied.

Overall, waitlisted patients with DILI were predominantly female (74.5%) and White (68.7%), with a median age of 32 years (IQR 22–45). There were no significant differences in MELD score at listing or education level between patients waitlisted due to non-HDS versus HDS DILI (Table 2), but HDS DILI patients were more likely to be older (Median age 38 vs 31 y p=0.03) and male (40.6% vs 24.9% P=0.003). However, both above findings lost statistical significance when APAP was excluded due to the high prevalence of young woman in the APAP cases.

During the study period, 1092 patients were transplanted and categorized as “AHN” cases, of whom 736 had DILI with a specific agent implicated (Fig. 1). Of the 736 patients

transplanted due to DILI, 41 (5.6%) had HDS DILI and 695 (94.4%) had non-HDS DILI including 426 (61.2%) due to APAP. APAP waitlisted cases were notably less likely to undergo LT (Table 1). Similar to the waitlisted DILI patients, overall, those transplanted due to DILI were predominantly female (71.7%) and White (66.3%), with a median age of 35 (IQR range: 25–47) years. There were no significant differences in age distribution between patients transplanted due to HDS versus non-HDS DILI, nor in sex, or educational level (Table 3). Interestingly, median MELD score at time of listing but not transplantation was lower in HDS as compared to non-HDS (31.5 vs 37  $p=0.02$ ) cases. However, the finding was not statistically significant when APAP cases were excluded from the comparison. (Table 3)

However, the distributions of ethnicities differed significantly between non-HDS versus HDS patients for both waitlisted (Table 2) and transplanted (Table 3) patients.

Asians constituted 17.4% of patients waitlisted due to HDS DILI but only 3.8% ( $p<0.001$ ) of those waitlisted due to non-HDS DILI (Table 2). Similarly, Asians constituted 17.1% of transplant recipients for HDS DILI but only 3.0% ( $p<0.001$ ) of transplant recipients due to non-HDS DILI (Table 3). Asian HDS use consisted predominantly of drugs categorized as supplements and not strictly herbal products. In multi-variate model for waitlisted patients, the risk of having HDS as the cause of DILI was almost 5 times higher for Asians versus Whites (OR 5.09, 95% CI: 2.5–10.3,  $p<0.001$ ) (Table 4). Other significant associations identified were older age ( $p=0.06$ ) and female sex ( $p=0.004$ ). Blacks had a lower risk of have HDS as cause of DILI, however, it did not reach statistical significance ( $p=0.45$ ) unless APAP cases were excluded. In multivariate models for transplantation adjusted for the risk of having HDS as the cause of DILI for transplant recipients was 5.8 times higher for Asian versus White patients (95% CI: 2.2–15.6,  $P<0.001$ ) (Table 5). Similarly, as waitlist Blacks had a lower risk of have HDS as cause of DILI for transplantation, however, it did not reach statistical significance ( $p=0.55$ ). Other predictors for were late transplantation years.

### Temporal Trends in HDS DILI

Almost 60% of patients waitlisted for LT for HDS DILI were listed in 2010–2020, with a significant trend by listing year in the proportion due to HDS DILI ( $p$  for trend =0.004). Similarly, more than 70% of patients transplanted for HDS DILI were transplanted in 2010–2020, with a significant trend by year of transplant in the proportion due to HDS DILI ( $p$  for trend =0.001). Longitudinal trends in waitlisting and transplantation for HDS DILI persisted even if APAP cases were excluded (Tables 2 and 3).

### One-year transplant-free survival of patients transplanted for AHN due to DILI.

HDS cases had good one year transplant-free survival as compared to APAP and non-APAP, non-HDS DILI cases after liver transplantation (89.7% vs 74% vs 78.7%  $P=0.048$ ). In multivariate modelling also the odds of one year transplant-free survival for transplantation due to non-APAP, non-HDS was 1.5 times the APAP post-transplant survival percentage (CI: 1.02 –2.32,  $P=0.04$ ). Other predictors for one year transplant free survival were years transplanted (Table 6).

