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Authors

Rubin, Jessica B
Hameed, Bilal
Gottfried, Michelle
et al.

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Acetaminophen-induced Acute Liver Failure is More Common and More Severe in Women

Jessica B. Rubin¹, Bilal Hameed¹, Michelle Gottfried², William M. Lee³, and Monika Sarkar¹
for the Acute Liver Failure Study Group

¹Division of Gastroenterology and Hepatology, Department of Medicine, University of California San Francisco (UCSF), San Francisco, CA

²Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC

³Division of Digestive and Liver Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX

Abstract

Background & Aims—Acetaminophen overdose is the leading cause of acute liver injury (ALI) and acute liver failure (ALF) in the developed world. Sex differences in acetaminophen-induced hepatotoxicity have not been described.

Methods—We collected data from the Acute Liver Failure Study Group cohort, a national registry of 32 academic medical centers in North America of adults with ALI or ALF, including 1162 patients with acetaminophen-induced ALI (n=250) or acetaminophen-induced ALF (n=912) from January 2000 through September 2016. We analyzed data on patient presentation, disease course, demographics, medical and psychiatric history, medication use, substance use, and details of acetaminophen ingestion. Sex differences in continuous and categorical variables were evaluated by Wilcoxon rank-sum and χ^2 analysis or the Fisher exact test. Our primary aim was to evaluate sex differences in the presentation and clinical course of acetaminophen-induced acute liver injury or liver failure, and our secondary goal was to compare overall and transplant-free survival between sexes.

Correspondence: Monika Sarkar, MD, MAS, University of California, San Francisco, Division of Gastroenterology and Hepatology, 513 Parnassus Ave, Room S-357, San Francisco, CA 94143-0358, Phone: 415-502-2656, Fax: 415-476-0659, monika.sarkar@ucsf.edu.

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Author contributions:

Rubin: study concept and design, analysis and interpretation of data, drafting and revision of the manuscript, critical revision of the manuscript for important intellectual content

Hameed: study concept and design, acquisition of data, analysis and interpretation of data, study supervision

Gottfried: statistical analysis

Lee: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision

Sarkar: study concept and design, analysis and interpretation of data, drafting and revision of the manuscript, critical revision of the manuscript for important intellectual content, study supervision

Results—Most patients with acetaminophen-induced ALI (68%) or ALF (76%) were women. Higher proportions of women than men had psychiatric disease (60% of women vs 48% of men, $P < .01$) and had co-ingestion with sedating agents (70% of women vs 52% of men, $P < .01$)—more than half of which were opioids. Higher proportions of women had severe hepatic encephalopathy (HE) (68% of women vs 58% of men), and required intubation (67% of women vs 59% of men, P values $< .03$). Higher proportions of women used vasopressors (26% of women vs 19% of men, $P = .04$) or mannitol (13% of women vs 6% of men, $P < .01$); proportions of male vs female patients with transplant-free survival were similar (68%). On adjusted analysis, women had higher risk of severe HE (adjusted odds ratio [AOR], 1.66; 95% CI, 1.17–2.35). We found a significant interaction between sex and co-ingestion of sedating agents ($P < .01$); co-ingestion increased odds of severe HE in women 2-fold (AOR, 1.86; 95% CI, 1.28–2.69; $P < .01$) but not in men (AOR; 0.62, 95% CI 0.34–1.13; $P = .12$).

Conclusion—In an analysis of the Acute Liver Failure Study Group cohort, we found acetaminophen-induced ALI and ALF to be more common among women. Women have greater critical care needs than men, and increased risk for severe HE, which could be due in part to increased use of sedatives. Future studies should investigate sex differences in acetaminophen metabolism and hepatotoxicity, particularly among users of opioids.

Keywords

APAP; ALFSG; Tylenol; paracetamol; gender; narcotics

Acetaminophen is one of the most commonly consumed medications worldwide, either alone or in combination with other over the counter or prescription products, including opioids (1). In the United States (US), 82,000 emergency room visits and 26,000 hospitalizations are attributed to acetaminophen overdose annually (2,3). Acetaminophen toxicity is also the leading cause of acute liver injury (ALI) and acute liver failure (ALF) in the US, accounting for approximately 50% of all ALF cases. Given the clinical implications of this disease, as well as the growing opioid epidemic in the United States, it is essential to identify those at highest risk.

Sex differences in the epidemiology and natural history of many diseases are evident, with growing adoption of sex-based models of care for medical conditions outside the realm of hepatology (4–6). Sex differences are also described in the presentation and clinical course of many liver diseases (7), including a higher risk of ALF in women for many etiologies (8–11). Prior data on sex and ALF outcomes have largely focused on idiopathic drug injury (DILI), where women are noted to be at increased risk of progression to ALF (12). The reasons for increased prevalence and severity of DILI in women are not clear, though may relate to greater use of hepatotoxic medications in women (1, 13), and differential drug metabolism by sex (14). Despite apparent sex differences in the prevalence and progression of other etiologies of ALF, less is known regarding the natural history of acetaminophen-induced ALF in men and women.

Using data from the prospective, multi-center Acute Liver Failure Study Group (ALFSG) cohort we aimed to evaluate sex differences in the presentation and clinical course of acetaminophen-induced ALI and ALF, and to secondarily compare overall and transplant-

free survival by sex. Understanding the differential risk and clinical course of acetaminophen-induced ALI and ALF in men and women could help to reduce the burden of disease, while optimizing the management of those that progress to liver failure.

