Therapeutic hypothermia in acute liver failure: a multi-center retrospective cohort analysis

Constantine J. Karvellas, MD SM[1], **R. Todd Stravitz, MD**[2], **Holly Battenhouse, MSc**[3], **William M. Lee, MD**[4], **Michael L. Schilsky, MD**[5], and **for the US Acute Liver Failure Study Group**

Constantine J. Karvellas: dean.karvellas@ualberta.ca; R. Todd Stravitz: rstravit@hsc.vcu.edu; Holly Battenhouse: battenho@musc.edu; William M. Lee: william.lee@utsouthwestern.edu; Michael L. Schilsky: michael.schilsky@yale.edu

[1]Divisions of Hepatology and Critical Care Medicine, University of Alberta, Edmonton, Canada.

[2]Division of Gastroenterology and Hepatology, Virginia Commonwealth University, Richmond, USA.

[3]Faculty of Medicine, Medical University of South Carolina, Charleston, USA.

[4]Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

[5]Division of Digestive Diseases and Transplant and Immunology, Yale University School of Medicine, New Haven, USA.

Abstract

Background—The benefit of therapeutic hypothermia (TH) in Acute Liver Failure (ALF) has not been previously demonstrated in a controlled fashion. This study aimed to determine the impact of TH on 21-day survival and complications in ALF patients at high risk for cerebral edema.

Methods—Retrospective cohort study of ALF patients in the US ALFSG with Grade III or IV hepatic encephalopathy. TH (32°C – 35°C) was used in 97 (8%) patients; 1135 (92%) not cooled were controls.

Results—Intracranial pressure (ICP) was monitored in 38 (40%) TH ALF patients (vs. 22% controls, p=0.0001). Rates of bleeding (12% in both), bloodstream (17% vs. 18) and tracheal infections (21% vs. 23%, p> 0.5 for all) were similar. Unadjusted 21-day overall (62% vs. 60%) and transplant-free survival (45 vs. 39%, p>0.4 for both) were similar. Multivariable models were created for acetaminophen (APAP) (n= 582) and non-APAP (n=613) patients. For APAP patients, MELD (Odds ratio 0.91 per increment; 95% CI 0.89–0.94, p <0.001) and vasopressors (OR 0.16; 0.11–0.24, p < 0.0001) were associated with decreased 21-day spontaneous survival. Survival was improved with TH in APAP patients aged < 25y (Age 25: OR 2.735; 95% CI 1.001 – 7.467) but worsened in 64y or older APAP patients (Age = 64: OR 0.167; 95%CI 0.028 – 0.999). For non-APAP patients, MELD (OR 0.93 per increment; 0.91–0.95, p < 0.0001) and vasopressors (OR 0.60; 0.40–0.90, p=0.01) were associated with worse outcomes while TH had no impact (p= 0.93).

Conclusions—Therapeutic hypothermia in ALF was not associated with increased bleeding or infections. While young APAP-ALF patients may benefit, TH did not consistently impact 21-day survival. A prospective trial is required to clarify the utility of TH in ALF patients.

Keywords

Acute liver failure; cerebral edema; fulminant hepatic failure; intracranial hypertension; therapeutic hypothermia

Introduction

Acute liver failure (ALF) is defined by hepatic encephalopathy (HE) and synthetic dysfunction within 26 weeks of the first symptoms of liver disease(1). The most common cause of ALF in North America is acetaminophen (APAP) (2, 3). Particularly in APAP-induced ALF, cerebral edema and intracranial hypertension (ICH) continue to be major causes of morbidity and mortality(4, 5). Medical interventions to reduce ICH might prevent brain injury; the presence of clinically significant ICH prior to emergency LT portends a higher likelihood of ischemic brain injury (6, 7). Reducing ICH may be undertaken using osmotic agents (mannitol or hypertonic saline)(8), control of blood pressure, ammonia-lowering therapies (e.g., hemofiltration(9)) and therapeutic hypothermia (TH) (10). While these interventions are frequently employed, it is not clear which are more effective. Indeed, multiple interventions may be initiated simultaneously in these patients.

Therapeutic cooling might protect against cerebral edema by various mechanisms: normalization of cerebral blood flow, decreased cerebral metabolic rate, decreased cytokine production and decreased conversion of glutamate to glutamine, the active osmole precipitating cerebral edema in astrocytes(11–13). This has been shown in animal and humans: decreased intracranial pressure (ICP), cerebral blood flow and increased cerebral perfusion pressure (CPP) have been demonstrated using moderate (32 – 35 C) hypothermia(10, 14). Despite the potential utility of TH, there are concerns that lowering core temperature might lead to increased bleeding events(15), microbial infections(16), cardiac dysrhythmias(17) and potentially reduced hepatic regeneration(18). Currently there are no controlled data examining the effect of TH in ALF and no evidence based guidelines for its use in these patients.