## Discussion:

For patients presenting with acute liver injury, rapid identification of its etiology and severity is important to identify patients at risk for progression to liver failure and possibly death. Prior multi-site registration studies have characterized those with medication and HDS related acute liver injury to help providers more quickly assess similar cases. Utilizing the larger national UNOS database, we have further characterized severe cases of drug induced liver injury. Our study population of waitlisted patients likely included those with more severe liver injury than the prior US-DILIN studies and may be particularly useful in assessing hospitalized patients with drug induced liver injury.

The results of this study confirm several of the previously reported associations for acute liver injury due to medications and HDS with regards to female sex, older age, as well as its increasing incidence (9,11). Worse outcomes have been reported for Asians with DILI related acute liver injury (10) and those with HDS related acute liver injury (11). The finding that DILI related acute liver injury in waitlisted Asian patients was almost 5 times more likely to be due to HDS than for Whites may help explain the worse outcomes for Asians with DILI related acute liver injury. The opposite trend was noted for Blacks when excluding APAP cases.

In many cases of drug induced acute liver injury, patients are taking both HDS and non-HDS medications. For Asian patients with drug-induced liver injury, HDS is a more likely cause, while for Blacks, non-HDS, non-APAP medications is the more likely etiology.

Several factors may contribute to poorer outcomes from HDS related AHN. HDS are readily available over the counter, do not require prescriptions from providers, and are not rigorously regulated by the FDA. Clinical trials to assure their safety are not required prior to dissemination of most HDS. Additionally, the contents of HDS implicated in DILI are frequently mislabeled (18).

There is very limited data regarding the frequency and type of HDS use amongst different ethnic groups. In the 2002 Health and Diet Survey sponsored by the FDA, there was a significant difference in HDS use frequency by self-declared ethnic group with higher use reported in Whites and the “Other” group (4). Asian ethnicity was not studied individually and was included within “Other”, and details regarding the types of HDS being used were incomplete. In another survey of complementary and alternative medication, use rate of herbal and natural products was higher among those with Asian ethnicity, American Indians, or “multi-racial” individuals (19). Of note, in some Asian countries, HDS are a more common cause of DILI than acetaminophen or other conventional medications (20). Of course, HDS use may vary by country even amongst those of similar ethnic backgrounds.

Alternatively, as posed by US-DILIN researchers, genetic susceptibility, delayed presentation for care, or impaired liver regeneration in Asian patients would each conceivably contribute to worse outcomes from DILI related acute liver injury (10) even if HDS use is similar across ethnic groups. Indeed, HLA associations with genetic susceptibility to DILI from specific medications have been published suggesting an immune component to DILI (21). HLA alleles and haplotypes do vary significantly between ethnic

groups. Some with Asian ethnicity may have increased susceptibility to DILI from specific HDS compared to other ethnic groups due to differences in HLA or non-HLA immune variant expression (22). Recently HLA-B\*35:01 was identified as a high-risk allele for Polygonum multi-florum and green tea induced liver injury (23,24). Regardless of the mechanism for worse outcomes for HDS related DILI, clinicians should be particularly alert to HDS use amongst those with Asian ethnicity who develop severe acute liver injury.

The ALFSG network reviewed 927 patients who presented for management of ALF. These patients were 81.8% White, 12.8% Black, and 5.4% Asian, a similar population to our study (11). Within their cohort those classified as Asian or Black were significantly more likely to have ALF due to DILI than Whites. Our study did not include non-DILI causes of ALF so a direct comparison cannot be made. Their study did not report how many DILI cases were due to HDS use. They also found that those with Asian ethnicity and ALF were more likely to undergo LT with an odds ratio of 2.8, though this finding was attenuated and lost significance in the adjusted analysis. Another retrospective US cohort study utilizing the Drug-Induced Liver Injury Network (US DILIN) database, looked at 660 adults with definite, highly likely, or probable DILI with the aim of identifying demographic factors associated with early liver-related death or transplantation (11). In this group, self-declared Asian ethnicity was found to be independently associated with liver-related death or transplantation. Our data does not suggest increased risk of transplantation based on the ethnicity of those waitlisted for AHN due to DILI. Most US-DILIN patients were not waitlisted for liver transplantation as in our study population nor hospitalized as in the ALFSG cohort. Conceivably Whites with mild cases of DILI are more likely to enroll in US-DILIN than Asians.