PATIENTS AND METHODS

Study Population

We evaluated differences in presentation and clinical course between men and women with acetaminophen-induced ALI and ALF within the ALFSG. The ALFSG is a national registry of 32 academic medical centers in North America designed to examine clinical data and outcomes in adults with ALI and ALF. Detailed study protocols are previously described (15). ALI was defined as acute hepatic illness <2 weeks with international normalized ratio (INR) ≥ 2.0 , as well as alanine aminotransferase (ALT) >10 times the upper limit of normal and total serum bilirubin >3 mg/dL, without encephalopathy. ALF was defined by an INR of ≥ 1.5 , disease duration of <26 weeks, the absence of prior chronic liver disease, with the presence of hepatic encephalopathy. Patients with acetaminophen overdose between January 1, 2000 and September 27, 2016 were included in the current study. Acetaminophen was determined to be the etiology of ALI or ALF if there was a history of potentially toxic acetaminophen ingestion within a week of presentation, detection of any level of acetaminophen in the serum, or ALT >1000 IU/L with any history of acetaminophen ingestion irrespective of acetaminophen level. Per institutional review board guidelines, informed consent was obtained from patients or next of kin prior to enrollment. Patients with missing or unknown 21-day follow-up status, or liver transplant prior to study enrollment, were excluded.

Data Collection

Patient demographics (age, sex, race, and ethnicity), medical and psychiatric history, medication use, substance use (alcohol and illicit drugs), and acetaminophen ingestion details (suicidal intent, dose, timing, co-ingestions), were obtained at study entry from the patient or primary contact, as history was limited by hepatic encephalopathy in most patients. Data were often corroborated with patient after recovery. The case report forms also allowed investigators to describe other medical or psychiatric illnesses. Check boxes were available on data collection forms for most major medical/psychiatric conditions. Endocrine disorders reflected a single check box for any endocrine disorder (such as diabetes). Psychiatric medications included antidepressants, antipsychotics, and non-benzodiazepine anxiolytics. Heavy alcohol use was defined as >14 drinks per week within the past 6 months. Co-ingestions were considered those combining acetaminophen with other medications with sedating properties including opioids, benzodiazepines, and diphenhydramine. Intentionality was defined as a probable suicide attempt if a large quantity of acetaminophen was ingested at single time point or if suicidal intent was acknowledged by the patient or surrogate. Physical exam, laboratory values, and details of hospital course were obtained by study coordinators daily for seven days, or until day of discharge if prior to seven days. "Pre-study" data reflects peak labs values or clinical interventions performed at outside hospitals prior to ALFSG enrollment. These data were captured when available (in approximately 80% of patients). Seven-day follow up reflects cumulative interventions through day 7 post-

enrollment or through hospital discharge if patient discharged before day 7. Hepatic encephalopathy (HE) was graded 1 to 4 by the West Haven criteria; with grade 1 defined as mild changes in sensorium to grade 4 defined as coma (16). The King's College criteria for acetaminophen-induced ALF were defined as having an arterial pH <7.30 or all 3 of the following: (1) grade 3 or 4 encephalopathy; (2) prothrombin time >100 seconds (INR >6.5); and (3) serum creatinine >3.4 mg/dL (17). Standard 21-day outcome data captured by the ALFSG includes death, listing for liver transplant, transplant-free and overall patient survival.

Statistical Analysis

Descriptive statistics were used to describe demographics, clinical characteristics, and outcomes. Continuous variables were reported as medians with interquartile ranges (IQR) due to non-normal distributions. Sex differences in continuous and categorical variables were evaluated by Wilcoxon rank-sum and Chi Square or Fisher exact test, respectively. All tests were 2-sided and p values <0.05 were considered significant. Multivariate models were performed using logistic regression with backward covariate selection. Variables were also excluded from the multivariable model if there was substantial missing data. We evaluated for interactions between sex and relevant clinical characteristics, with interaction p values of 0.10 considered statistically significant. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Demographics and Co-Morbidities

Among the 1162 patients with acetaminophen toxicity enrolled between January 2000 and September 2016, 250 (22%) had acetaminophen-induced ALI and 912 (78%) had acetaminophen-induced ALF. There were 17 patients in the cohort that presented with ALI and progressed to ALF who were analyzed only within the ALF group. Of patients in the ALFSG cohort with either acetaminophen-induced ALI or ALF, 864 (74%) were women, including 170 (68%) of the ALI patients and 694 (76%) of the ALF patients.

Table 1 displays the baseline demographics, medical comorbidities, and ingestion characteristics for patients with acetaminophen-induced ALF stratified by sex. Women were older than men, with a median age of 37 (IQR 29–47) versus 33 (IQR 25–45) years ($p<0.01$). The racial/ethnic distribution was similar by sex, with the majority (85%) of the cohort being white, and approximately 7% of all racial groups reporting Hispanic ethnicity. A greater proportion of women than men reported over 12 years of formal education (42% vs 28%, $p=0.01$).

Regarding co-morbid conditions, women with acetaminophen-induced ALF were more likely to have psychiatric disease (60% vs 48%, $p<0.01$) and were more likely to be taking psychiatric medications (42% vs 25%, $p<0.001$). Half of patients with psychiatric comorbidities had depression (52% in men, 48% in women), and an additional 15% had anxiety or a combination of anxiety and depression. Distribution of psychiatric illnesses did not differ between men and women ($p=0.62$). Regarding substance use, men were more

likely to have a history of intravenous drug use (15% vs 7%, $p<0.01$). Alcohol data were missing in 66% of the cohort, although a higher proportion of men than women reported recent heavy use (39% vs 19%, $p<0.01$). Endocrine disorders were more common in women (60% vs 48%, $p<0.001$), and a similar proportion (~ 25%) of men and women were obese (BMI >30).

