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ALCOHOL CONSUMPTION IS ASSOCIATED WITH THE SEVERITY AND OUTCOME OF ACUTE LIVER INJURY/FAILURE

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Short Title: Effects of alcohol on acute liver failure

Abbreviations.

ALF, acute liver failure

ALI, acute liver injury

ALT, alanine aminotransferase

APAP, acetaminophen

AST, aspartate aminotransferase

AUC, area-under-the-curve

CRRT, continuous renal replacement therapy

HE, hepatic encephalopathy

INR, International Normalized Ratio of the prothrombin time

IQR, interquartile range

LT, liver transplantation

MOSF, multi-organ system failure

NIAAA, National Institute of Alcohol Abuse and Alcoholism

WBC, white blood cells

Lay Summary: Acute liver failure is a life-threatening condition. Most often, it is related to Tylenol® (acetaminophen) overdose. This study from Acute Liver Failure Study Group suggests that 3 or more alcoholic drinks a week can result more in severe disease presentation and cause worse outcomes in both Tylenol® related and due to other causes of acute liver injury/failure.

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Abstract.

Background & Aims. Non-medical factors which contribute to the severity of acute liver failure (ALF) remain poorly defined. The association of alcohol consumption on the severity of presentation and outcome were determined in patients with ALF and acute liver injury (ALI) in a large, multi-center registry. **Methods.** Alcohol consumption during the 6 months prior to study entry was analyzed in 1170 patients enrolled in the ALF Study Group Registry. Consumption was categorized as none/minimal (<3 alcoholic beverages/week) or at least moderate (≥3/week). Clinical characteristics, the severity of liver injury at presentation (ALI or ALF), and outcome were compared. **Results.** In patients with acetaminophen (APAP) overdose, at least moderate alcohol consumption was associated with higher peak aminotransferases, bilirubin, creatinine, and INR on admission, compared to no/minimal consumption. In patients with non-APAP ALI/ALF, at least moderate alcohol consumption was associated with higher peak aminotransferases and creatinine. In APAP, non-APAP, or all etiologies, at least moderate alcohol consumption was associated with a 75%, 89%, and 82% higher odds, respectively, of presenting as ALF rather than ALI (all P<0.005). At least moderate alcohol consumption increased the odds of death by 45% (P=0.01) across all etiologies. In multivariate analysis, older age, non-Caucasian race, peak INR, peak bilirubin, and at least moderate alcohol consumption were significantly associated with death. Finally, in Kaplan-Meier analysis of patients with all etiologies, at least moderate alcohol consumption was associated with decreased time-dependent

survival (P=0.002). **Conclusion**. Alcohol consumption adversely affects the presentation and outcome of both APAP- and non-APAP-induced ALI/ALF.

Key words: acetaminophen, alcohol, ethanol, hepatic encephalopathy, coagulopathy, acute liver failure.

Introduction

Acute liver failure (ALF) is a clinical syndrome consisting of a primary liver injury followed by secondary multi-organ system failure (MOSF), culminating in death or the need for liver transplantation (LT) in more than half of affected individuals(1). The etiology of the primary liver injury may be a toxin or drug, or less commonly, a viral, vascular, or metabolic injury. In the United States and parts of Western Europe, acetaminophen (APAP) is the most common toxin incriminated in ALF, accounting for nearly half of cases(1;2). Clinical features of patients with ALI/ALF which increase the susceptibility to, or severity of, primary liver injury have not been well-defined.

Although alcohol consumption has been reported to decrease the threshold of APAP hepatotoxicity(3), the interaction is complex, and studies have not universally agreed that alcohol increases the hepatotoxicity of APAP. In experimental animals (highly controlled conditions), alcohol increases hepatotoxicity of APAP by induction of specific cytochrome P-450's (both P-450 3a and 1a(4)), thereby shunting more APAP into the metabolic pathway to produce the toxic metabolite, *N*-acetyl-p-benzoquinoneimine (NAPQI), and away from the non-toxic production of glucuronides or sulfates(5). In humans (highly variable conditions), the timing, chronicity, and quantity of both the alcohol and the APAP exposure determine the degree of liver injury. Other poorly-defined cofactors modulate this interaction, such as fasting and/or the nutritional state of the patient, which determine glutathione reserves(6;7). A less well-documented interaction between alcohol and APAP-induced liver injury has been hypothesized to occur with the co-ingestion of alcohol and APAP, in which experimental animals and humans appear to be more resistant to liver injury due to competition of alcohol and APAP for metabolism by the same cytochrome P450's, resulting in decreased NAPQI formation(8;9).

