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Impact of Duration of N-Acetylcysteine in Non-Acetaminophen-Induced Acute Liver Failure

OBJECTIVES: Studies of the use of IV N-acetylcysteine in the management of non-acetaminophen-induced acute liver failure have evaluated various dosing regimens. The only randomized trial studying this application described a 72-hour regimen. However, observational studies have reported extended duration until normalization of international normalized ratio. This study seeks to compare differences in patient outcomes based on IV N-acetylcysteine duration.

DESIGN: Retrospective cohort study.

SETTING: Medical ICU at a large quaternary care academic medical institution and liver transplant center.

PATIENTS: Adult patients admitted to the medical ICU who received IV N-acetylcysteine for the treatment of non-acetaminophen-induced acute liver failure.

INTERVENTIONS: Patients were divided into cohorts based on duration; standard duration of IV N-acetylcysteine was considered 72 hours, whereas extended duration was defined as continuation beyond 72 hours.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was time to normalization of international normalized ratio to less than 1.3 or less than 1.5; secondary outcomes included all-cause mortality and transplant-free survival at 3 weeks. In total, 53 patients were included: 40 in the standard duration cohort and 13 in the extended duration. There were no major differences in baseline characteristics. There was no significant difference in time to international normalized ratio normalization between cohorts. Transplant-free survival was higher with extended duration (76.9% extended vs 41.4% standard; $p = 0.03$). All-cause mortality at 3 weeks was numerically lower in the extended duration group (0% extended vs 24.1% standard; $p = 0.08$).

CONCLUSIONS: Patients with non-acetaminophen-induced acute liver failure who received extended duration N-acetylcysteine were found to have significantly higher transplant-free survival than patients who received standard duration, although there was no significant difference in time to normalization of international normalized ratio or overall survival. Prospective, randomized, multicenter study is warranted to identify subpopulations of patients with non-acetaminophen-induced acute liver failure who could benefit from extended treatment duration as a bridge to transplant or spontaneous recovery.

KEY WORDS: international normalized ratio; non-acetaminophen-induced acute liver failure; N-acetylcysteine; transplant; transplant-free survival

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Non-acetaminophen-induced acute liver failure (NAI-ALF), defined as acute-onset hepatic dysfunction of less than 26 weeks duration, evidenced by new-onset encephalopathy and coagulopathy (international normalized ratio [INR] ≥ 1.5) in the absence of chronic underlying liver disease, is a rare clinical syndrome related to an illness or drug other than acetaminophen (1, 2). Unfortunately, the condition carries a high mortality rate in the absence of widely supported therapies aside from liver transplantation (LT). One proposed therapy for the treatment of NAI-ALF has been IV N-acetylcysteine (3). Although IV N-acetylcysteine is only Food and Drug Administration approved for the treatment of acetaminophen overdose, it is widely prescribed off-label for NAI-ALF; in this setting, the role of IV N-acetylcysteine is not to serve as an antidote but rather to act as a free-radical scavenger and improves oxidative stress. Additionally, N-acetylcysteine may improve hepatic perfusion through vasodilation (3, 4).

Studies of the use of IV N-acetylcysteine for NAI-ALF have consistently demonstrated improved transplant-free survival (5–8); however, various dosing regimens have been employed. The only large ($n = 173$) randomized controlled trial of IV N-acetylcysteine for NAI-ALF in adult patients used a 72-hour regimen and did not evaluate liver biomarkers to guide extended duration (8). In this trial, IV N-acetylcysteine was dosed as 150 mg/kg for the first hour, followed by 12.5 mg/kg/hr for the next 4 hours and then 6.25 mg/kg/hr for the remaining 67 hours. However, two observational studies of IV N-acetylcysteine for NAI-ALF have described dosing regimens with extended duration until normalization of liver biomarkers, particularly INR; in these studies, IV N-acetylcysteine was continued for a median of 5 and 8 days, respectively (6, 7). Additionally, a randomized controlled trial in pediatric patients with NAI-ALF reported continuing IV N-acetylcysteine for up to 7 days (9). Therefore, the optimal strategy for duration of IV N-acetylcysteine in NAI-ALF is as yet undefined. With a paucity of literature to guide standardization of care, the optimal strategy for achieving meaningful clinical endpoints related to IV N-acetylcysteine duration in NAI-ALF has warranted further study. This analysis seeks to compare the impact of standard versus extended duration N-acetylcysteine on important patient-centered outcomes, including biomarkers of hepatic recovery,

transplant-free survival, and all-cause mortality at 3 weeks.

METHODS AND METHODS

Study Design

This retrospective cohort study was designed to assess the impact of standard (72 hr or less) versus extended duration N-acetylcysteine (> 72 hr) on markers of spontaneous hepatic recovery (defined as time to INR normalization) as well as all-cause mortality in patients with NAI-ALF. This study was conducted in the medical ICU at a large quaternary care academic medical institution and LT center. The Institutional Review Board (IRB) of the Cleveland Clinic Foundation reviewed and approved this study (IRB number 19-004).

Adult patients (age ≥ 18 yr) who were admitted to the medical ICU between January 2008 and December 2018 and who received IV N-acetylcysteine for the diagnosis of NAI-ALF were included. Patients were identified based on an electronic medical records query of pharmacy records for patients who received IV N-acetylcysteine in the medical ICU within the designated timeframe. Diagnosis of NAI-ALF was considered acute-onset hepatic dysfunction of less than 24 weeks duration, evidenced by new-onset hepatic encephalopathy and coagulopathy (INR ≥ 1.5) in the absence of chronic underlying liver disease (1, 2). The 24-week duration of acute hepatic dysfunction was chosen in order to best equate the study design by Lee et al (8). Patients were excluded from the study first if they did not meet the defined criteria for ALF and second if the etiology of ALF was attributed to acetaminophen overdose, hypoxic hepatitis or alcohol-associated hepatitis.