Interestingly, in our study there were no significant differences in age distribution between patients transplanted due to HDS versus non-HDS DILI, however waitlisted patient due to HDS DILI were slightly older (Median age 38 vs 31 years for non-HDS DILI). There was also a difference in MELD score at listing with HDS DILI patient having a low MELD score at time for listing for transplant as compared to non-HDS DILI (31.5 vs 37). Likewise, with regard to sex, rurality and education level there was no significant differences between the patient groups. Some studies have seen an association between herbal medicine use and higher education levels as well with those between 25 and 49 years old (25,26). Our results did not indicate such a relationship, but our sample size was relatively small.

Independent of ethnicity this study showed that both the incidence and the proportion of cases of severe AHN due to HDS DILI in the US are increasing over time. As noted above, it is uncertain if this simply reflects increased use of HDS by the general population over time or a change in the types of HDS being consumed. These findings should encourage an increased awareness of the potential harm from HDS use amongst clinicians and purchasers of HDS.

There are several limitations to this study. As opposed to registry studies, one cannot verify data independently nor obtain additional clinical information as desired. The adjudication process utilized to diagnose DILI and to identify the implicated drug recorded in the UNOS database is likely quite variable and may not be highly rigorous. It would be beneficial to

future studies if more specific data on the implicated HDS products and a more formal causality review process for non-APAP DILI listed cases were available. Despite utilization of a national database, the total sample size in our study remained small. For many cases within the database, information was missing regarding rurality and education. The conclusions regarding ethnicity are subject to error since data on ethnic differences in HDS use in the US are limited as mentioned above, the overall limited information regarding the total number of individuals using HDS is also a major barrier in assessing the overall safety of HDS use.

In conclusion, severe DILI amongst Asians is more commonly due to HDS use than other ethnic groups, especially Blacks. Liver failure caused by HDS requiring LT should be expected to be a growing problem with increasing use of HDS.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

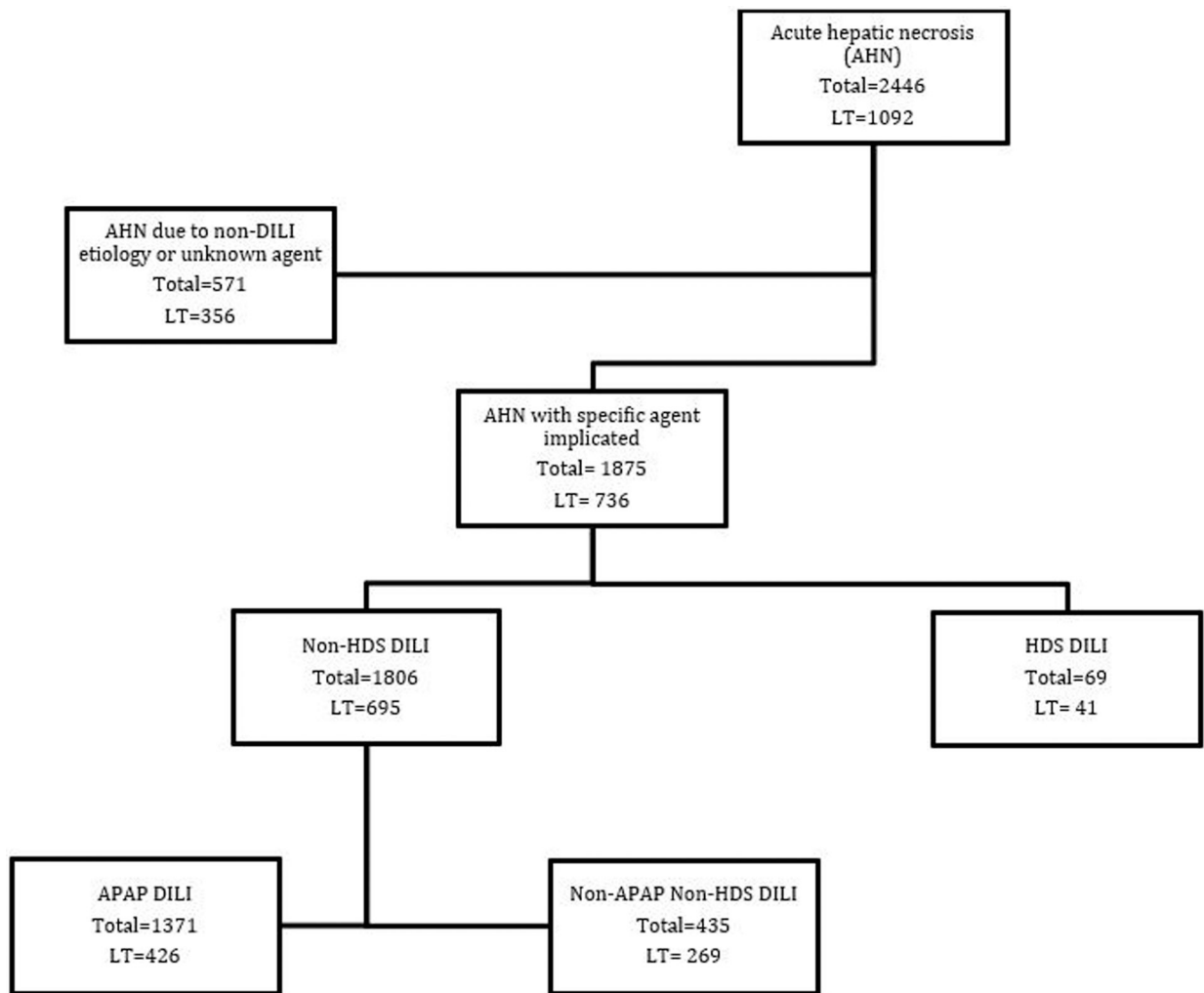
<b>ALFSG</b>	Acute Liver Failure Study Group
<b>ALF</b>	Acute Liver Failure
<b>APAP</b>	Acetaminophen
<b>AHN</b>	Acute Hepatic Necrosis
<b>DILI</b>	Drug induced liver injury
<b>FDA</b>	Food and Drug Administration
<b>HDS</b>	Herbal and Dietary Supplements
<b>LT</b>	Liver Transplantation
<b>OPTN</b>	Organ Procurement and Transplantation Network
<b>ULN</b>	Upper limit of normal
<b>UNOS</b>	United Network for Organ Sharing
<b>WL</b>	Wait list