The aim of this study was to determine retrospectively the role and value of TH in prevention or management of cerebral edema in ALF in the large prospective ALFSG registry; whether TH impacted transplant-free survival compared to those not receiving TH (controls). Furthermore, we examined in this ALF cohort whether treatment with TH was associated with more complications (infection, bleeding, dysrhythmias) as suggested by the current literature.

MATERIALS AND METHODS

The reporting of this study followed the STROBE guideline (19).

Design and Setting

The ALF registry has prospectively collected clinical and laboratory data on over 2,300 patients with ALF over the past 15 years. In the present study, we focused on patients who had highest risk for cerebral edema or ICH, namely those with grade III or IV HE, by performing a retrospective cohort study of 1232 ALF patients with Grade III or IV HE enrolled into the US ALFSG registry between January 1998 and August 2013. While the use of TH was governed by local center protocol, we identified that ~ 8% (97/1232) of our study patients were treated with this intervention. All enrolling centers were tertiary academic centers and all but one were liver transplant centers. The Institutional Review Board at each participating center approved the ALFSG protocols. Because of HE in all patients, next of kin provided consent for study participation. Each center implemented monitoring and therapeutic interventions according to institutional standards of care. TH implied the use of an active cooling device (e.g., Arctic Sun™) with temperature target between 32–35C. The individual practicing clinician determined decisions regarding initiation and maintenance of TH and the type of active cooling device. Passive cooling (e.g. due to the use of renal replacement therapy (RRT)) did not meet criteria for TH within the ALFSG registry. While there were no study-wide protocols for application of TH across the US ALFSG sites, based on previously published US and UK literature some indications for TH may include hyperammonemia (ammonia > 150 μmol/L), listing for LT, meeting King's College criteria, or presence of multisystem organ failure(20, 21).

Participants

Inclusion criteria were: 1) evidence of ALF according to the enrollment criteria for the ALFSG (see operational definitions) AND 2) age   18 years; and 3) Grade III or IV HE during the first seven days of study admission (West Haven Criteria)(22, 23). *Exclusion criteria* were: 1) Cirrhosis/acute on chronic liver failure; 2) patients < 18 years; and 3) HE coma grade 1 or 2.

Operational Definitions

For the purposes of this study, ALF was defined as INR   1.5 and HE within the first 26 weeks of liver disease in a patient with an acute hepatic insult (24). HE grade was defined by the West Haven Criteria (simplified) as follows; grade 1 ~ any alteration in mentation, grade 2 being somnolent or obtunded but easily rousable or presence of asterixis, grade 3 being rousable with difficulty and, grade 4: unresponsive to deep pain (22, 23).

Variables

The exposure of interest was use of active TH in patients with ALF (both APAP and non-APAP). The primary outcomes of interest were overall and spontaneous survival at 21 days (absence of transplant). Secondary outcomes included complications possibly attributed to or prevented by TH ~ infection (bacteremia, tracheal aspirates), bleeding (gastrointestinal or other), coagulopathy (requirement for hematological factors), cardiac dysrhythmias. Confounding factors, which may impact the primary outcome (mortality), included age, gender, etiology of ALF (APAP vs. non-APAP), requirement for organ support (vasopressors, mechanical ventilation [MV]), renal replacement therapy (RRT), and LT.

Data Sources and Collection

Data were collected prospectively as part of the US ALFSG and retrospectively analyzed. Prior to February 2010, each individual site sent case report forms to the University of Texas Southwestern for entry into a central database. Following this date, individual sites entered data electronically into a central database housed at the ALFSG Data Coordinating Center at the Medical University of South Carolina (Charleston, SC, USA). Registry data assessed in this study included demographics (age, race, sex), etiology of ALF, biochemistry, days of TH, daily minimum and maximum temperature, requirement for organ support during first 7 days, requirement for ICP related therapies and outcomes including receipt of LT and death at 21 days.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 19 (2010) and SAS version 9.2 (SAS Institute, North Carolina, USA). In the event of missing values, data were not replaced or estimated. Data were analyzed using descriptive statistics to characterize demographics and other clinical variables. Categorical variables were compared using the Chi-square test or Fisher's exact test (< 5 cell counts). For continuous variables, normally distributed variables were reported as means with standard deviations (SD) and compared by Student's t-test. Non-normally distributed continuous data were reported as medians with inter-quartile ranges (IQR) and compared by Wilcoxon rank sum test. Survival was defined as the dichotomous outcome, alive at 21-days (transplant and transplant free) after enrollment into the Registry. Transplant and transplant free refer to whether patients received LT during the first 21-days of follow-up. A two-sided significance level of <0.05 was used for all comparisons.