Patients screened without exclusion criteria were then divided into cohorts based on duration of IV N-acetylcysteine. Standard duration was considered 72-hour duration or less, whereas extended duration was defined as continuation of IV N-acetylcysteine beyond 72 hours. **Figure 1** summarizes the patient screening and allocation process.

Data Collection and Study Outcomes

Data, including demographic information, severity of illness, etiology of liver disease, IV N-acetylcysteine dosing and administration, baseline laboratory markers, and clinical outcomes, were extracted from the

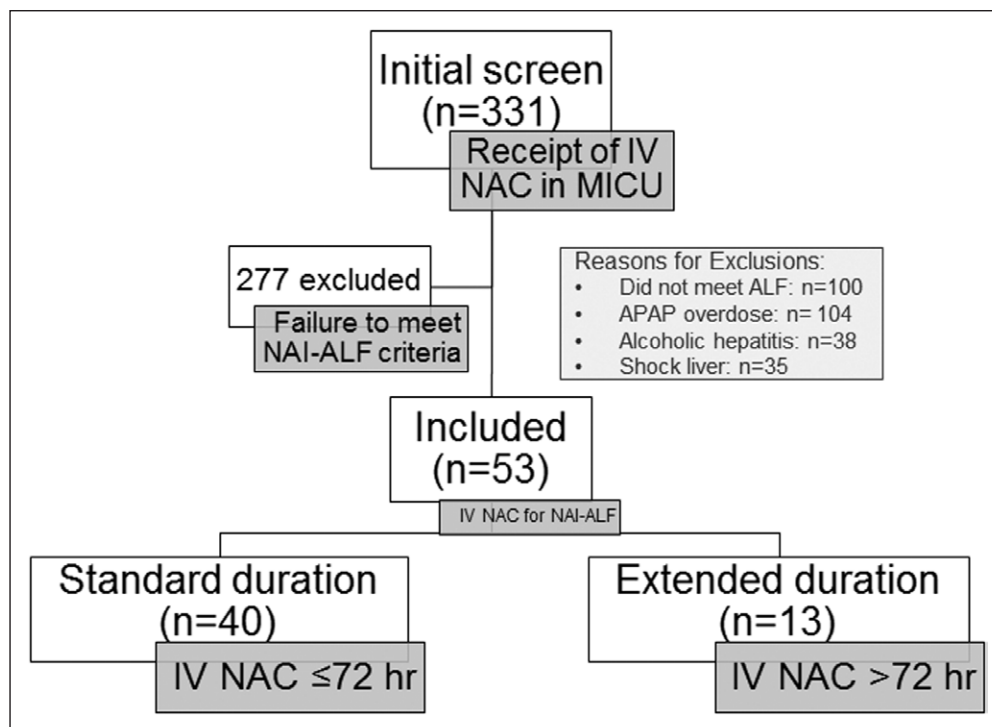


Figure 1. Patient screening and allocation. APAP = acetaminophen, ALF = acute liver failure, MICU = medical ICU, NAC = N-acetylcysteine, NAI-ALF = non-acetaminophen-induced acute liver failure.

electronic medical record. Severity of illness at baseline was assessed via the Model for End-Stage Liver Disease (MELD) score (10) and baseline laboratory markers. Clinical laboratory values were collected within the first 6 hours of IV N-acetylcysteine administration at our institution. Data relating to IV N-acetylcysteine dosing was collected and included dose per IV N-acetylcysteine bag given, total infusion time, and total mg/kg dose. For patients who were transferred from an outside hospital already receiving IV N-acetylcysteine, only doses administered at our institution were considered for total duration of therapy. Finally, clinical outcomes data were collected and included transplantation rate, ICU and hospital length of stay (LOS), transplant-free survival at 3 weeks, and all-cause mortality at 3 weeks.

Time to INR normalization between patients who received standard duration versus extended duration IV N-acetylcysteine was defined as the primary outcome. INR normalization was defined as two consecutive INR measurements of both INR less than 1.5 (similar to Kortsalioudaki et al [6]) and additionally INR less than 1.3 (similar to Darweesh et al [7]). Consecutive measurements of INR below each threshold on 2 separate days were necessary to ensure normalization of

INR was not secondary to blood product administration; however, the first day that the INR was below the target threshold was considered the time to INR normalization for study purposes. Key secondary outcomes of the study included all-cause mortality at 3 weeks, transplant-free survival at 3 weeks, and transplantation rate (8). Transplant-free survival was defined as patients alive in the absence of LT within 3 weeks of initiation of IV N-acetylcysteine. Patients who died within the first 72 hours of initiation of IV N-acetylcysteine administration were excluded

from the secondary outcome analysis. Finally, ICU and hospital LOS as well as liver biochemistries at the time of N-acetylcysteine discontinuation were compared between patients who received standard versus extended duration IV N-acetylcysteine.

Statistical Analysis

The primary outcome of time to INR normalization was analyzed using Kaplan-Meier curves, and differences between the two curves were compared with the log-rank test. All patients were included in this analysis, and patients were right censored if they experienced death or LT prior to the endpoint of INR normalization. For additional analyses, nominal data were analyzed using the chi-square test or Fisher exact test, as appropriate. For continuous data, the normalcy of continuous data was assessed by visually estimating a histogram and normal quantile plots; continuous normally distributed data were analyzed with the Student *t* test and continuous nonnormally distributed data with the Mann-Whitney *U* test. All statistics were performed using STATA statistical software, Version 14.1 (StataCorp, College Station, TX). A *p* value of 0.05 or less was considered statistically significant.