The independent contribution of regular alcohol consumption (not abuse) to the severity of presentation and outcome of ALI/ALF has not been well-established in patients with APAP

overdose partly because study populations have not been large enough to account for the heterogeneity of alcohol and APAP ingestion. Furthermore, the association of alcohol consumption on the severity on ALI/ALF of non-APAP-induced liver injury has not been explored. The ALF Study Group Registry has prospectively collected alcohol consumption data on participants with ALF and ALI (a less severe liver injury without hepatic encephalopathy) since its inception in 1998. The work presented herein attempts to quantify the association of alcohol consumption on the severity of liver injury in patients with ALI/ALF of diverse etiologies, and to determine whether alcohol consumption adversely affects the clinical course of patients with non-APAP liver injury.

Methods.

Study subjects. Patient accrual followed the algorithm in **Figure 1**. Between 1998 and 2015, 2670 patients with ALI and ALF have been enrolled in the ALF Study Group Registry wherein detailed data and daily bio-samples are collected over 7 days. All study patients met criteria for ALF or ALI as defined previously; in order to ensure patients with ALI had severe liver dysfunction, we have previously defined ALI as INR ≥ 2.0 (1;10). Patients were excluded if they had underlying liver disease, including a previous history of alcohol-induced liver injury. Consent was provided by the patient if they exhibited no evidence of hepatic encephalopathy (ALI), and the patients' legal next-of-kin, if they had any signs of encephalopathy (ALF). Institutional Review Boards of each participating institution have approved the ALF Study Group Registry.

Of the 2670 patients with ALI/ALF who were screened, data on alcohol use were available in 1170 subjects (**Figure** 1). Of the 1500 excluded subjects, alcohol use data were missing on 1202 and 21-day outcome on the remaining subjects. The ALF Study Group began recruiting patients with ALI in 2010, and data regarding alcohol consumption were less completely collected before this time. As a consequence, only 4.6% of the patients excluded from the study had ALI compared to 26% of the included group (P<0.0001), and the excluded

group was, therefore, more likely to have poor outcomes (death or LT) than the included group (P<0.0001; data not shown).

The etiology of ALI/ALF was APAP in 591 patients (51%), and non-APAP in 579 patients (49%). Among the non-APAP etiologies, autoimmune hepatitis was diagnosed in 8%, drug-induced in 7.6%, hepatitis B in 7.3%, shock/ischemia in 6.6%, and other minor etiologies in 5.7% (pregnancy-associated liver failure, Budd-Chiari Syndrome, hepatitis A, C and E, other viruses, mushroom poisoning, and Wilson disease; each 1% or less). Indeterminate etiology was diagnosed after extensive but unrevealing evaluation in 10%. Spontaneous (transplant-free) survival at day 21 was reported in 703 (60%), overall survival in 895 (77%), LT in 177 (15%), and death in 275 (24%).

Definitions of alcohol consumption. On the day of admission to the Registry, sites were asked to record the patient's "usual intake of alcohol during the last 6 months." One "drink" of alcohol was defined as 12 oz. (1 can or bottle) of beer, 5 oz. (1 glass) of wine, 1.5 oz. of hard liquor, or 12 oz. (1 bottle) of wine cooler. The sum of the number of drinks per week was then recorded as none (<1 drink/week), 1, 2, 3-6, 7-14, and >14 drinks/week. The number of weeks of alcohol consumption during the last 6 months was also recorded. Patients were distributed into groups according to alcohol consumption as follows: none (<1 drink/week), minimal (<3 drinks/week), or at least moderate (≥3 drinks/week). The no alcohol and minimal alcohol groups were combined as they were shown to be similar in demographics, laboratories and outcomes (data not shown).

Statistical analyses. The association of alcohol consumption on the severity and outcome of liver injury was analyzed separately in patients with APAP-induced and non-APAP-induced ALI/ALF. The effects of alcohol consumption on the severity of presentation and outcomes of ALI/ALF were, therefore, analyzed comparing patients who consumed no/minimal *vs.* those who consumed at least moderate alcohol. The statistical methods included descriptive statistics, multiple logistic regression, Kaplan-Meier curves, and log-rank test.

Results.

Patient characteristics according to alcohol consumption in the 6 months prior to presentation for ALI/ALF.