Multivariable analysis

In order to control for variables that may confound the effect of TH on 21-day spontaneous (transplant-free) survival multivariable logistic regression analyses were performed. Two separate logistic regression models to predict spontaneous survival at 21-days were performed. Transplant was considered as a composite endpoint with death at 21 days. The pre-specified prognostic variables included age at admission into the registry, gender, MELD score (admission), requirement during the 7-days post study admission of MV, vasopressors, RRT and TH. Model performance was assessed using the c-statistic and the Hosmer-

Lemeshow test for goodness of fit. Multivariate associations are reported as odds ratios (OR) with 95% confidence limits.

RESULTS

General characteristics of 1232 ALF patients with Grade III/IV hepatic coma

Therapeutic hypothermia was used in 97 (8%) of patients with Grade III-IV HE. All patients were cooled between 32–35 C and for a median of 2 (1–3) days. Of 28 enrolling sites, 19 (68%) performed TH in at least one ALF patient; 24 patients were cooled for > 3 (4–7) days. The median target temperature was significantly cooler in TH patients (while being cooled) than controls (34.1 vs. 36.6 C, p < 0.0001).

Demographic, biochemical and therapeutic characteristics of treated patients (n=97) and controls (n=1135) are shown in Table 1. There were no significant differences in gender (71% female) and race (77% Caucasian) between groups. The most common etiology of ALF was APAP (TH 64%, Controls 47%, p= 0.04). Overall, TH patients were significantly younger (36 vs. 40 years; p < 0.03). On study admission (Table 1), hematological indicators were similar (platelet count TH 105 vs. controls 125; p=0.10). There were no differences between TH and control patients in admission serum creatinine (1.5 vs. 2.0 mg/dL; p=0.08), phosphate (mg/dL) (2.8 vs. 3.2, p= 0.06) and MELD scores (median 32 vs. 34, p=0.23). On admission, there were no differences in the presence of pupillary dilatation between TH patients and controls (22% vs. 18%, p=0.3).

During the first 7 study days, TH patients were more likely to be on RRT (63% vs. 40%), MV (100% vs. 86%) and vasopressors (61% vs. 43%, p < 0.001 for all). More TH patients received intracranial hypertension (ICH) directed therapies; including mannitol (62% vs. 27%), hypertonic saline (34% vs. 6%), barbiturates (17% vs. 9%) and sedatives (91% vs. 77%; p < 0.03 for all). More TH patients had ICP monitors in situ (39% vs. 22%, p=0.0001) and received blood products (fresh frozen plasma: 83% vs. 68%, p=0.003; platelets: 39% vs. 29%, p=0.04) than controls. Where data were available in those monitored with an ICP monitor, more TH patients had an ICP value over 25 mm Hg (ICH ~ (23/38 ~ 61% vs. 35/218 ~ 16%, p < 0.0001).

Outcomes in 1232 ALF patients with Grade III-IV HE

Complications and outcomes are shown in Table 2. During the first 7 days of study, TH patients were more likely to have cardiac arrhythmias (38% vs. 27%, p=0.03) but not when considering arrhythmias (n=29) following initiation of TH (28% vs. 27%, p=0.9). More TH patients had abnormalities of chest radiograph (87% vs. 77%, p=0.02) than controls. Though more TH patients had an abnormal head CT compared with controls the difference was not statistically significant (53% vs. 41%, p=0.08). In addition, there were no significant differences in other complications (seizures, GI bleeding, bacteremia, tracheal aspirate infection, p >0.1 for all comparisons). In 12 TH patients who developed GI bleeding, most of the bleeding events (n=10, 83%) occurred following initiation of TH. In comparing 24 patients receiving TH for > 3 days to those who received TH for less than 3 days (n=73) there were no significant differences in arrhythmias (38% vs. 37, p=0.94), bloodstream (29

vs. 12%, p=0.07) and tracheal infections (33 vs. 16%, p=0.09). In comparing 29 patients who had recorded temperatures below 33 °C for at least on day vs. 68 patients who were not there were no significant differences in arrhythmias (52% vs. 32%, p=0.07) and bloodstream infections (28 vs. 12%, p=0.07) but significantly more tracheal infections (35 vs. 15%, p=0.03).