RESULTS

Patient Characteristics

A total of 331 patients were screened for study inclusion. Of those, 53 met inclusion criteria: 40 in the standard duration group and 13 in the extended duration group. Figure 1 summarizes the patient screening and allocation process. Baseline patient characteristics are summarized in **Table 1**. Patients in the standard duration group weighed more on average than those who received IV N-acetylcysteine for longer than 72 hours (89.7 ± 23.9 kg vs 69.3 ± 18.2 kg; $p < 0.01$), but baseline characteristics were otherwise well-matched between groups. ALF was attributed to a variety of different causes, with viral hepatitis (10 patients; 18.8%) and drug-induced liver injury (9 patients; 16.9%) being the most common etiologies overall. Although not statistically significant, there were numerically more patients with Amanita mushroom toxicity-related ALF in the extended duration group. There were no significant differences in baseline MELD scores or other hepatic biomarkers between groups. The median MELD score at baseline was greater than 30 in both groups, correlating with an estimated 3-month mortality above 50% (11). Although total bilirubin was numerically higher in the standard duration group, this difference did not achieve statistical significance (7.3 mg/dL vs 4.7 mg/dL; $p = 0.08$).

Median total duration of IV N-acetylcysteine therapy was 32.6 hours in the standard duration group compared with 106.3 hours in the extended duration group ($p < 0.01$). Forty-seven of the 53 study patients (88%) were transferred from an outside hospital, and 13 of these (28%) had been treated with IV N-acetylcysteine prior to transfer. Receipt of IV N-acetylcysteine at a previous institution was more common in the extended duration group than in the standard duration cohort (8 [61.5%] vs 5 [9.8%]; $p < 0.01$).

Outcomes

Time to INR normalization was similar between groups, regardless of INR goal (**Figs. 2 and 3**). Median time to INR less than 1.5 was 4 days in both groups (standard duration 4 d [2–10 d] vs extended duration 4 d [2–6 d]; $p = 0.61$). Median time to INR less than 1.3 was also 4 days in both groups (standard duration 4 d [3–10 d] vs extended duration 4 d [3–6 d]; $p = 0.84$). A higher proportion of patients in the extended duration group achieved

INR normalization compared with the standard duration group (INR < 1.5 : 52.5% standard duration vs 84.6% extended duration [$p = 0.04$]; INR < 1.3 : 50% standard duration vs 84.6% extended duration [$p = 0.03$]). At time of N-acetylcysteine discontinuation, INR was significantly lower in the extended duration group than in the standard duration group (2.2 standard duration vs 1.2 extended duration; $p < 0.01$).

Clinical outcomes are summarized in **Table 2**. Rates of LT were similar between groups (standard duration 27.5% vs extended duration 23%; $p = 1$). **Figure 4** displays Kaplan-Meier curves comparing overall survival between groups; there was a significant difference between overall survival curves between groups ($p = 0.005$ by log-rank test). However, all-cause mortality at 3 weeks was not significantly different between groups after excluding patients who did not survive to 72 hours ($n = 11$) although more patients (7 patients [24.1%]) in the standard duration group died compared with those in the extended duration cohort (0 patients [0%]) ($p = 0.08$). Additionally, transplant-free survival at 3 weeks, in patients who survived beyond 72 hours, was significantly greater in the extended duration group compared with the standard duration group (12 [41.4%] standard duration vs 10 [76.9%] extended duration; $p = 0.03$). No differences in either hospital or ICU lengths of stay were observed between groups. Because there were numerically more patients with Amanita mushroom poisoning in the extended duration group, a sensitivity analysis was performed excluding these patients (**Table 2**). In the sensitivity analysis, numerically, the survival benefit of extended duration N-acetylcysteine persisted but did not reach statistical significance ($n = 8$ in extended duration group). Additionally, a subgroup analysis was conducted based on duration of IV N-acetylcysteine and demonstrated similar rates of LT and differences in transplant-free survival and all-cause mortality at 3 weeks based on duration of N-acetylcysteine (**Supplementary Appendix Table 1**, <http://links.lww.com/CCX/A599>).

With the exception of bilirubin, selected hepatic biomarkers decreased from baseline to the end of the study. Median aspartate aminotransferase at the end of treatment was significantly lower in the extended duration group compared with those who received N-acetylcysteine for less than or equal to 72 hours (standard duration 395 [264–1,253] vs extended

TABLE 1.
Baseline Characteristics of Patients Who Received N-Acetylcysteine for Non-Acetaminophen-Induced Acute Liver Failure