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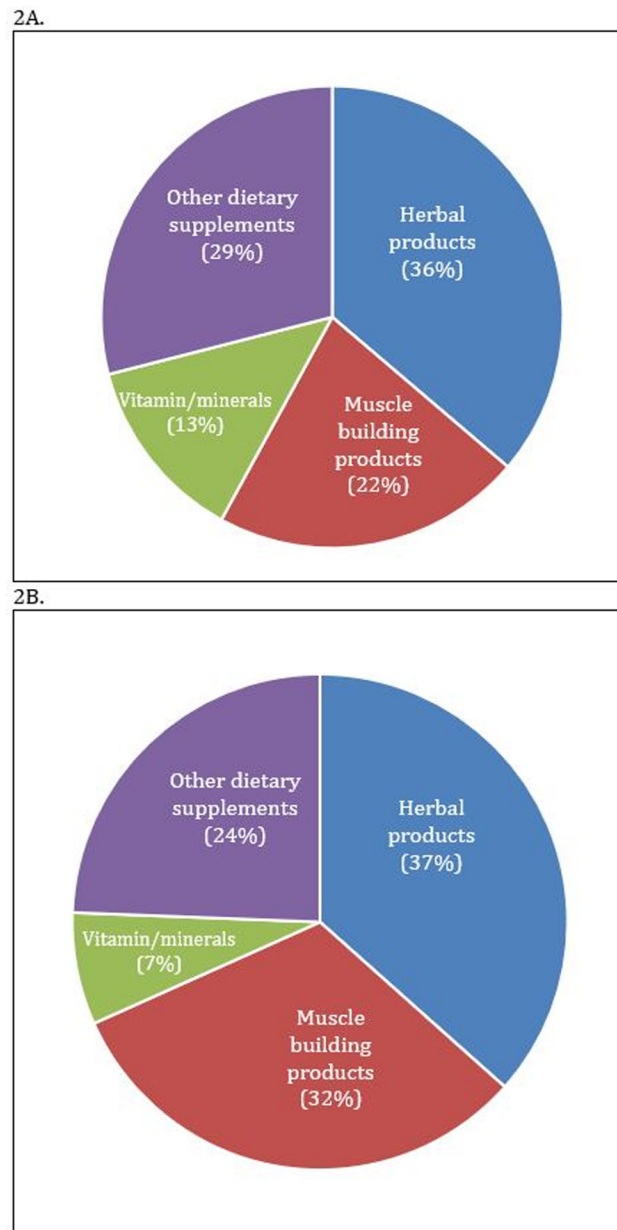


**Figure 1.**

Flow chart of AHN patient subgroups with drug induced liver injury (DILI).