Characteristics of Acetaminophen Use

Approximately half of patients with acetaminophen-induced ALF had unintentional acetaminophen overdose (53%), while 40% were suicide attempts (unknown intentionality in remaining 7%). Rates of suicide attempt were similar between men and women (44% and 38%, respectively, $p=0.15$). In those using acetaminophen for therapeutic purposes, acetaminophen use was more often self-initiated (77%) than recommended by physicians (23%); this was similar for men and women $p=0.19$. Only 15% of patients provided indications for acetaminophen use, of whom 42% reported use for chronic pain and 28% for acute pain, which was also similar by sex ($p=0.5$). There was no sex difference in reported total acetaminophen dose, even when adjusted for body weight ($p=0.57$). Interestingly, in women first acetaminophen level was performed a median of 48 hours (IQR 24–72) after acetaminophen ingestion, compared to 24 hours (IQR 24–72) in men ($p=0.088$), though median time to transfer to transplant center, and median time from symptom onset to either initial hospitalization or maximum HE were similar (p values >0.2). At the time of study enrollment, 90% of all patients had been started on N-acetyl cysteine.

Co-Ingestions

A greater proportion of women had co-ingestions with either opioids, benzodiazepines or diphenhydramine (70% vs 52%, $p<0.001$). This was true for patients with and without suicide attempts. Interestingly, the prevalence of co-ingestions was lower in patients with documented suicide attempts, compared to those without (43% vs 65%, $p<0.001$). Just over half of co-ingestions in women reflected opioid use, and all individual co-ingestion categories were more common in women than men (Figure 1). Approximately 25% of patients used a combination of sedating medications.

Clinical Characteristics by Sex

Pre-study peak, study entry, and peak clinical characteristics by sex are shown in Table 2. At all time points, men had higher median ALT, bilirubin, creatinine, albumin and model for end-stage liver disease (MELD) scores, and lower sodium levels than women (p values 0.02). However, weight adjust ALT was similar between men and women (55.2 vs 51.8, $p=0.23$). Women had lower phosphorus levels at study entry ($p<0.01$) and follow-up ($p=0.06$), and lower study entry pH levels ($p=0.04$). INR, ammonia, acetaminophen, glucose, and lactate levels were not significantly different by sex (p values 0.06). A higher proportion of men met Kings College Criteria at study entry, although this did not reach statistical significance ($p=0.09$).

Regarding complications of ALF, women were more likely to have high-grade hepatic encephalopathy (grade 3–4) at study entry (58% vs 42%) and during the 7-day follow-up period (68% vs 58%, p values <0.01) (Figure 2). Likewise, women were more likely to be

intubated at study entry (60% vs 45%, $p<0.001$) and during follow-up (67% vs 59%, $p=0.03$). Vasopressor (26% vs 19%, $p=0.04$) and mannitol use (13% vs 6%, $p<0.01$) were also greater at study entry in women. Mannitol (22% vs 17%, $p=0.09$) and antibiotic use (14% vs 9%, $p=0.06$) were also more commonly used in women during follow-up. Despite these greater critical care needs in women, length of intensive care unit stay was similar by sex ($p=0.29$).

Risk of Severe Hepatic Encephalopathy

Given marked sex differences in prevalence of severe HE (grade 3–4), we evaluated whether female sex was an independent predictor of severe HE at study entry and follow-up. On univariate analysis, female sex was associated with increased risk of severe HE at both study entry (OR 1.95, 95% CI 1.43–2.67, $p<0.01$) and follow-up (OR 1.60, 95% CI 1.17–2.20, $p<0.01$). Covariates associated with severe HE are shown in Table 3, which included co-ingestion use at study entry (OR 1.64, 95% CI 1.24–2.18, $p<0.01$). On multivariate analysis the odds of severe HE remained significantly higher in women than men at both study entry (AOR 1.78, 95% CI 1.28–2.51, $p<0.01$) and follow-up (AOR 1.66, 95% CI 1.17–2.35, $p<0.01$), independent of age, co-ingestions, study entry MELD, and ALT levels. Importantly, we identified a significant interaction between sex and co-ingestions (study entry $p=0.1$; follow up $p<0.01$). On adjusted analysis, co-ingestions in women conferred a nearly two-fold higher odds of severe HE at both study entry (AOR 1.81, 95% CI 1.26–2.59, $p<0.01$) and follow-up (AOR 1.86, 95% CI 1.28–2.69, $p<0.01$). In contrast, there was no significant difference in risk of severe HE in men by co-ingestion history at either study entry (AOR 1.03, 95% CI 0.57–1.84, $p=0.93$) or follow-up (AOR 0.62, 95% CI 0.34–1.13, $p=0.12$).

Overall and Transplant Free Survival

Clinical outcomes at day 21, stratified by sex, are shown in Figure 3. The majority of patients with acetaminophen-induced ALF (75%) were alive at 21 days. Approximately 20% of patients were listed for liver transplant, 35% of which received a transplant. The median time to transplantation was 2.0 days. There were no significant sex differences in overall or transplant-free survival at 21 days (p values = 0.57).