Variables	Standard Duration N-acetylcysteine (≤ 72 hr)	Extended Duration N-acetylcysteine (> 72 hr)	p
	(n = 40)	(n = 13)	
Age, yr, mean ± sd	52.2 ± 15.5	52.2 ± 13.2	0.99
Female sex, n (%)	28 (70)	9 (69.2)	1.0
Weight, kg, mean ± sd	89.7 ± 23.9	69.3±18.2	< 0.01
Etiology of non-acetaminophen-induced acute liver failure, n (%)			0.79
Viral hepatitis	7 (17.5)	3 (23.1)	
Autoimmune hepatitis	1 (2.5)	0 (0)	
Drug-induced liver injury	6 (15)	3 (23.1)	
Amanita mushroom	2 (5)	5 (38.5)	
Hemophagocytic lymphohistiocytosis	4 (10)	0	
Wilson disease	3 (7.5)	0	
Rhabdomyolysis	3 (7.5)	1 (7.7)	
Other ^a	6 (15)	0	
Unknown	8 (20)	1 (7.7)	
Median coma grade ^b on day of N-acetylcysteine initiation	2 (2-3)	2 (1-3)	0.35
Coma grade, ^b by group, n (%)			0.37
Coma grade I-II	22 (55)	9 (69.2)	
Coma grade III-IV	18 (45)	4 (30.8)	
Aspartate aminotransferase on day of N-acetylcysteine initiation, median (interquartile range)	1,368 (609-6,005)	3,128 (935-3,709)	0.7
Alanine aminotransferase on day of N-acetylcysteine initiation, median (interquartile range)	1,625 (326-4,125)	2,787 (882-5,060)	0.26
International normalized ratio on day of N-acetylcysteine initiation, median (interquartile range)	3 (2.2-3.7)	2.5 (1.8-7)	0.8
Bilirubin on day of N-acetylcysteine initiation, mg/dL, median (interquartile range)	7.3 (3.6-15.7)	4.7 (1.6-7.6)	0.08
Model for End-Stage Liver Disease score on day of N-acetylcysteine initiation, median (interquartile range)	33.8 (27.7-38.8)	30.3 (13-38.4)	0.29
Serum creatinine on day of N-acetylcysteine initiation, mg/dL, median (interquartile range)	2.2 (1.3-3.7)	1 (0.6-2.2)	0.05

(Continued)

TABLE 1. (Continued).
Baseline Characteristics of Patients Who Received N-Acetylcysteine for Non-Acetaminophen-Induced Acute Liver Failure

Variables	Standard Duration N-acetylcysteine (≤ 72 hr)	Extended Duration N-acetylcysteine (> 72 hr)	p
	(n = 40)	(n = 13)	
RRT on day of N-acetylcysteine initiation, n (%)	2 (5)	0 (0)	1.0
RRT at any time during N-acetylcysteine administration, n (%)	13 (32.5)	3 (23.1)	0.73
Median duration of RRT, d, median (interquartile range)	1 (1–6)	8 (3–9)	0.07
Median fresh frozen plasma administered during N-acetylcysteine administration, U, median (interquartile range)	0 (0–4)	0 (0–4.5)	0.98
Median vitamin K administered during N-acetylcysteine administration, mg, median (interquartile range)	10 (0–20)	30 (2.5–30)	0.11
Outside hospital transfer, n (%)	34 (85)	13 (100)	0.32
Use of vasopressors on day of N-acetylcysteine initiation, n (%)	12 (30)	3 (23.1)	1.0
Receipt of N-acetylcysteine prior to admission, n (%)	5 (9.8)	8 (61.5)	0.01
Receipt of N-acetylcysteine loading dose ^c , n (%)	37 (92.5)	9 (69.2)	0.05
Receipt of N-acetylcysteine second dose ^c , n (%)	38 (95)	10 (76.9)	0.09
Receipt of N-acetylcysteine third dose ^c , n (%)	30 (75)	9 (69.2)	0.73
Receipt of N-acetylcysteine continuous dose, n (%)	27 (67.5)	13 (100)	0.02
Total duration of N-acetylcysteine, hr, median (interquartile range)	32.6 (21–51.3)	106.3 (84.5–142.6)	< 0.01
Total dose in mg/kg received, median (interquartile range)	330 (300–452.9)	753.7 (697–1,003.6)	< 0.01
Total cost of N-acetylcysteine therapy, U.S. dollars ^d , median (interquartile range)	1,396.61 (1,121.46–1,755.63)	2,430.90 (2,003.89–3,111.94)	< 0.01

RRT = renal replacement therapy.

^aOther etiologies include cholestasis (n = 2), Budd-Chiari (n = 1), congestive hepatopathy (n = 2), sickle cell (n = 1).

^bPer West Haven criteria.

^cDoses of IV N-acetylcysteine given prior to admission were not included.

^dBased on average wholesale price of \$8.62 per 200 mg/mL vial.

duration 78 [60–243]; $p < 0.01$), but median alanine aminotransferase and bilirubin were similar between groups. Median MELD score improved in both groups and was significantly lower in the extended duration group (standard duration 27.3 [21.2–42.2] vs extended duration 24.1 [13.8–30.6]; $p = 0.04$) on the day of N-acetylcysteine discontinuation although median

MELD score in both groups was associated with similar expected 3-month mortality.

DISCUSSION

IV N-acetylcysteine has been studied and is recommended for use in the management of NAI-ALF (2).