Both the total number of patients in each group and the number transplanted are shown.

AHN: acute hepatic necrosis, HDS: herbal and dietary supplements, APAP: acetaminophen, LT: liver transplantation, WL: Waitlist



**Figure 2.** Breakdown of HDS products in waitlisted patients (A) and the subgroup of transplanted patients (B).

Use of muscle building HDS products were more frequent amongst the transplanted patient subgroup than the overall group of waitlisted patients.

HDS: Herbal and Dietary supplements

**Table 1.** Proportions of patients waitlisted for AHN who were transplanted based on cause of DILI.

Cause of DILI:	Waitlisted (n = 1,875)	Transplanted (n = 736)	P
Acetaminophen	1,371	426 (31.1%)	<0.001
Non-acetaminophen, non-HDS	435	269 (61.8%)	
HDS	69	41 (59.4%)	
Common categories of non-acetaminophen, non-HDS DILI:			0.83
Antituberculosis drugs <sup>1</sup>	88	52 (59.1%)	
Antibiotics <sup>2</sup>	75	50 (66.7%)	
Antiepileptic drugs <sup>3</sup>	66	39 (59.1%)	
Antineoplastic agents <sup>4</sup>	20	11 (55.0%)	
Nonsteroidal anti-inflammatory drugs (NSAIDs) <sup>5</sup>	20	12 (60.0%)	
Statins <sup>6</sup>	16	12 (75.0%)	
Antihypertensive drugs <sup>7</sup>	14	9 (64.3%)	
Antidepressants <sup>8</sup>	12	5 (41.7%)	
Antiretroviral therapy <sup>9</sup>	8	5 (62.5%)	
Azoles <sup>10</sup>	7	5 (71.4%)	
Common specific causes of non-acetaminophen, non-HDS DILI:			0.17
Isoniazid	81	49 (60.5%)	
Phenytoin	35	19 (54.3%)	
Propylthiouracil	23	15 (65.2%)	
Valproic acid	19	13 (68.4%)	
Trimethoprim/sulfamethoxazole	16	10 (62.5%)	
Disulfiram	14	13 (92.9%)	
Nitrofurantoin	14	12 (85.7%)	
Amoxicillin/clavulanic acid	12	7 (58.3%)	
Methotrexate	10	5 (50.0%)	

Tests for significance with chi-squared tests or Fisher exact tests.

- 1 Includes: isoniazid (n = 81), rifampin (n = 3), and combination or unspecified antituberculosis drugs (n = 4).
- 2 Includes: trimethoprim/sulfamethoxazole (n = 16), nitrofurantoin (n = 14), amoxicillin/clavulanic acid (n = 12), azithromycin (n = 5), amoxicillin (n = 4), ciprofloxacin (n = 3), doxycycline (n = 3), levofloxacin (n = 3), minocycline (n = 2), clarithromycin (n = 1), dapson (n = 1), moxifloxacin (n = 1), telithromycin (n = 1), trovafloxacin (n = 1), vancomycin (n = 1), and combination or unspecified antibiotics (n = 6).
- 3 Includes: phenytoin (n = 35), valproic acid (n = 19), carbamazepine (n = 6), lamotrigine (n = 2), felbamate (n = 1), levetiracetam (n = 1), and combination or unspecified antiepileptic drugs (n = 2).
- 4 Includes: methotrexate (n = 10), azathioprine or 6-mercaptopurine (n = 5), asparaginase (n = 1), cyclophosphamide (n = 1), mitotane (n = 1), and combination or unspecified antineoplastic agents (n = 2).
- 5 Includes: diclofenac (n = 4), aspirin (n = 3), ibuprofen (n = 3), bromfenac (n = 2), indomethacin (n = 1), nabumetone (n = 1), naproxen (n = 1), salicylate (n = 1), and combination or unspecified NSAIDs (n = 4).
- 6 Includes: atorvastatin (n = 3), cerivastatin (n = 3), simvastatin (n = 3), ezetimibe/simvastatin (n = 2), fluvastatin (n = 1), pravastatin (n = 1), or unspecified statin (n = 2).
- 7 Includes: methyl dopa (n = 6), diltiazem (n = 2), hydralazine (n = 2), lisinopril (n = 2), valsartan (n = 1), and unspecified antihypertensive drug (n = 1).
- 8 Includes: nefazodone (n = 5), paroxetine (n = 2), amitriptyline (n = 1), bupropion (n = 1), duloxetine (n = 1), and unspecified tricyclic antidepressant (n = 2).
- 9 Includes: efavirenz/emtricitabine/tenofovir (n = 3), efavirenz (n = 1), nevirapine (n = 1), and combination or unspecified antiretroviral therapies for HIV (n = 3).
- 10 Includes: ketoconazole (n = 5), albendazole (n = 1), and itraconazole (n = 1).