TH was used slightly more often in patients who were listed for LT (44% vs. 40%) and slightly less receiving TH received a LT (18% vs. 25%), but these differences were not statistically significant (p > 0.10 for both, see Table 2). Overall 21-day spontaneous survival was similar between TH patients and controls when all patients were included (45% vs. 39%, p= 0.24), and did not change when only APAP (57 vs. 56%, p=0. 78) or non-APAP (25% vs. 25%, p=0.90;see Figure 1) patients were considered. In the TH group, 11 (15%) died of neurological complications (cerebral edema or intracranial hemorrhage) compared with 105 (14%), p-value=0.75) in the control group.

Multivariable analysis of APAP-induced ALF patients

Within the study population, rates of LT (12% vs.34 %, p < 0.0001) and 21-day mortality (34% vs. 46%, p <0.0001) differed between APAP and non-APAP patients. The cohort was therefore stratified to APAP and non-APAP etiology of ALF to assess adjusted transplant-free survival by controlling for confounding factors. The APAP-ALF model included 582 patients (16 subjects were excluded due to missing data for at least one prognostic variable). Multivariable logistic regression results are shown in Table 3. The c-statistic (i.e., how well the model distinguishes between transplant-free survivors and transplanted/non-survivors at 21 days) was 0.812 (good predictive accuracy). Increasing admission MELD (Odds Ratio: OR 0.91 (95% CI 0.89–0.94 per increment); p <0.0001) and requirement for vasopressors within 7 days (OR 0.16 (0.11–0.24), p < 0.0001) were significantly associated with decreased 21-day transplant free (spontaneous) survival after controlling for confounding factors. RRT and MV were not included in the final model due to colinearity with other variables. Gender was not significant in the final model. A qualitative interaction effect was found between age and TH (p=0.023). When accounting for other factors, younger APAP patients were more likely to spontaneously survive to 21 days when treated with TH and older APAP patients were less likely to spontaneously survive when treated with TH (*see* Supplementary Table 1). The odds ratio is > 1 (protective, does not cross unity) for those aged 18–25 (n=101) (Age 25: OR: 2.735 (1.001 – 7.467)). The odds ratio is < 1 (deleterious, does not cross unity) for those over 63 (n=13) (Age 64: OR: 0.167 (0.028 – 0.999)).

Multivariable analysis of 613 Non-Acetaminophen-induced ALF patients

Multivariable logistic regression results of 613 non-APAP ALF patients are shown in Table 4 (21 patients had missing data). The model c-statistic was 0.70. Male gender (OR 1.618 [1.083, 22.146]) was independently associated with improved 21-day transplant free survival. Requirement for vasopressors (OR 0.60 [0.40, 0.904]), and increased MELD (OR 0.929 [0.906, 0.952]) were associated with significantly decreased 21-day transplant-free survival. Age (p=0.11 per year) and hypothermia (p=0.93) were not significantly associated with 21-day transplant-free survival in Non-APAP ALF patients after controlling for confounding factors.

DISCUSSION

Summary of Key Results

In this retrospective study we aimed to evaluate a large multi-center experience with TH (n=97) in the treatment of patients with ALF with advanced (III/IV) HE (total cohort n=1232). TH was used infrequently, in only ~8% of registrants. It was overall not associated with increased bleeding or infectious complications. TH potentially increased infection rates in those with recorded temperatures below 33 °C. TH did not appear to improve overall and transplant-free survival. ICP monitoring was not universally used in TH patients (~ 40%). After controlling for confounding by severity of illness (MELD, organ support), TH was not significantly associated with 21-day spontaneous survival in non-APAP patients. In APAP patients, TH may potentially be associated with benefit in patients less than 26 years of age.