DISCUSSION

In this large U.S. cohort, we identified novel sex differences in the presentation and clinical course of acetaminophen-induced ALI and ALF. Importantly, nearly three quarters of patients with acetaminophen overdose were women. Moreover, women with acetaminophen-induced ALF were more likely to present with high-grade hepatic encephalopathy and to have critical care needs at both study entry and throughout hospitalization. Co-ingestions with sedating agents were not only more common in women, but also contributed to their greater risk for severe HE.

Prior data on sex differences in ALF have largely focused on idiosyncratic (non-acetaminophen) drug-induced liver injury (DILI), suggesting that women may be more sensitive to hepatotoxicity. Women are more likely to present with DILI-induced ALF (12) and to require subsequent liver transplant (18). While recent studies have questioned

whether women are systematically at greater risk of hepatotoxicity (11, 19), it is clear that women are more likely to progress to DILI-induced ALF, and to have increased susceptibility to hepatotoxicity caused by specific medications (11, 20–22).

A striking finding in the current study was the higher prevalence of co-ingestions in women, most notably with combination opioid-acetaminophen products. These results have important public health implications in light of the current opioid epidemic in the US (23–25), particularly among younger Americans (23, 26). According to NHANES, 2 million Americans adults report using acetaminophen plus an opioid combination with acetaminophen (13). In a 2015 study of patients with new acetaminophen-containing prescriptions, less than one third were aware that their medication contained acetaminophen. Moreover, acetaminophen was identified on the primary container label by the full name “acetaminophen” on only one in 14 prescriptions (27). In a US-based study of patients interviewed about their knowledge of over the counter acetaminophen-containing products, less than half were aware of potential risks of overdose by combining products (28). More transparency in medication labeling as well as greater patient education regarding combination drug ingredients may help to reduce the morbidity and mortality associated with acetaminophen hepatotoxicity.

In the current study, women were not only more likely to ingest sedating agents but the risk of severe HE was nearly 2-fold higher among women with co-ingestions as compared to those without. This increased risk by co-ingestion history was not evident in men. Prior data from the ALFSG have shown that acetaminophen in combination with opioids resulted in higher-grade encephalopathy than acetaminophen/diphenhydramine or acetaminophen alone (29). However, despite greater co-ingestion use in the current study, female sex remained independently associated with severe HE at both study enrollment and follow-up. This suggests that factors beyond their greater co-ingestion use are at play, and could potentially reflect factors such as differences in acetaminophen metabolism by sex or differential patterns of acetaminophen use (14, 30, 31).

In humans, acetaminophen clearance has been shown to be 22% greater in men than women due to increased glucuronidation activity in men (30), a key enzyme in acetaminophen metabolism (31). These sex differences in glucuronidation activity are mitigated by oral contraceptive use, suggesting a potential hormonal contribution (30). Studies from both the US and Europe have also shown that women across age groups are more likely to use prescription and over-the-counter analgesics than men (1, 13, 32, 33). Data from the US-based National Health and Nutrition Examination Survey (NHANES) from 1988–2004 found that women in the US were more likely to use acetaminophen for pain, while men were more likely to use aspirin. In this study women were also more likely to use OTC analgesics on a regular basis (13).

Women in the current study were more likely to have psychiatric disease, including anxiety and depression. Prior data from this cohort evaluating detailed psychiatric history found that rates of psychiatric illness in acetaminophen-induced ALF patients were higher than in the general population, in both intentional and unintentional overdoses (34). In our cohort, suicidal intent was approximately 40% overall, and similar by sex. Acetaminophen dosage

adjusted by weight and acetaminophen levels were also similar. Timing from ingestion to first acetaminophen measurement did vary by sex, with women having first levels drawn a median of 48 hours after ingestion, compared to 24 hours in men. Hepatotoxicity in women may have been recognized later than in men, leading to later and more severe illness on presentation or referral to tertiary care centers. Although there were no reported differences in time from symptom onset to initial hospitalization or in time to transfer to transplant center, data from outside hospitals prior to study enrollment are limited.

There are several notable limitations of the current study, including variable timing from outside hospital presentation to study enrollment. Details on outside hospital clinical parameters and interventions are not always recorded, such as timing from initial presentation to NAC administration, although approximately 90% of all patients were on NAC at the time of study enrollment. Though NAC use was not reported in 10% of suspected acetaminophen-induced ALF cases, this is likely due to underreporting of NAC in certain centers, particularly prior to 2010, which has been identified in prior ALFSG analyses (data not shown). Underlying hepatic encephalopathy may also affect patient recall, including amount, timing, and co-ingestions details, although this information was extracted from medication records and/or patient families, then later verified with patients in most cases. Acetaminophen levels were missing on approximately one third of patients, and alcohol history was missing in 66% of the cohort, the latter of which is a known P450 inducer that increases production of the toxic acetaminophen metabolite N-acetyl-p-benzoquinone imine (NAPQI) (35). Despite these limitations, the ALFSG is the largest cohort of patients with acetaminophen-induced ALI and ALF to date, providing daily serologic and clinical measures, which allowed us to capture novel differences in the clinical course of acetaminophen-induced ALF between men and women. These findings can help to inform risk in women with combination acetaminophen and sedative use, and support the need for more restrictive use of opiates, particularly when used in combination with acetaminophen.