The clinical characteristics of study participants are displayed in **Table 1** (comparing demographic and peak laboratory values) and **Supplemental Table 1** (comparing admission laboratory values) dichotomized by the etiology of liver injury, APAP-induced and non-APAP-induced. Overall, 615 patients (53%) consumed no/minimal amounts of alcohol in the 6 months prior to admission, and 555 (47%) consumed at least moderate amounts. The number of subjects who reported weekly alcohol consumption of 3-6 drinks (n=129), 7-14 drinks (n=124), >14 drinks (n=302) represented the group with at least moderate amounts of alcohol consumption.

The clinical characteristics of study participants differed significantly between the dichotomized etiologies of ALI/ALF. Patients with APAP-induced liver injury were younger and more predominantly female compared to patients with non-APAP-induced ALI/ALF (37.3 ± 12.7 *vs.* 45.0 ± 15.8 years, and 70% *vs.* 58%, respectively; both P<0.0001). As is characteristic of APAP-induced liver injury, aminotransferases were 3-4-fold higher, and total bilirubin levels were ~75% lower, than those with non-APAP-induced ALI/ALF (both P<0.001). Admission serum creatinine was also significantly higher in patients with APAP *vs.* non-APAP etiology (1.5 [0.8-3.1] *vs.* 1.25 [0.8-2.4] mg/dl, respectively; P=0.01, data not shown).

Of those with APAP-induced ALI/ALF, female patients were more commonly observed in the group who consumed no/minimal amounts of alcohol compared to the group who consumed at least moderate amounts (78.2 *vs.* 63.8%, P=0.0002) (Table 1). Peak AST and ALT levels were significantly higher in patients who consumed at least moderate alcohol compared to those who consumed no/minimal quantities (8000 *vs.* 5279 IU/L [P<0.0001] and 5373 *vs.* 4667 IU/L [P=0.018], respectively). Patients who consumed at least moderate quantities of alcohol also developed significantly higher peak total bilirubin (P<0.0001) and creatinine (P<0.0001), than patients who consumed no/minimal amounts of alcohol. Similar trends were observed in laboratory values on admission to the Registry (Supplemental Table 1).

Of patients with non-APAP-induced ALI/ALF (Table 1), more females were again observed in the no/minimal alcohol group (P=0.0005), and Caucasians were more frequently observed in the at least moderate alcohol group (P=0.0001). Peak AST and ALT were also higher in the group who consumed at least moderate alcohol than those in the none/minimal group (2184 *vs.* 1776 IU/L [P=0.04] and 1953 *vs.* 1490 IU/L [P=0.017], respectively), as was the peak serum creatinine (1.6 [0.9-3.2] *vs.* 1.2 [0.8-2.4] mg/dl, respectively; P=0.007). Similar trends were observed in laboratory values on admission (Supplemental Table 1).

Association of alcohol consumption on the presentation and outcome of ALI/ALF.

The association of alcohol consumption on the severity of liver injury on presentation and the outcome at 21 days are depicted in **Table 2**. For the severity of presentation, at least moderate alcohol consumption was associated with an increased odds of ALF *vs.* ALI of 75% in patients with APAP etiology (OR 1.75 [1.20-2.54]; P=0.003), of 89% in patients with non-APAP etiology (OR 1.89 [1.24-2.92]; P=0.002), and of 82% in patients with all etiologies (OR 1.82 [1.38-2.42]; P<0.0001), compared to patients with no/minimal alcohol consumption in the 6 months prior to admission. Alcohol consumption was also associated with adverse outcomes of ALI/ALF. In patients with ALF/ALI of all etiologies, at least moderate alcohol consumption increased the odds of death or LT by 30% compared to those who consumed no/minimal quantities (OR 1.30 [1.01-1.68]; P=0.046). One hundred thirty patients in no/minimal category and 47 patients with at least moderate alcohol consumption underwent LT. Among the APAP-induced ALI/ALF, 15 patients in no/minimal category and 7 patients with at least moderate amounts of alcohol underwent LT. Overall survival was also adversely affected by alcohol consumption in patients with APAP-induced ALI/ALF, with a 77% increase in the odds of death in patients who consumed at least moderate amounts compared to no/minimal amounts (OR 1.77 [1.13-2.77]; P=0.01), and an increase of 45% in all patients regardless of etiology (OR 1.45 [1.09-1.94]; P=0.01).