AHN: acute hepatic necrosis, DILI: drug-induced liver injury, HDS: herbal and dietary supplements

**Table 2.**

Characteristics of patients waitlisted for AHN due to HDS DILI vs non-HDS DILI.

	HDS DILI (n = 69)	Non-HDS DILI (n = 1,806)	P	Non-APAP, non-HDS DILI (n = 435)	P
Sex:					
Female	41 (59.4%)	1,357 (75.1%)		298 (68.5%)	
Male	28 (40.6%)	449 (24.9%)	0.003	137 (31.5%)	0.14
Age (years):					
Median [IQR]	38 [23.5–53.5]	31 [22–44]	0.03	43 [27–55]	0.17
19	10 (14.5%)	340 (18.8%)		58 (13.3%)	
20–29	14 (20.3%)	467 (25.9%)		68 (15.6%)	
30–39	12 (17.4%)	390 (21.6%)		63 (14.5%)	
40–49	13 (18.8%)	323 (17.9%)		88 (20.2%)	
50–59	13 (18.8%)	184 (10.2%)		97 (22.3%)	
60	7 (10.1%)	102 (5.7%)	0.12	61 (14.0%)	0.82
			P <sub>trend</sub> 0.02		P <sub>trend</sub> 0.24
Ethnicity:					
White	39 (56.5%)	1,250 (69.2%)		217 (49.9%)	
Black	6 (8.7%)	248 (13.7%)		110 (25.3%)	
Hispanic	8 (11.6%)	190 (10.5%)		63 (14.5%)	
Asian	12 (17.4%)	68 (3.8%)		28 (6.4%)	
Other	4 (5.8%)	50 (2.8%)		17 (3.9%)	0.001
Education beyond high school: <sup>1</sup>					
No	25 (47.2%)	712 (59.1%)		165 (56.7%)	
Yes	28 (52.8%)	492 (40.9%)	0.08	126 (43.3%)	0.20
Year listed:					
1994–1999	18 (27.3%)	410 (23.3%)		133 (31.2%)	
2000–2004	1 (1.5%)	371 (21.1%)		90 (21.1%)	
2005–2009	10 (15.2%)	419 (23.8%)		83 (19.4%)	
2010–2014	18 (27.3%)	311 (17.7%)		64 (15.0%)	
2015–2020	22 (31.9%)	295 (16.3%)	<0.001	65 (14.9%)	<0.001
			P <sub>trend</sub> 0.004		P <sub>trend</sub> 0.001
MELD score at listing <sup>2</sup> , median [IQR]	31 [26–37.5]	35 [29–41]	0.06	32 [27.5–39]	0.66

Tests for significance with chi-squared tests or Fisher exact tests for categorical variables, Kruskal-Wallis rank tests for continuous variables, and univariate logistic regression for trends.

<sup>1</sup>Missing for n = 618 patients (16 with HDS DILI and 602 with non-HDS DILI including 144 with non-APAP/non-HDS DILI).

<sup>2</sup>Available for patients waitlisted in 2002 onward only and additionally missing for n = 17 patients with non-HDS DILI (including n = 2 with non-APAP/non-HDS DILI) from those years.

AHN: acute hepatic necrosis, APAP: acetaminophen, DILI: drug-induced liver injury, HDS: herbal and dietary supplements, IQR: interquartile range, MELD = Model for End-stage Liver Disease

**Table 3.**

Characteristics of patients transplanted for AHN due to HDS DILI vs non-HDS DILI.