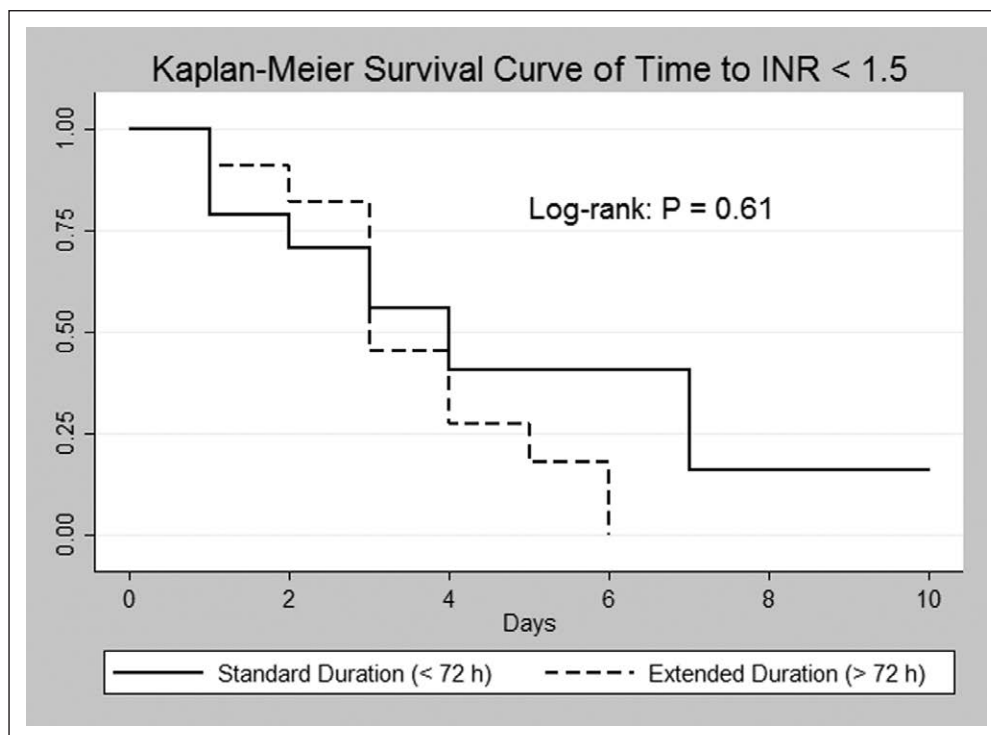


Figure 2. Kaplan-Meier survival curve of time to international normalized ratio (INR) less than 1.5 for patients who received N-acetylcysteine for non-acetaminophen-induced acute liver failure.

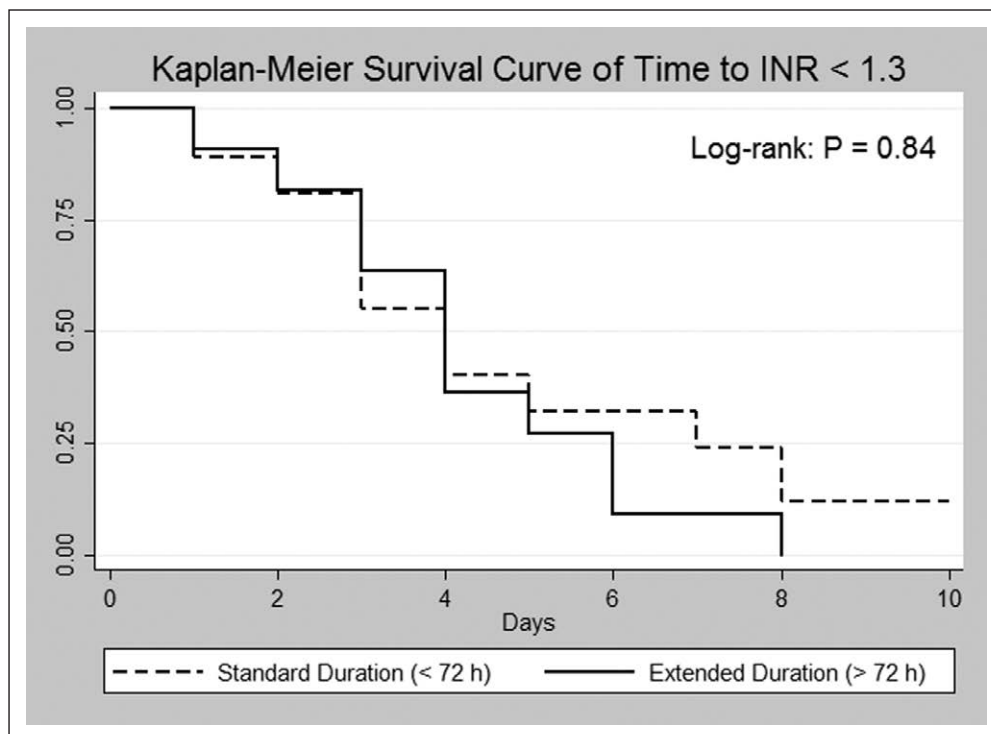


Figure 3. Kaplan-Meier survival curve of time to international normalized ratio (INR) less than 1.3 for patients who received N-acetylcysteine for non-acetaminophen-induced acute liver failure.

Although NAI-ALF as a clinical entity encompasses liver failure as a consequence of multiple etiologies, the organ dysfunction that results from NAI-ALF is thought to be related to the oxidative stress on the liver.

continued until improvement in liver biomarkers. In a 2008 pediatric study by Kortsalioudaki et al (6), IV N-acetylcysteine was continued until INR less than 1.5 or until death or LT; the median duration

As such, acetylcysteine may be beneficial as a source of glutathione supplementation as a free-radical scavenger (3). Additionally, IV N-acetylcysteine may augment both hepatic and global perfusion by causing vasodilation; this hypothesis was generated by a small study of patients with ALF who demonstrated improvements in oxygen delivery and consumption as evidenced by improvements in cardiac index and mean arterial pressure after IV N-acetylcysteine treatment (12).