In multivariate analysis, older age, non-Caucasian race, peak INR, peak bilirubin and at least moderate alcohol consumption were significantly associated with death at 21 days after enrollment in the ALF Study Group Registry (**Table 3**). Substitution of admission laboratory values into the multivariate analysis yielded similar results, except that higher AST, ALT, and creatinine were also associated with death, while at least moderate alcohol consumption was not (P=0.14). Finally, Kaplan-Meier curves showed a significant reduction in 21-day survival in patients with a history of at least moderate alcohol consumption compared to no/minimal alcohol consumption (**Figure 2**; P=0.002 by log-rank test).

Discussion.

The data presented suggest that alcohol consumption adversely affects the severity of clinical presentation and outcome of both APAP- and non-APAP-induced ALF/ALI. Patients with at least moderate alcohol consumption were 75% (APAP) and 89% (non-APAP) more likely to present with ALF *vs.* ALI, compared to patients with no/minimal alcohol consumption in the 6 months prior to presentation with liver injury. A similar adverse effect on outcome was observed for all etiologies in patients with at least moderate alcohol consumption compared to no/minimal consumption, with a 30% increase in death or LT and 45% increase in overall death. We also found that alcohol consumption increased the risk of overall death exclusive of the risk on LT. In fact, alcohol consumption did not significantly affect LT rates, suggesting that alcohol consumption did not bias our results by affecting access to transplant (the transplant rate in the no/minimal group was 13.4% *vs.* 17.7% in the at least moderate group; P=0.08). This observation also supports a general consensus by transplant clinicians at our study sites that few patients in our population abused alcohol.

Although an adverse effect of chronic alcohol abuse on the outcome of APAP overdose has been previously observed, our data are primarily based upon consumers of alcohol, not those who would be considered having a risk of "alcohol use disorder" as defined by the National Institute of Alcohol Abuse and Alcoholism (NIAAA); fewer than half of patients who consumed any alcohol in the 6 months prior to presentation would meet criteria for possible alcohol use disorder (data not shown). Thus, our findings raise concern that alcohol consumption even in modest amounts may be a co-factor in the clinical course of liver injury regardless of etiology. We had no way to exclude the possibility of a role of subclinical alcoholic liver disease in the acute injury experienced by our cohort of study patients. However, overt alcoholic liver disease and a history of any chronic liver disease were exclusion criteria for entry into the Registry. Therefore, since the majority of our patients would not be considered to have abused alcohol, we believe pre-existing, clinically significant alcoholic liver disease was an unlikely explanation for the more severe presentation and increased poor outcomes in our study population with ALI/ALF.

Previous studies have generally suggested that chronic alcohol *consumption* does not increase APAP hepatotoxicity; the association was termed "at best, ambiguous" by the authors of the largest study prior to the present(9). In this cohort of 645 patients with single-dose APAP overdose, however, chronic alcohol *abuse* was an independent risk factor for hepatic

encephalopathy and mortality. Many less rigorously-collected databases have not revealed alcohol consumption as a risk factor for mortality after APAP overdose(11). In an analysis from the King's College(12), overall survival of patients with a history of heavy alcohol consumption was similar to non-drinkers. In a small subset of our ALF Study Group Registry patients enrolled between 1998 and 2003(13), alcohol use was not associated with adverse outcome (based upon 273 patients; P=0.21), and alcohol abuse was actually associated with higher transplant-free survival (based upon 196 patients; P=0.04). However, those with a history of alcohol abuse presented with lower grade hepatic encephalopathy, suggesting that they were less acutely ill. The fact that chronic heavy alcohol consumption increases mortality inconsistently after APAP overdose may lie in poorly-defined features of the APAP ingestion, which differ according to single ingestions with suicidal intent or the "therapeutic misadventure" unintentional overdose, or an association of heavy alcohol consumption with larger doses of ingested APAP(12;14). There are other historical features of these complex ingestions which have proved almost impossible to collect accurately, such as the precise dose and timing of APAP ingestion, whether there were chronic, repeated exposures to APAP such as in bundled narcotic abuse, and fasting and nutritional state before the APAP ingestion.