Comparison with Previous Literature

This ALF cohort (TH and control patients) shared similar demographics with all patients entering into the overall ALFSG registry and with other series from North America and Europe; most were female, young, and APAP was the most common etiology. Patients who received TH were significantly younger than controls (36 versus 40 years, p=0.03) and were more likely to be diagnosed with APAP-induced ALF (64% vs. 47%, p=0.04). The higher percent of TH use in APAP cases may be explained by the 'hyperacute' nature of ALF in patients with this etiology of injury where progression of liver injury/multi-organ dysfunction often occurs very rapidly and where ICH is thought to be more frequent(1). Similar to our findings, Bernal and colleagues have previously reported that patients with the highest risk of clinically significant ICH had high serum ammonia levels, required RRT, were hemodynamically unstable (required vasopressors) and were younger (20). In our cohort, patients who underwent TH also had increased requirements for RRT and vasopressors during the first 7 days. Overall, TH did not affect outcomes, but its selective use in those thought to be at highest risk: under 26 years of age with acetaminophen overdose, bears further study.

The severity of illness between the TH and control group was similar when examined by MELD score or by hematological parameters. However, TH patients were on RRT and required vasopressor support, and were on MV more frequently than controls, suggesting more severe multi-organ systems failure not captured by MELD in these individuals. That this was likely true is reflected in the more frequent use of ICH directed therapies as well as the reporting of a higher frequency of an abnormal CT of the brain in patients in the TH group. Thus, it was not surprising that more TH patients had ICP monitors used than controls (39% vs. 22%, p=0.0001) given the higher likelihood these patients had evidence for, or might be expected to have, cerebral edema. Unfortunately, we can only speculate on this point, as we were unable to objectively determine in those without ICP monitoring whether increased ICP was indeed present. TH patients more frequently received blood products (fresh frozen plasma: 83% vs. 68%; platelets: 39% vs. 29%) than controls (p < 0.05 for both). While it is plausible that the use of the blood products was due to more frequent ICP monitor placement in TH patients and the perception of the need to correct the coagulation abnormalities, there were no differences amongst TH patients with (n=38) and

without (n=59) ICP monitor in situ regarding use of fresh frozen plasma (18 vs. 17%, p=0.85) or platelets (58% vs. 63%) during 7 days of inpatient study.

Despite animal(11–13) and uncontrolled human data(10, 14) suggesting a potential benefit of TH in mitigating ICH in ALF, our study failed to show a consistent measurable benefit for TH on overall survival. While an interaction term was observed between age and TH for 21-day spontaneous survival in APAP-ALF patients suggesting a possible benefit in patients aged 25 (OR/95% CI > 1), this study did not show a consistent benefit of TH in other groups of either APAP or non-APAP ALF patients, after adjusting for confounding by severity of illness. These results are consistent with recent findings in the anoxic brain injury population, where initial studies of TH following cardiac arrest showed benefit(25, 26), but a more recent larger study by Nielsen and colleagues concluded that cooling to a core body temperature of 33° C yielded no significant improvement in outcome compared to 36°C(27). Hence, while it is well accepted that hyperthermia portends a worse outcome in ALF patients at risk for ICH, it is possible that more-than-moderate TH may not necessarily yield additive benefit over normothermia.

As the safety of using TH for ALF patients has previously been called into question, we specifically examined the frequency of complications in this cohort as granular data was captured in our case report forms. While there have been theoretical concerns of inhibition of hepatic regeneration(18), infection, bleeding and arrhythmias have been cited as more significant concerns. Regarding hepatic regeneration, almost half (45.4%) of the patients undergoing TH in this cohort were able to survive without the need of liver transplant. A recent meta-analysis by Geurts and colleagues revealed that while overall rates of infection were similar, general critical care patients receiving TH had higher rates of pneumonia and sepsis/bacteremia(16). In our study, rates of bloodstream infection and tracheal infection were not different between ALF patients receiving TH and controls. Furthermore despite concerns of potentially exacerbating coagulopathy(15) we did not observe differences in gastrointestinal bleeding rates between treatment groups. In addition, while there were significantly more cardiac arrhythmias identified in our ALF patients treated with TH (p=0.03), there was no significant difference when considering arrhythmias occurring following TH initiation (p=0.9). Finally, though no survival benefit could be demonstrated, TH was well tolerated with few adverse events.

Study limitations

Our study has limitations that warrant consideration. First, it is a retrospective analysis of prospectively collected data, thereby potentially predisposed to selection bias. Individual centers vary in volume and made independent decisions about listing for LT, insertion of an ICPM, and use of TH. The practicing clinician made decisions about initiation and discontinuation of TH. While common indications for TH described in the methods are based on recent recommendations from data from King's College Hospital(20) and the US ALFSG(21), identifying patients at highest risk of cerebral edema, both of these studies were published after this cohort began. Patients were not assigned randomly to receive TH and it is possible that TH was undertaken in sicker patients (i.e. higher risk of cerebral edema) as patients in the TH group also received more ICP-directed therapies, had more

abnormal findings on CT of the brain and had higher use of vasopressor agents. We attempted to control for confounding by performing multivariable analysis accounting for severity of liver dysfunction (MELD) and multi-organ failure (requirement for vasopressors, RRT and MV). SOFA and APACHE II could not be accurately calculated due to lack of detailed information on vasopressor doses (SOFA) and GCS (APACHE II; only hepatic coma grade available).