Several studies have consistently demonstrated improvements in transplant-free survival with the use of IV N-acetylcysteine for NAI-ALF (6–8). The largest of these was a randomized controlled trial of 173 adult patients conducted by Lee et al (8) and used a 72-hour IV N-acetylcysteine regimen. In this study, transplant-free survival was found to be significantly increased in the IV N-acetylcysteine group (40% vs 27%; $p = 0.04$), particularly in the subgroups of patients with low-grade encephalopathy, drug-induced liver injury, and hepatitis B virus-associated ALF. In subsequent observational studies, IV N-acetylcysteine has been prescribed and con-

TABLE 2.
Primary and Secondary Outcomes of Patients Who Received N-Acetylcysteine for Non-Acetaminophen-Induced Acute Liver Failure

Variables	Standard Duration N-acetylcysteine (≤ 72 hr)	Extended Duration N-acetylcysteine (> 72 hr)	p
	(n = 40)	(n = 13)	
Clinical outcomes			
Liver transplant, n (%)	11 (27.5)	3 (23)	1.0
Transplant-free survival ^a , n (%)	12/29 (41.4)	10/13 (76.9)	0.03
All-cause mortality at 3 wk ^a , n (%)	7/29 (24.1)	0/13 (0)	0.08
ICU LOS (survivors), d, median (interquartile range)	8 (3–11)	8 (7–11)	0.92
Hospital LOS (survivors), d, median (interquartile range)	16 (10–22)	12 (10–17)	0.47
Sensitivity analysis (excluding patients with mushroom poisoning), n (%)			
Transplant-free survival ^a	12/27 (44.4)	6/8 (75)	0.23
All-cause mortality at 3 wk ^a	7/27 (25.9)	0/8 (0)	0.17
Liver function tests			
Time to INR < 1.5, d, median (interquartile range)	4 (2–10)	4 (2–6)	0.61
Proportion achieving INR < 1.5, median (interquartile range)	21 (52.5)	11 (84.6)	0.04
Time to INR < 1.3, d, median (interquartile range)	4 (3–10)	4 (3–6)	0.84
Proportion achieving INR < 1.3, n (%)	20 (50)	11 (84.6)	0.03
Aspartate aminotransferase on day of N-acetylcysteine discontinuation, median (interquartile range)	395 (264–1,253)	78 (60–243)	< 0.01
Alanine aminotransferase on day of N-acetylcysteine discontinuation, median (interquartile range)	646 (344–1,586)	482 (357–693)	0.18
INR on day of N-acetylcysteine discontinuation, median (interquartile range)	2.2 (1.5–2.9)	1.2 (1.2–1.4)	< 0.01
Bilirubin on day of N-acetylcysteine discontinuation, mg/dL, median (interquartile range)	8 (3.2–16.8)	10.2 (1.4–17.7)	0.74
Model for End-Stage Liver Disease score on day of N-acetylcysteine discontinuation, median (interquartile range)	27.3 (21.2–42.2)	24.1 (13.8–30.6)	0.04

INR = international normalized ratio, LOS = length of stay.

^aExcludes those who died within the first 72 hr (n = 11).

of IV N-acetylcysteine in this study was 5 days. The use of IV N-acetylcysteine significantly increased transplant-free survival rates compared with a historical cohort (43% vs 22%; $p = 0.05$). Similarly, Darweesh et al (7) conducted an observational study of IV N-acetylcysteine for NAI-ALF and continued

until INR less than 1.3; the median duration of IV N-acetylcysteine was 8 days. This strategy was also associated with a higher transplant-free survival rate compared with historical controls (96.4% vs 23.3%; $p < 0.01$). Based on these data, a 2015 meta-analysis was conducted evaluating the role of N-acetylcysteine in

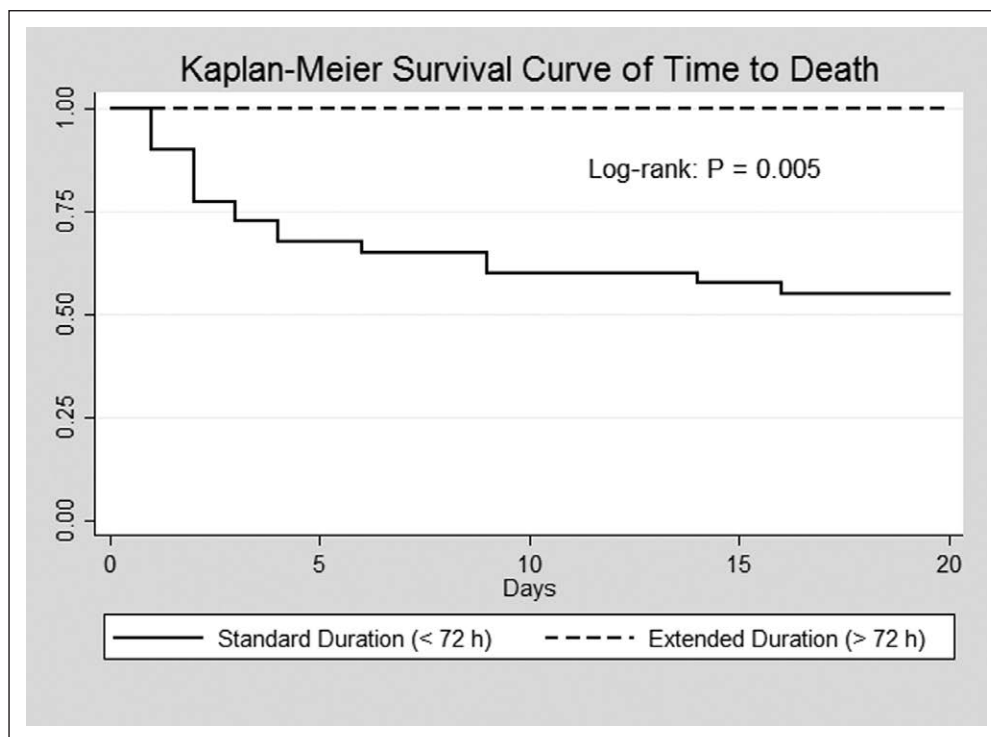


Figure 4. Kaplan-Meier survival curve of overall survival for patients who received N-acetylcysteine for non-acetaminophen-induced acute liver failure.