	HDS DILI (n = 41)	Non-HDS DILI (n = 695)	P	Non-APAP, non-HDS DILI (n = 335)	P
Sex:					
Female	26 (63.4%)	502 (72.2%)		182 (67.7%)	
Male	15 (36.6%)	193 (27.8%)	0.22	87 (32.3%)	0.59
Age (years):					
Median [IQR]	36 [24.5–52.5]	35 [25–47]	0.65	43 [27–54]	0.18
19	3 (7.3%)	82 (11.8%)		33 (12.3%)	
20–29	12 (29.3%)	179 (25.8%)		44 (16.4%)	
30–39	9 (22.0%)	152 (21.9%)		41 (15.2%)	
40–49	6 (14.6%)	145 (20.9%)		56 (20.8%)	
50–59	8 (19.5%)	81 (11.7%)		55 (20.5%)	
60	3 (7.3%)	56 (8.1%)	0.64	40 (14.9%)	0.24
			P <sub>trend</sub> 0.52		P <sub>trend</sub> 0.34
Ethnicity:					
White	22 (53.7%)	466 (67.1%)		140 (52.0%)	
Black	4 (9.8%)	119 (17.1%)		70 (26.0%)	
Hispanic	6 (14.6%)	66 (9.5%)		33 (12.3%)	
Asian	7 (17.1%)	21 (3.0%)		15 (5.6%)	
Other	2 (4.9%)	23 (3.3%)	0.001	11 (4.1%)	0.03
Education beyond high school: <sup>1</sup>					
No	14 (40.0%)	269 (54.7%)		100 (52.9%)	
Yes	21 (60.0%)	223 (45.3%)	0.09	89 (47.1%)	0.16
Year transplanted:					
1994–1999	6 (15.4%)	125 (18.6%)		71 (27.0%)	
2000–2004	1 (2.6%)	131 (19.4%)		53 (20.2%)	
2005–2009	4 (10.3%)	178 (26.4%)		56 (21.3%)	
2010–2014	15 (38.5%)	139 (20.6%)		46 (17.5%)	
2015–2020	15 (36.6%)	122 (17.6%)	<0.001	43 (16.0%)	<0.001
			P <sub>trend</sub> 0.001		P <sub>trend</sub> <0.001
MELD score at listing <sup>2</sup> , median [IQR]	31.5 [28–37]	37 [30–42]	0.02	33 [29–40]	0.37
MELD score at transplant <sup>3</sup> , median [IQR]	35 [30–42.25]	36 [29–41]	0.70	34 [29–41]	0.38

Tests for significance with chi-squared tests or Fisher exact tests for categorical variables, Kruskal-Wallis rank tests for continuous variables, and univariate logistic regression for trends.

<sup>1</sup>Missing for n = 209 patients (6 with HDS DILI and 203 with non-HDS DILI including 80 with non-APAP/non-HDS DILI).

<sup>2</sup>Available for patients waitlisted in 2002 onward only and additionally missing for n = 4 patients with non-HDS DILI due to APAP from those years.



<sup>3</sup> Available for patients waitlisted in 2002 onward only and additionally missing for n = 4 patients with non-HDS DILI due to APAP from those years.

AHN: acute hepatic necrosis, APAP: acetaminophen, DILI: drug-induced liver injury, HDS: herbal and dietary supplements, IQR: interquartile range, MELD = Model for End-stage Liver Disease

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**Table 4.**

Multivariate predictors of HDS as the cause of DILI-related AHN requiring waitlisting.

	Odds of HDS as cause of DILI-related AHN			Odds of HDS as cause of non-APAP DILI-related AHN		
	OR	95% CI	P	OR	95% CI	P
Age (per year)	1.02	0.99–1.03	0.06	0.98	0.96–0.99	0.02
Year listed (per year, after 1994)	1.05	1.01–1.08	0.009	1.07	1.03–1.11	<0.001
Sex:	1.00 (ref)			1.00 (ref)		
Female	2.10	1.26–3.46	0.004	1.25	0.72–2.16	0.42
Male						
Ethnicity:	1.00 (ref)			1.00 (ref)		
White	0.78	0.32–1.86	0.57	0.29	0.11–0.73	0.008
Black	1.36	0.61–2.97	0.45	0.65	0.28–1.50	0.31
Hispanic	5.09	2.50–10.33	<0.001	2.09	0.95–4.56	0.07
Asian	2.59	0.87–7.62	0.09	1.38	0.42–4.49	0.59
Other						

AHN: acute hepatic necrosis, APAP: acetaminophen, DILI: drug-induced liver injury, HDS: herbal and dietary supplements

**Table 5.**

Multivariate predictors of HDS as the cause of transplantation for DILI-related AHN.