In contrast to chronic alcohol consumption, acute alcohol exposure has been postulated to protect against APAP hepatotoxicity(8;9); thus, the timing of the APAP ingestion after ethanol consumption appears to be a determinant of the odds of enhanced liver injury, and could have confounded our data. Although we did not collect the time of most recent alcohol consumption before APAP ingestion, the benefit of recent alcohol ingestion on APAP overdose appears to be short-lived. In a human study, APAP ingestion eight hours after an ethanol infusion was associated with a 22% increase in NAPQI in blood and urine compared to APAP ingestion after a glucose infusion(15), suggesting that even a near-contemporaneous exposure to alcohol may not diminish APAP hepatotoxicity. Although a protective effect of recent alcohol consumption on APAP hepatotoxicity has been shown in laboratory animals(8;16), a possible benefit has been difficult to observe even in carefully-executed human studies in which the investigators recorded instances of co-ingestion of APAP and alcohol. Specifically, Schmidt, *et al* (9) found a protective effect of acute alcohol ingestion (defined as alcohol consumption as part of the APAP intoxication) on APAP hepatotoxicity only in the subset of patients with a history chronic alcohol consumption; acute alcohol consumption was not protective in non-alcoholic patients.

Previous studies have identified other patient characteristics which appear to potentiate the toxicity of APAP on the liver. Older age has been shown to increase the mortality of APAP and non-APAP ALF(9;17-19). Specific medications which modulate tissue injury and repair, such as statins and non-steroidal inflammatory drugs, have been associated with decreased hepatotoxicity from APAP overdose(20;21). Fasting and malnutrition increases APAP hepatotoxicity by depleting glutathione stores(6); somewhat paradoxically, obesity and previous bariatric surgery have also been incriminated(22;23). We found that, in addition to older age and at least moderate alcohol consumption, non-Caucasian race was an independent predictor of higher overall 21-day mortality, which could reflect differences in access to medical care or liver transplantation, or genetic differences in the metabolism of APAP.

Consistent with data regarding presentation and outcome, alcohol consumption also increased biochemical evidence of liver injury, depending upon whether peak (Table 1) or admission (Supplemental Table 1) laboratory values were examined. For peak labs, AST, ALT, and creatinine were higher for both APAP and non-APAP etiologies in patients who consumed at least moderate alcohol compared to those who consumed no/minimal alcohol, as was peak bilirubin in those with APAP overdose. Similar trends were observed regarding admission laboratories, where bilirubin and INR were significantly higher in those with APAP overdose who consumed at least moderate alcohol, but differences were less striking in those with non-APAP etiology. The finding that alcohol may increase liver injury in non-APAP ALI/ALF has not been previously reported. As shown in Table 3 and Supplemental Table 2, many features (age, race, laboratory data, etiology, and alcohol consumption) contribute to the risk of death after ALI/ALF depending upon which laboratories are entered into the multivariate model. The finding that alcohol consumption drops out of the model if admission rather than peak laboratories are used reflects the complex interaction of these variables, and may be the reason that previous studies have not consistently found an adverse effect of alcohol consumption on the outcome of ALF.

We acknowledge limitations of our study. Most importantly, granular details regarding ethanol consumption history were not available, in particular, the timing of the last alcohol ingestion. Similarly, granular details regarding the dose and timing of one or more APAP ingestions are also exceedingly difficult to obtain in this critically ill population. The reliability and accuracy of the semi-quantitative assessment of alcohol consumption by patients with altered

mentation may be questioned. The timing of last meal, as an indicator of fasting state, was also not collected. The large number of patients excluded for missing critical data (alcohol consumption and/or outcome) is also a significant limitation, although after comparing the included and excluded populations (data not shown), it is not clear how this affected our results.

In conclusion, alcohol consumption, including a modest consumption, may increase the risk of presenting with hepatic encephalopathy (ALF) rather than ALI for patients with APAP- and non-APAP-induced liver injury. At least moderate alcohol consumption may increase the risk of death in patients with ALF/ALI of all etiologies, although the interplay between risk variables is complex. Further study to explain the mechanism by which alcohol consumption increases the liver injury after a non-APAP insult should be undertaken to better prove the association.

Figure Legends.
Figure 1. Study overview.
Figure 2. Kaplan-Meier survival of patients with ALI/ALF (all etiologies) according to alcohol consumption, At Least Moderate *vs*. None/Minimal (*Log-Rank test P=0.002).