Because each center determined its own protocol, there was no uniformity in the timing or parameters for use of TH amongst centers or even at a center over time given that the study period was over 15 years. However, despite these limitations, we were able to observe whether TH was used with or without ICP monitoring, and examine whether the use of this intervention was associated with changes in survival at 21 days or with increased complications during the 7-day period of data collection on study entry.

To unequivocally answer these issues of bias, a prospective randomized study with standardized management protocols would be required. While no prospective studies have been published to date, a prospective randomized multicenter European Study is ongoing. Hence in the absence of published prospective controlled data in patients with ALF, the data presented largely suggests no benefit of TH, but also no harm.

CONCLUSIONS

In ALF patients with high-grade hepatic coma, TH appears safe and was not associated with increased bleeding or infectious complications. No differences in overall and transplant free survival in ALF patients with high grade HE were evident between the groups, even after adjusting for confounding factors related to severity of illness, however a subset of young patients with APAP etiology for ALF might benefit from TH. ICP monitoring was not universally used in patients receiving TH in this cohort (~ 40%). While our results cannot conclusively confirm or refute the utility of TH in ALF patients, prospective studies are awaited to conclusively account for confounding by etiology and illness severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

ALF	Acute Liver Failure
APAP	Acetaminophen
CRRT	Continuous renal replacement therapy
HBV	Hepatitis B
HE	Hepatic Encephalopathy
ICH	Intracranial hypertension
ICP	Intracranial Pressure
ICPM	Intracranial Pressure monitor/monitoring
ICU	Intensive Care Unit
LT	Liver transplant
MELD	Model for End-stage Liver Disease
MV	Mechanical ventilation
RRT	Renal replacement therapy
TH	Therapeutic hypothermia
US ALFSG	United States Acute Liver Failure Study Group

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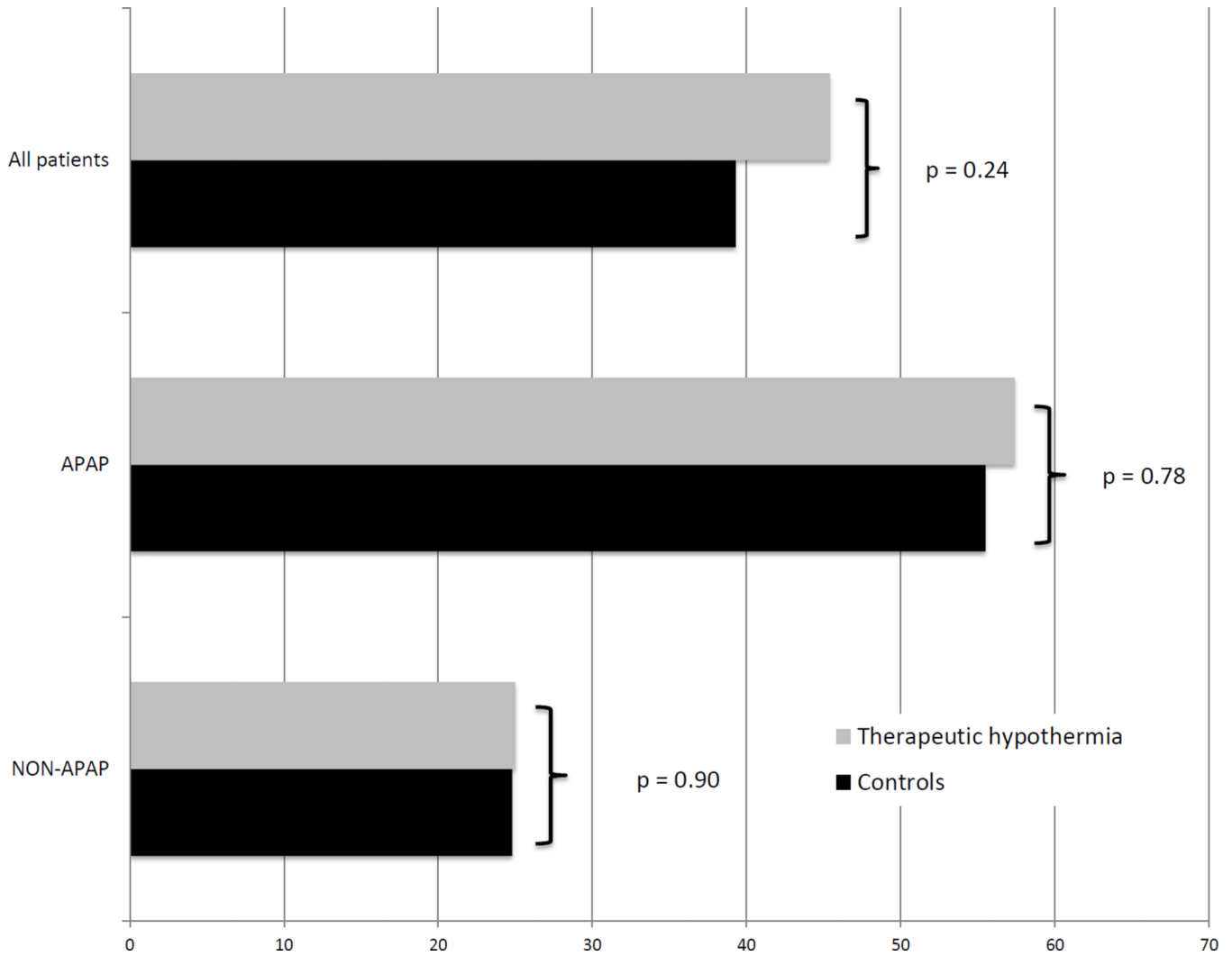
Figure 1.
21-day spontaneous survival (unadjusted) percentage for 1232 ALF patients with Grade III/IV Hepatic Encephalopathy