	Odds of HDS as cause of DILI-related AHN transplant			Odds of HDS as cause of non-APAP DILI-related AHN transplant		
	OR	95% CI	P	OR	95% CI	P
Age (per year)	1.00	0.97–1.02	0.95	0.98	0.95–1.00	0.05
Year listed (per year, after 1994)	1.09	1.03–1.15	0.001	1.11	1.05–1.17	<0.001
Sex:						
Female	1.00 (ref)			1.00 (ref)		
Male	1.52	0.77–3.01	0.22	0.98	0.47–2.03	0.96
Ethnicity:						
White	1.00 (ref)			1.00 (ref)		
Black	0.71	0.23–2.13	0.55	0.38	0.12–1.20	0.10
Hispanic	1.79	0.68–4.65	0.23	1.14	0.41–3.16	0.80
Asian	5.84	2.18–15.60	<0.001	2.45	0.85–7.02	0.10
Other	1.79	0.38–8.32	0.46	1.31	0.24–6.95	0.75

AHN: acute hepatic necrosis, APAP: acetaminophen, DILI: drug-induced liver injury, HDS: herbal and dietary supplements

**Table 6.**

One-year transplant-free survival of patients transplanted for AHN due to DILI.

	n surviving / N	Survival (%)	Univariate P	Multivariate odds of 1-year transplant-free survival		
				OR	95% CI	P
Cause of DILI:			0.048			
Acetaminophen	304 / 411	74.0%		1.00 (ref)		
Non-acetaminophen, non-HDS	207 / 263	78.7%		1.54	1.02–2.32	0.04
HDS	35 / 39	89.7%		2.07	0.81–5.28	0.13
Sex:			0.18			
Female	386 / 513	75.2%		1.00 (ref)		
Male	160 / 200	80.0%		1.21	0.82–1.80	0.33
Age (years):			0.22			
19	55 / 83	66.3%		0.65	0.36–1.15	0.14
20–29	143 / 183	78.1%		1.00 (ref)		
30–39	120 / 158	76.0%		0.99	0.60–1.64	0.98
40–49	116 / 146	79.5%		1.05	0.62–1.76	0.86
50–59	69 / 85	81.2%		0.88	0.46–1.66	0.69
60	43 / 58	74.1%		0.73	0.36–1.48	0.39
Ethnicity:			0.61			
White	362 / 473	76.5%		1.00 (ref)		
Black	86 / 119	72.3%		0.69	0.43–1.09	0.11
Hispanic	57 / 69	82.6%		1.39	0.74–2.61	0.30
Asian	21 / 27	77.8%		0.69	0.26–1.77	0.44
Other	20 / 25	80.0%		1.18	0.42–3.30	0.75
Education beyond high school: <sup>1</sup>			0.997	Excluded from model		
No	211 / 271	77.9%				
Yes	183 / 235	77.9%				
Year transplanted:			<0.001			
1994–1999	95 / 131	72.5%		0.99	0.56–1.74	0.98
2000–2004	84 / 132	63.6%		0.72	0.42–1.23	0.23
2005–2009	136 / 182	74.7%		1.20	0.71–2.01	0.48
2010–2014	134 / 154	87.0%		2.72	1.47–5.03	0.001
2015–2019	99 / 137	72.3%		1.00 (ref)		

Excluded patients transplanted in 2020 due to &lt;1 year follow-up available (n = 23).

Tests for significance with chi-squared tests or Fisher exact tests for univariate comparisons and logistic regression for multivariate model.

<sup>1</sup>Missing for n = 207 patients including 152 who were transplanted.

AHN: acute hepatic necrosis, DILI: drug-induced liver injury, HDS: herbal and dietary supplements