In summary, women comprise near three-quarters of patients presenting with acetaminophen-induced ALI and ALF in the United States. Women with acetaminophen-induced ALF have greater critical care needs than men, including more severe encephalopathy. These findings may help to guide inpatient management of women with acetaminophen hepatotoxicity, including consideration for earlier transfer to intensive care units, and aggressive monitoring of neurologic status. Importantly, co-ingestions are more common in women with acetaminophen-induced ALF, which differentially increases their risk of high-grade encephalopathy. In light of the current opioid epidemic, there is a greater need for awareness of the risk of combination acetaminophen-opioid agents in the outpatient setting, which differentially affects the morbidity of women with acetaminophen-induced ALF.

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Abbreviations

ALF	acute liver failure
ALFSG	Acute Liver Failure Study Group
ALI	acute liver injury
ALT	alanine aminotransferase
AOR	adjusted odds ratio
CI	confidence interval
DILI	drug-induced liver injury
HE	hepatic encephalopathy
INR	international normalized ratio
IQR	interquartile range
MELD	model for end-stage liver disease
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
US	United States

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LAY SUMMARY

Women are more likely than men to have liver failure from acetaminophen (Tylenol, paracetamol) overdose. Women are also more likely to develop changes in mental status requiring more intensive medical care, particularly in those with concurrent opioid use.

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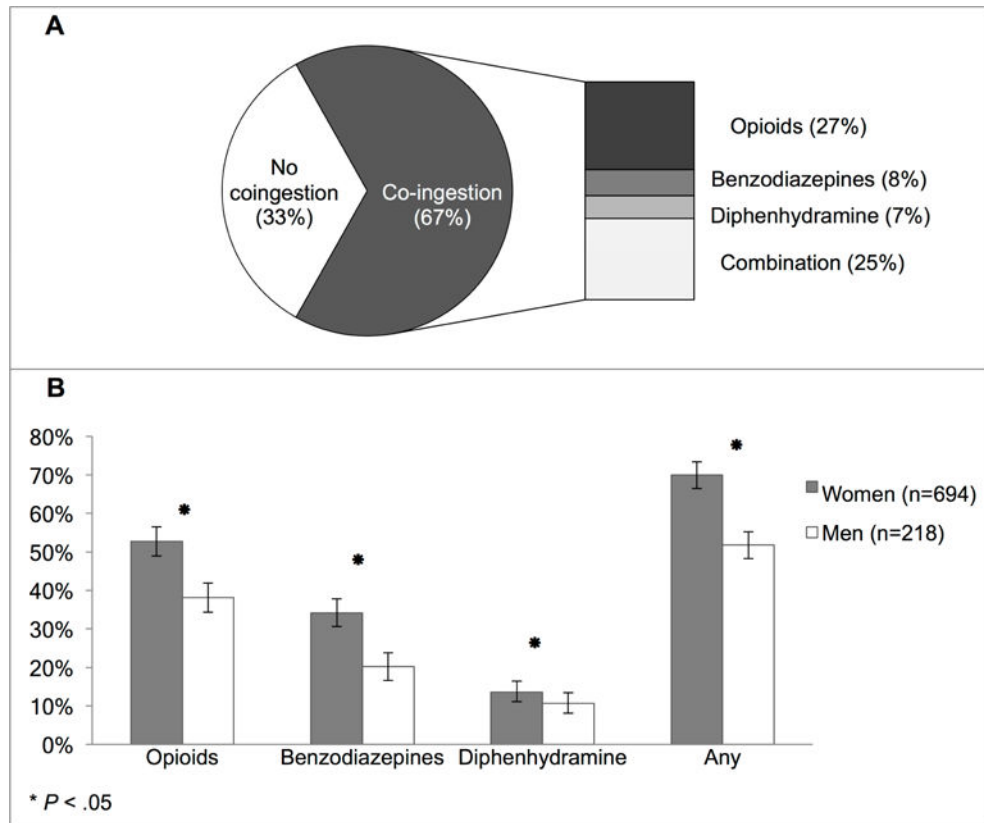


Figure 1. Co-ingestion with sedating medications in acetaminophen-induced ALF (A) Proportion with co-ingestion, by type. (B) Proportion with any sedating medication use, by sex.