the treatment of NAI-ALF (5). The authors concluded that N-acetylcysteine can improve transplant-free survival (41% N-acetylcysteine vs 30% control; $p = 0.01$) although no difference was found in overall survival (71% N-acetylcysteine vs 67% control; $p = 0.42$). However, the authors noted that further studies are needed to determine the optimal dose and duration of N-acetylcysteine therapy to drive these improved outcomes due to the heterogeneity of dosing regimens in the included studies (5).

In this retrospective cohort study, no difference was identified in time to INR normalization, defined as either INR less than 1.5 or INR less than 1.3, for adult patients with NAI-ALF who received either standard duration IV N-acetylcysteine or extended duration IV N-acetylcysteine. INR normalization was selected as a surrogate for liver function and as a cessation endpoint for IV N-acetylcysteine based on the previous retrospective observational studies which demonstrated improved transplant-free survival when these cessation endpoints were selected (6, 7). In this analysis, the median time to INR normalization of INR less than 1.5 and less than 1.3, respectively, was approximately 4 days in both groups, which is similar to the median time to INR normalization less than 1.5 of 5

days (range, 1–77 d) in the study by Kortsalioudaki et al (6). Furthermore, Kaplan-Meier curves demonstrated no difference in time to INR normalization between treatment groups, suggesting that INR normalization may not be a meaningful clinical endpoint for directing IV N-acetylcysteine duration. However, the proportion of patients who achieved INR normalization was significantly higher in those patients in the extended duration group. Notably, a significant proportion of patients in the extended duration group received IV N-acetylcysteine prior to admission (9.8% standard

duration group vs 61.5% extended duration, $p = 0.01$). As a result, although this study did not find a difference in time to INR normalization, it is likely that there was a longer time to INR normalization in the extended duration group when taking into consideration the time from IV N-acetylcysteine initiation at the outside institution to INR endpoints met at our institution; this should be considered a study limitation.

In terms of meaningful patient outcomes, transplant-free survival was significantly higher in NAI-ALF patients who received extended duration IV N-acetylcysteine compared with those who received standard duration IV N-acetylcysteine (12/29 standard duration 41.4% vs 10/13 extended duration 76.9%, $p = 0.03$). Our findings in the standard duration group are similar to the rates of transplant-free survival reported in the study by Lee et al (40%) (8) and a pediatric trial of IV N-acetylcysteine for NAI-ALF (43%) (6). Although there was no difference in overall transplant rate based on duration of IV N-acetylcysteine (23% extended duration vs 27.5% standard duration; $p = 1.0$), the rates of transplantation in NAI-ALF are similar to those reported by Lee et al (32%) (8).

Finally, although not statistically significant between groups, all-cause mortality at 3 weeks was numerically

lower in patients with NAI-ALF who received extended duration IV N-acetylcysteine than those who received standard duration IV N-acetylcysteine (24.1% standard duration vs 0% extended duration; $p = 0.08$). Of note, the mortality rate in the standard duration group was lower than that reported in the literature for patients with NAI-ALF receiving IV N-acetylcysteine (~30%) (5, 8); however, there is still a large absolute mortality difference between groups. In order to account for the bias driven by early mortality, patients who experienced early mortality within 72 hours were excluded from analysis of overall and transplant-free survival. Therefore, we would argue that the survival advantage of extended duration IV N-acetylcysteine may be clinically significant. This finding warrants further analysis in large, randomized, multicenter study, as previous prospective studies and meta-analysis have not established an effect on mortality with the use of IV N-acetylcysteine in NAI-ALF (5, 8).

Existing literature and guidelines lack well-defined criteria to guide duration of IV N-acetylcysteine in NAI-ALF (2), this ambiguity has led to a heterogeneity in clinical practice. As a result, clinicians must rely on hepatic biomarkers, assessments of disease severity, and survival analysis tools to direct decision-making regarding the extension of standard duration of IV N-acetylcysteine therapy in specific patients. Although the findings of this single-center analysis do not support the application of INR normalization to guide duration of IV N-acetylcysteine therapy, improved transplant-free survival rates suggest that there may be a physiologic benefit of extending the duration of IV N-acetylcysteine past 72 hours. This conclusion is supported by the hypothesis that, in cases of NAI-ALF, the physiologic benefits of IV N-acetylcysteine, including both its antioxidant and vasodilatory properties, may extend beyond the first few days of liver injury (3). Extending the duration of IV N-acetylcysteine may improve both hepatic perfusion and systemic end-organ perfusion as evidenced by the observed significant improvements in median MELD on day of N-acetylcysteine discontinuation (standard duration: 27.3 [21.2–42.2] vs extended duration: 24.1 [13.8–30.6]; $p = 0.04$) as well the reduction in serum creatinine on day of N-acetylcysteine discontinuation (standard duration: 2.74 mg/dL [1.28–4 mg/dL] vs extended duration: 2.36 mg/dL [1–4 mg/dL]; $p = 0.78$). Prospective study should be undertaken to identify markers of

hepatic recovery that better guide endpoints for cessation of IV N-acetylcysteine in NAI-ALF.

