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Article in Press

## Acetaminophen is Undetectable in Plasma From More Than Half of Patients Believed to Have Acute Liver Failure Due to Overdose

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Evaluation of patients with acute liver injury (ALI) or acute liver failure (ALF) often includes measurement of plasma levels of acetaminophen, to determine exposure and/or toxicity. However, once liver injury has developed, acetaminophen might be undetectable in plasma. We investigated the association between level of acetaminophen measured and outcomes of patients designated as having ALF or ALI due to acetaminophen toxicity.

**Methods**

We performed a retrospective analysis of data from 434 subjects in the Acute Liver Failure Study Group who met criteria for ALF (coagulopathy and hepatic encephalopathy within 26 weeks of the first symptoms, without pre-existing liver disease) or ALI (severe liver injury with coagulopathy but no encephalopathy) due to acetaminophen toxicity from January 1, 2010 through December 31, 2014. We collected data on patient demographics, biochemical features, reported acetaminophen use, N-acetylcysteine therapy, liver transplant, and outcomes. Descriptive statistics were used to assess patient demographics, clinical characteristics, and outcomes whereas differences in continuous variables between patients with vs without acetaminophen detection on admission were analyzed using the Wilcoxon rank-sum test. The primary aim was to determine the proportion of patients with detectable plasma levels of acetaminophen.

**Results**

Acetaminophen was undetectable in serum samples from 227 patients (52%). There were no significant differences between groups of patients with detectable vs undetectable levels in demographic features, alcohol use, median levels of alanine aspartate, or use of N-acetylcysteine (given to 94.7% of patients with detectable acetaminophen vs 95.9% of those with undetectable acetaminophen;  $P=.63$ ). We observed a significant difference in median dose taken between patients with detectable (29,500 mg; interquartile range, 15,000 mg–50,007 mg) vs no detectable parent compound (14,950 mg; interquartile range, 3960 mg–25,000) ( $P=.003$ ). A lower proportion of patients with detectable plasma levels of acetaminophen (72.3%) survived without a liver transplant than of patients with undetectable levels (86.3%) in univariate analysis ( $P=.0006$ ), although this was not significant in multivariable analysis ( $P=.12$ ). Although most patients had unintentional overdoses, a higher proportion of patients with suicidal overdoses (43%) had detectable levels of acetaminophen than patients with accidental overdoses (29.3%;  $P=.01$ ).

**Conclusion**

More than half of patients who present at the hospital with acetaminophen-induced ALI or ALF have undetectable levels of acetaminophen. Clinicians should not exclude acetaminophen toxicity because of undetectable levels or withhold N-acetylcysteine for patients with ALI or ALF when acetaminophen toxicity is suspected.

**KEY WORDS:**[ALFSG](#), [overdose](#), [NAC](#), [hepatotoxicity](#)**Abbreviations used in this paper:**

[ALF](#) (acute liver failure), [ALFSG](#) (Acute Liver Failure Study Group), [ALI](#) (acute liver injury), [APAP](#) (acetaminophen), [ICU](#) (intensive care unit), [INR](#) (international normalized ratio), [IQR](#) (interquartile range), [MELD](#) (model for end-stage liver disease), [NAC](#) (N-acetylcysteine), [US](#) (United States of America)

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