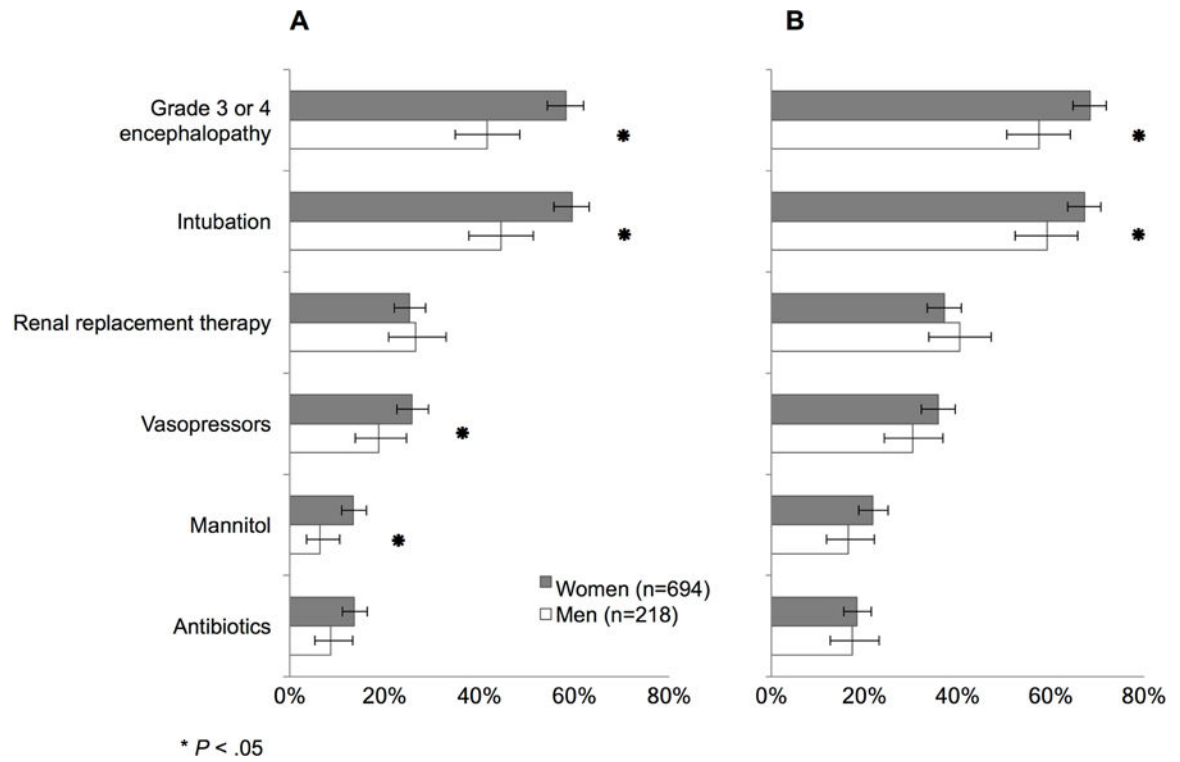


Figure 2. Clinical characteristics in acetaminophen-induced ALF by sex at (A) study entry (B) during cumulative 7-day follow up.

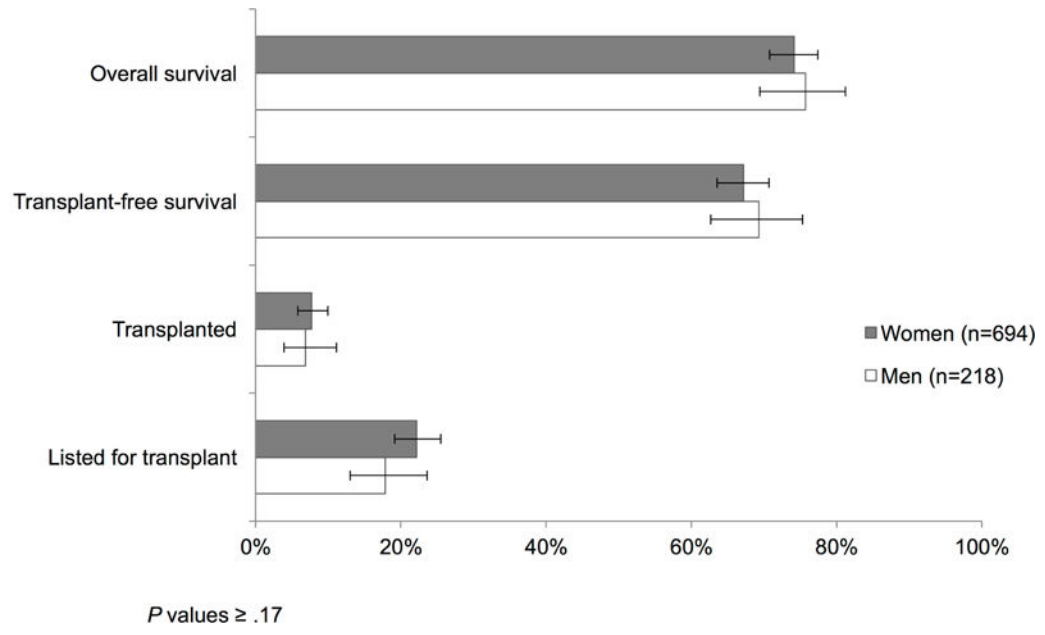


Figure 3. Clinical outcomes for acetaminophen-induced ALF at 21 days, by sex.

Table 1

Baseline Demographics, Comorbidities, and Ingestion Characteristics for Acetaminophen-Induced ALF By Sex

	Women (n = 694)	Men (n = 218)	p value
Median age (IQR), years	37 (29–47)	33 (25–45)	0.0015
Race			
White	589 (84.9)	182 (83.5)	0.84
Black	58 (8.4)	21 (9.6)	
Other	47 (6.8)	15 (6.9)	
Hispanic ethnicity	42 (6.1)	18 (8.3)	0.25
Years of education ^I			
0–7	5 (1.2)	3 (2.4)	0.014
8–12	234 (56.4)	88 (69.3)	
>12	176 (42.4)	36 (28.4)	
US census region			
Northeast	102 (14.7)	38 (17.4)	0.34
South	184 (26.5)	54 (24.8)	
Midwest	162 (23.3)	61 (28.0)	
West	233 (33.6)	60 (27.5)	
Canada	13 (1.9)	5 (2.3)	
Comorbidities (ever)			
Psychiatric disease	415 (60.0)	104 (47.7)	0.0014
Intravenous drug use	49 (7.1)	31 (14.5)	0.0010
Hypertension	93 (13.4)	26 (11.9)	0.56
Endocrine	102 (14.7)	16 (7.3)	0.0046
Heart disease	41 (5.9)	11 (5.1)	0.63
BMI ≥ 30 (Obesity) ^I	139 (24.3)	44 (24.4)	0.9687
Alcohol intake, drinks per week ^I			
0–6	170 (72.3)	36 (52.2)	0.0017
7–14	21 (8.9)	6 (8.7)	
>14	44 (18.7)	27 (39.1)	
Psychiatric medication use (per patient report)	289 (42.3)	54 (24.9)	<0.001
Oral contraceptive use	38 (5.5)	–	–
Hormone replacement therapy use	37 (5.4)	1 (0.5)	0.0016
Intentionality			
Suicide attempt	254 (38.4)	88 (43.6)	0.15