- All patients: Controls= 1135, Therapeutic Hypothermia (TH) =97 (p= 0.24)

- Acetaminophen (APAP) patients: Controls = 537, TH=61 (p= 0.78)

- Non-acetaminophen (non-APAP) patients: Controls= 598, TH=36 (p= 0.90)

Table 1

Demographic, Clinical and Biochemical Parameters in 1232 ALF patients with Grade III/IV Hepatic encephalopathy treated with therapeutic hypothermia (N=97) and controls (n=1135).

	No Hypothermia (control group) (N=1135)		Hypothermia group (N=97)		
	N	Number (%) or median (IQR)	N	Number (%) or median (IQR)	P value
Age	1135	40.0 (29.0 – 51.0)	97	36.0 (29.0 – 46.0)	**0.03**
Sex (female)	1135	801 (70.6%)	97	75 (77.3%)	0.16
Race	1135		97		0.88
White		865 (76.2%)		76 (78.4%)	
African-American		174 (15.3%)		14 (14.4%)	
Other		96 (8.5%)		7 (7.2%)	
Ethnicity	1133		95		0.13
Hispanic/Latino		92 (8.1%)		12 (12.6%)	
Not Hispanic/Latino		1041 (91.9%)		83 (87.4%)	
Etiology	1134		96		**0.04**
Acetaminophen		537 (47.4%)		61 (63.5%)	
Viral hepatitis		111 (9.8%)		9 (9.4%)	
Drug Induced		112 (9.9%)		6 (6.3%)	
Indeterminate		148 (13.1%)		7 (7.3%)	
Other		226 (19.9%)		13 (13.5%)	
Admission biochemistry					
Hemoglobin (g/dl)	1125	10.6 (9.3 – 12.2)	97	10.0 (8.9 – 12.0)	0.10
White Blood count (x10⁹/L)	1130	10.8 (7.1 – 15.8)	97	10.0 (6.6 – 15.1)	0.30
Platelet count (x10⁹/L)	1128	124.5 (77.5 – 187.0)	97	105.0 (70.0 – 172.0)	0.10
INR	1116	2.8 (2.0 – 4.4)	97	3.0 (2.1 – 4.8)	0.60
AST (IU/L)	1122	1648.0 (524.0 – 5775.0)	95	2315.0 (576.0 – 6109.0)	0.32
ALT (IU/L)	1118	1954.0 (697.0 – 4441.0)	94	2651.0 (963.0 – 4500.0)	0.19
Bilirubin (mg/dl)	1123	7.1 (3.9 – 19.1)	94	6.8 (4.3 – 11.8)	0.39