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Clinical Feature	Alcohol Consumption		P*
	None/Minimal N = 615	At Least Moderate N = 555	P*
Acetaminophen Etiology (N = 591)	N = 243	N = 348	
Age (y)	37.6±14.1	36.9±11.7	0.50
Gender (% female)	78.2	63.8	0.0002
Race (% Caucasian)	83.5	85.1	0.61
Peak AST (IU/L)	5279 (2606-8853)	8000 (3857-13785)	<0.0001
Peak ALT (IU/L)	4667 (2003-7432)	5373 (2593-8887)	0.018
Peak Bilirubin (mg/dl)	3.6 (2.2-5.0)	5.0 (3.2-7.4)	<0.0001
Peak Creatinine (mg/dl)	1.5 (0.9-2.7)	2.2 (1.1-3.6)	<0.0001
Peak INR	3.8 (2.6-5.8)	4.2 (2.8-6.2)	0.16
Non-Acetaminophen Etiology (N = 579)	N = 372	N = 207	
Age (y)	45.4±16.2	44.1±15.1	0.34
Gender (% female)	63.7	48.8	0.0005
Race (% Caucasian)	61.0	76.8	0.0001
Peak AST (IU/L)	1776 (752-3819)	2184 (938-5732)	0.04
Peak ALT (IU/L)	1490 (635-3195)	1953 (869-4755)	0.017
Peak Bilirubin (mg/dl)	15.6 (6.2-23.6)	12.8 (5.9-23.2)	0.50
Peak Creatinine (mg/dl)	1.2 (0.8-2.4)	1.6 (0.9-3.2)	0.007
Peak INR	2.8 (2.0-4.4)	3.0 (2.2-4.8)	0.63

Table 1. **Clinical and peak laboratory features of study population according to alcohol consumption during the six months prior to admission for ALI/ALF.** Peak values were the highest recorded during the first 7 days of admission (prior to liver transplantation, if applicable). *As defined in Methods, data from patients with no/minimal alcohol consumption are compared to those with at least moderate alcohol consumption.

(Normal data are expressed as mean ±SD; non-normal data are expressed as median (IQR 25-75%).

Presentation or Outcome	Etiology of ALI/ALF	Odds Ratio	95% CI	P
ALF vs. ALI	APAP	1.75	1.20-2.54	0.003
	Non-APAP	1.89	1.24-2.92	0.002
	All Etiologies	1.82	1.38-2.42	<0.0001
Death/LT vs. SS	APAP	1.28	0.87-1.89	0.19
	Non-APAP	1.31	0.93-1.85	0.12
	All Etiologies	1.30	1.01-1.68	0.046
Death vs. Alive	APAP	1.77	1.13-2.77	0.01
	Non-APAP	1.18	0.81-1.72	0.37
	All Etiologies	1.45	1.09-1.94	0.01

Table 2. **Effects of alcohol consumption on the presentation and outcome of ALI/ALF.**
Odds ratio and 95% confidence interval (CI) represents the increased risk of the more severe presentation or worse outcome in patients who consumed at least moderate alcohol compared to

those who consumed no or minimal alcohol in the 6 months prior to presenting with ALI or ALF, as defined in Methods.

APAP, acetaminophen; CI, confidence interval; LT, liver transplantation; SS, spontaneous (transplant-free) survival.
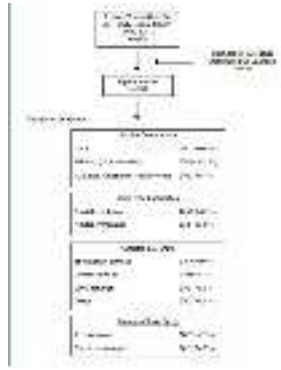
Clinical Feature	Univariate Analysis		Multivariate Analysis	
	OR	P	OR	P
Age	1.03	<0.0001	1.04	<0.0001
Female Gender	0.79	0.10	0.77	0.14
Caucasian Race	0.65	0.008	0.65	0.026
Peak AST	1.00	0.17	1.00	0.07
Peak ALT	0.99	0.043	0.99	0.26
Peak Bilirubin	1.02	<0.0001	1.01	0.007
Peak Creatinine	1.00	0.63	0.99	0.64
Peak INR	1.01	0.07	1.02	0.048
APAP Etiology	0.55	<0.0001	0.99	0.96
At Least Moderate Alcohol Consumption	1.22	0.15	1.44	0.039

Table 3. **Risk of death at 21 days after admission for ALI/ALF by multivariate analysis based upon peak laboratories (day 1-7)**.

OR, odds ratio of death (units OR for continuous variables [age, INR, AST, ALT, bilirubin, and creatinine] measuring per unit change in regressor).

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Figure 2