	Women (n = 694)	Men (n = 218)	p value
Unintentional	350 (53.0)	104 (51.5)	
Unknown	57 (8.6)	10 (4.9)	
Initiation of therapeutic acetaminophen use¹			
Physician recommended	69 (24.7)	15 (17.9)	0.19
Self-initiated	210 (75.3)	69 (82.1)	
Therapeutic intent^{1,2}			
Acute pain	28 (26.7)	10 (30.3)	0.48
Infectious process	9 (8.6)	1 (3.0)	
Sub-acute pain	22 (21.0)	10 (30.3)	
Chronic pain	46 (43.8)	12 (36.4)	
Median reported acetaminophen dose (IQR), <i>mg</i>	14,950 (4,000–36,000)	20,000 (5,000–50,000)	0.095
Median weight-adjusted acetaminophen dose (IQR), <i>mg/kg</i>	226.3 (57.4–523.3)	235.4 (59.2–595.2)	0.57
Median time from ingestion to acetaminophen level (IQR), <i>hours</i>	48 (24–72)	24 (24–72)	0.088
Median time from symptom onset to initial hospitalization (IQR), <i>hours</i>	24 (0–72)	24 (0–48)	0.56
Median time from symptom onset to maximum HE (IQR), <i>hours</i>	168 (96–216)	168.0 (96–216)	0.79
Median time from initial hospitalization to transfer to transplant center (IQR), <i>days</i>	4.9 (4.5–5.3)	4.8 (4.5–5.3)	0.26

NOTE: data shown are number (percentage) unless otherwise indicated

ALF = acute liver failure; IQR = interquartile range; BMI = body mass index; HE = hepatic encephalopathy

¹Incomplete data for these variables: for education level n = 542, for BMI >30 n = 752, for Alcohol intake n = 304, for Initiation of APAP use n = 363, for Therapeutic intent n = 138

²Acute pain = <1 week of symptoms, Sub-acute pain = 1–4 weeks of symptoms, Chronic pain = >4 weeks of symptoms

Table 2

Clinical Parameters for Acetaminophen-Induced ALF By Sex

	Women (n = 694)	Men (n = 218)	p value
<i>ALT, IU/L</i>			
Pre-study peak	4556 (2261–7595)	5374 (2545–9374)	0.017
Study entry	3406 (1845–5605)	4506 (2572–7115)	<0.001
Study peak	3865 (2113–6210)	4999 (2764–7825)	<0.001
<i>AST, IU/L</i>			
Pre-study peak	6125 (2663–10,314)	6364 (3156–11,044)	0.41
Study entry	3473 (1302–7578)	4165 (1968–7971)	0.077
Study peak	4029 (1480–8403)	4748 (2394–8360)	0.078
<i>INR</i>			
Pre-study peak	4.2 (2.8–6.2)	4.2 (3.1–6.6)	0.45
Study entry	2.9 (2.0–4.4)	3.0 (2.2–4.6)	0.14
Study peak	3.2 (2.1–4.8)	3.2 (2.3–5.5)	0.087
<i>Bilirubin, mg/dL</i>			
Pre-study peak	3.9 (2.5–5.7)	5.8 (3.4–8.0)	<0.001
Study entry	4.1 (2.6–5.9)	5.4 (3.3–7.7)	<0.001
Study peak	6.3 (3.7–11.1)	8.6 (4.4–14.2)	<0.001
<i>Creatinine, mg/dL</i>			
Pre-study peak	1.8 (1.0–3.1)	2.4 (1.4–3.6)	<0.001
Study entry	1.7 (0.9–3.0)	2.4 (1.0–4.1)	<0.001
Study peak	2.3 (1.0–4.2)	2.9 (1.1–5.7)	<0.001
<i>Arterial ammonia, umol/L¹</i>			
Study entry	97 (58–162)	109 (59–182)	0.52
Study peak	102 (62–164)	110 (59–175)	0.94
<i>Venous ammonia, umol/L¹</i>			
Study entry	102 (70–154)	89 (59–159)	0.28
Study peak	106 (76–163)	104 (70–167)	0.69
<i>Lactate, mmol/L</i>			
Study entry	4.3 (2.3–8.4)	3.5 (2.1–7.6)	0.32
Study peak	4.4 (2.4–8.8)	3.9 (2.2–7.7)	0.31
<i>pH</i>			
Study entry	7.41 (7.34–7.47)	7.43 (7.37–7.47)	0.041
Study peak	7.47 (7.42–7.52)	7.47 (7.42–7.52)	0.94
<i>Glucose, mg/dL</i>			