There were several limitations to this study. First, this retrospective cohort study was subject to the inherent flaws of that design. Most notably, the decision to extend the duration of IV N-acetylcysteine was clinician dependent and may have reflected clinical decision-making in the support of aggressive supportive care (i.e., in an effort to avoid LT based on patient factors) or even a selection bias due to observed positive response to therapy. To compound this limitation and conversely, many patients in the standard group received a duration much shorter than 72 hours based on clinician discretion (median duration standard group 32.6 hr), suggesting that the total difference in N-acetylcysteine duration between groups may be greater than described. The lower than expected median duration of IV N-acetylcysteine in the standard group was likely due to the long period of study inclusion and temporal variations in IV N-acetylcysteine protocols (i.e., the use of an acetaminophen-based IV N-acetylcysteine protocol for NAI-ALF in early years) as well as unaccounted for IV N-acetylcysteine doses received prior to referral center transfer. In an effort to account for these limitations, a subgroup analysis was performed based on duration of IV N-acetylcysteine and demonstrated comparable differences in transplant-free survival and mortality at 3 weeks (Supplementary Appendix Table 1, <http://links.lww.com/CCX/A599>). Additionally, as this study was performed at a quaternary referral center, any IV N-acetylcysteine that was administered prior to transfer to the referral center was unable to be accounted for. This is evidenced by the greater number of patients in the standard duration group who received the loading dose and second dose of IV N-acetylcysteine at our institution, compared with the extended duration group, likely because more patients in the extended duration group received N-acetylcysteine prior to admission. Of the 13 overall study patients (24%) who received IV N-acetylcysteine prior to transfer, the majority (61.5%) were in the extended duration group; IV N-acetylcysteine administered prior to transfer would have further extended the total duration of therapy. Furthermore, due to retrospective study design, we were unable to account for any potential increased adverse effects of extended duration IV N-acetylcysteine, such as hypotension

and flushing. However, as these reactions are rare and typically associated with loading doses, it is anticipated that the occurrence would be low with an extended continuous infusion. Finally, this analysis was limited by small sample size, particularly the number of patients in the extended duration group. This is of importance noting that numerically more patients in the extended duration group were treated for Amanita mushroom toxicity, a subpopulation of NAI-ALF patients that may manifest a more protracted clinical course (13). In a sensitivity analysis excluding these patients, transplant-free survival was higher, and all-cause mortality was lower in the extended duration group, but these differences did not achieve statistical significance, likely a consequence of small cohort size. With broader study, additional important secondary outcomes associated with IV N-acetylcysteine duration may emerge.

CONCLUSIONS

In this single-center retrospective cohort study, we demonstrate no significant difference in the time to INR normalization between adult patients with NAI-ALF treated with standard duration IV N-acetylcysteine compared with those treated with extended duration IV N-acetylcysteine. However, extended duration IV N-acetylcysteine was associated with an improved transplant-free survival at 3 weeks compared with standard duration IV N-acetylcysteine. Expanded prospective, randomized, multicenter study is needed to identify biomarkers to guide duration of N-acetylcysteine therapy as well as the subpopulations of patients with NAI-ALF who would most benefit from extended treatment duration either as a bridge to transplant or to spontaneous recovery.

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REFERENCES

1. Lee WM, Stravitz RT, Larson AM: Introduction to the revised American association for the study of liver diseases position paper on acute liver failure 2011. *Hepatology* 2012; 55:965–967
2. Wendon J, Cordoba J, Dhawan A, et al: EASL clinical practical guidelines on the management of acute (fulminant) liver failure. *J Hepatol* 2017; 66:1047–1081
3. Bass S, Zook N: Intravenous acetylcysteine for indications other than acetaminophen overdose. *Am J Health Syst Pharm* 2013; 70:1496–1501
4. Sklar GE, Subramaniam M: Acetylcysteine treatment for non-acetaminophen-induced acute liver failure. *Ann Pharmacother* 2004; 38:498–500
5. Hu J, Zhang Q, Ren X, et al: Efficacy and safety of acetylcysteine in “non-acetaminophen” acute liver failure: A meta-analysis of prospective clinical trials. *Clin Res Hepatol Gastroenterol* 2015; 39:594–599
6. Kortsalioudaki C, Taylor RM, Cheeseman P, et al: Safety and efficacy of N-acetylcysteine in children with non-acetaminophen-induced acute liver failure. *Liver Transpl* 2008; 14:25–30
7. Darweesh SK, Ibrahim MF, El-Tahawy MA: Effect of N-acetylcysteine on mortality and liver transplantation rate in non-acetaminophen-induced acute liver failure: A multicenter study. *Clin Drug Investig* 2017; 37:473–482
8. Lee WM, Hynan LS, Rossaro L, et al; Acute Liver Failure Study Group: Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009; 137:856–864, 864.e1
9. Squires RH, Dhawan A, Alonso E, et al; Pediatric Acute Liver Failure Study Group: Intravenous N-acetylcysteine in pediatric patients with non-acetaminophen acute liver failure: A placebo-controlled clinical trial. *Hepatology* 2013; 57:1542–1549
10. Katoonizadeh A, Decaestecker J, Wilmer A, et al: MELD score to predict outcome in adult patients with non-acetaminophen-induced acute liver failure. *Liver Int* 2007; 27:329–334
11. Kamath PS, Wiesner RH, Malinchoc M, et al: A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33:464–470
12. Harrison PM, Wendon JA, Gimson AE, et al: Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med* 1991; 324:1852–1857
13. Karlson-Stiber C, Persson H: Cytotoxic fungi—an overview. *Toxicol* 2003; 42:339–349