	Women (n = 694)	Men (n = 218)	p value
Study entry	122 (98–158)	119 (97–157)	0.56
Study peak	133 (106–168)	130 (107–171)	0.71
Albumin, g/dL			
Study entry	2.8 (2.5–3.2)	3.0 (2.7–3.4)	<0.001
Study peak	3.0 (2.7–3.4)	3.2 (2.9–3.6)	<0.001
Sodium, mmol/L			
Study entry	140 (137–144)	139 (136–142)	<0.001
Study peak	143 (139–147)	141 (138–144)	<0.001
Phosphate, mg/dL			
Study entry	2.5 (1.7–3.5)	2.9 (1.8–4.0)	0.0083
Study peak	3.5 (2.3–4.6)	3.8 (2.7–5.0)	0.059
MELD			
Study entry	32.5 (24.1–39.2)	34.9 (27.3–41.3)	0.0041
Study peak	34.3 (25.4–41.0)	36.3 (28.4–43.4)	0.0082
NAC Use, n (%)			
Study entry	621 (89.6)	195 (89.5)	0.95
Study peak	622 (89.8)	197 (90.4)	0.79
Acetaminophen level, mg/L			
Study entry	42.7 (18.0–107.0)	45.0 (20.5–97.0)	0.85
Met King's College Criteria, n (%)			
Study entry	65 (9.5)	29 (13.8)	0.075
Study entry HE grade, N (%)			
No coma	13 (2.0)	8 (3.7)	
I	152 (22.8)	70 (32.7)	
II	114 (17.1)	47 (22.0)	<0.001
III	166 (24.9)	28 (13.1)	
IV	222 (33.3)	61 (28.5)	
Maximum HE grade, N (%)			
No coma	14 (1.9)	7 (3.3)	
I	104 (15.4)	47 (22.0)	
II	96 (14.2)	37 (17.3)	0.023
III	136 (20.2)	28 (13.1)	
IV	325 (48.2)	95 (44.4)	
Length of ICU stay, days			
	4.0 (2.0–7.0)	4.0 (2.0–7.0)	0.29

NOTE: Data shown are Median (IQR), unless otherwise indicated

ALF = acute liver failure; INR = international normalized ratio; IQR = interquartile range; MELD = Model for End-Stage Liver Disease; NAC = N-acetylcysteine; HE = hepatic encephalopathy; ICP = intracranial pressure; ICU = intensive care unit

¹For arterial ammonia, on study entry n = 248, at study peak n = 278; for venous ammonia, on study entry n = 364, at study peak, n = 418

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Table 3

Factors Associated with Severe Hepatic Encephalopathy in Acetaminophen-Induced ALF at Study Entry and During Cumulative 7-Day Follow-Up

	Study Entry			Cumulative 7-Day Follow-Up		
	Univariate		Multivariate	Univariate		Multivariate
	OR (95% CI)	p value	AOR (95% CI)	p value	OR (95% CI)	p value
Covariates						
Age	1.016 (1.006–1.027)	0.0026	1.010 (0.999–1.021)	0.0820	1.101 (1.003–1.025)	0.012
Female sex	1.953 (1.429–2.669)	<0.001	1.787 (1.275–2.506)	<0.001	1.601 (1.168–2.196)	0.0035
White race	0.607 (0.351–1.050)	0.36	–	–	0.722 (0.405–1.290)	0.74
Psychiatric disease (Yes)	0.828 (0.633–1.083)	0.17	–	–	0.868 (0.655–1.149)	0.32
Alcohol (Yes) ¹	1.164 (0.706–1.918)	0.55	–	–	1.378 (0.822–2.312)	0.22
Co-ingestion	1.644 (1.242–2.177)	<0.001	1.552 (1.140–2.112)	0.0052	1.220 (0.921–1.615)	0.17
Acetaminophen level ¹	1.002 (1.000–1.003)	0.024	–	–	1.002 (1.000–1.004)	0.020
ALT (per 100 units increase)	0.991 (0.987–0.995)	<0.001	0.989 (0.984–0.993)	<0.001	0.995 (0.991–0.999)	0.0097
AST (per 100 units increase)	0.998 (0.996–1.001)	0.21	–	–	1.003 (1.00–1.006)	0.066
INR	0.975 (0.922–1.031)	0.38	–	–	1.067 (1.002–1.137)	0.043
Bilirubin	1.021 (0.992–1.051)	0.16	–	–	1.028 (0.995–1.062)	0.099
Creatinine	1.112 (1.031–1.199)	0.0059	–	–	1.187 (1.088–1.294)	<0.001
MELD	1.027 (1.013–1.042)	0.0001	1.047 (1.031–1.063)	<0.001	1.056 (1.041–1.073)	<0.001
Sodium	1.067 (1.042–1.092)	<0.001	–	–	1.063 (1.037–1.089)	<0.001
Phosphate	1.084 (1.008–1.167)	0.031	–	–	1.192 (1.088–1.306)	<0.001
Lactate	0.996 (0.971–1.022)	0.75	–	–	0.990 (0.965–1.017)	0.47
Glucose	1.000 (0.998–1.001)	0.73	–	–	0.999 (0.998–1.001)	0.48
PH	1.580 (0.552–4.525)	0.39	–	–	1.461 (0.498–4.283)	0.49
NAC Use	0.939 (0.593–1.488)	0.79	–	–	0.938 (0.579–1.520)	0.80

NOTE: laboratory values reflect study entry data

ALF = acute liver failure; HE = hepatic encephalopathy; OR = odds ratio; AOR = adjusted odds ratio; INR = international normalized ratio; NAC = N-acetylcysteine; MELD = model for end-stage liver disease

¹ 66% of Alcohol intake values missing; 34% of APAP level values missing