	No Hypothermia (control) group (N=1135)		Hypothermia group (N=97)		P value
	N	Number (%) or median (IQR)	N	Number (%) or median (IQR)	
pH	993	7.4 (7.3 – 7.5)	91	7.4 (7.4 – 7.5)	0.37
Ammonia (venous; µmol/L)	353	108.0 (73.0 – 168.0)	54	116.0 (79.0 – 170.0)	0.25
Creatinine (mg/dL)	1134	2.0 (1.0 – 3.4)	96	1.5 (1.0 – 3.1)	0.08
Lactate (mmol/L)	668	5.0 (3.0 – 10.2)	65	5.4 (3.1 – 9.1)	0.84
Phosphate (mg/dL)	989	3.2 (2.1 – 4.8)	92	2.8 (2.0 – 4.1)	0.06
PO2/FiO2 ratio	865	3.3 (2.1 – 4.4)	87	3.4 (2.4 – 4.5)	0.56
MELD (admission)	1105	33.6 (27.4 – 40.2)	93	32.1 (26.7 – 38.2)	0.23
Target Temperature*	1135	36.6 (36.1 – 37.0)	97	34.1 (32.9 – 35.3)	**<0.0001**
Organ support (7-days)**					
Mechanical ventilation	1135	975 (85.9%)	97	97 (100.0%)	**<0.0001**
Vasopressors	1135	491 (43.3%)	97	59 (60.8%)	**0.0008**
Renal Replacement therapy	1135	451 (39.7%)	97	61 (62.9%)	**<0.0001**
ICP therapies (7-days)					
Mannitol	1135	304 (26.8%)	97	60 (61.9%)	**<0.0001**
Hypertonic saline	1134	64 (5.6%)	97	33 (34.0%)	**<0.0001**
Barbiturates	1135	105 (9.3%)	97	16 (16.5%)	**0.02**
Sedatives	1135	873 (76.9%)	97	88 (90.7%)	**0.002**
ICP Monitor Placement	1002	218 (21.8%)	97	38 (39.2%)	**0.0001**
Blood products (7-days)					
Red Blood Cells	1135	530 (46.7%)	97	50 (51.6%)	0.36
Fresh Frozen Plasma	1135	768 (67.7%)	97	80 (82.5%)	**0.003**
Recombinant VIIA	1134	19 (1.7%)	97	7 (7.2%)	**0.0003**
Platelets	1135	330 (29.1%)	97	38 (39.2%)	**0.04**

Abbreviations: INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; pO2, partial pressure of oxygen, FiO2, fraction of inspired oxygen.

**Median target temperature where available in the No Hypothermia Group over all inpatient days (up to 7) and in the hypothermia group over all inpatient days actively treated with hypothermia.

**7-days: Values refer to therapies at any time during the 7-days of study

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Table 2

Outcomes of 1232 Acute Liver Failure Patients with Grade III/IV Hepatic Encephalopathy treated with (n=97) or without (n=1135) Therapeutic Hypothermia.

	No Hypothermia Control Group (N=1135)		Hypothermia group (N=97)		
	N	Number (%)	N	Number (%)	P value
ICU Complications (7-days)					
Seizures	1135	93 (8.2%)	97	13 (13.4%)	0.08
Arrhythmias	1135	310 (27.3%)	97	37 (38.1%)	*0.03**
Gastrointestinal bleeding	1135	138 (12.2%)	97	12 (12.4%)	0.95
Acute Respiratory Distress Syndrome	1134	24 (2.1%)	97	4 (4.1%)	0.20
Abnormal CT of head	319	132 (41.4%)	80	42 (52.5%)	0.08
Abnormal Chest X-ray	1091	837 (76.7%)	94	82 (87.2%)	**0.02**
Bacteremia/Blood stream infection	1135	207 (18.2%)	97	16 (16.5%)	0.67
Tracheal aspirate infection	1135	264 (23.3%)	97	20 (20.6%)	0.55
Listed for LT	1132	452 (39.9%)	96	42 (43.8%)	0.46
Received LT	1129	277 (24.5%)	97	17 (17.5%)	0.12
Time to Hospital Discharge					
From enrollment to home/other facility (days)	439	12.0 (8.0 – 18.0)	35	16.0 (11.0 – 20.0)	**0.03**
21-day spontaneous survival	1135	446(39.3%)	97	44 (45.4%)	0.24
Overall Survival	1135	679 (59.8%)	97	60 (61.9%)	0.70
Acetaminophen					
Transplanted	533	65 (12.2%)	61	6 (9.8%)	0.59
21 day spontaneous survival	537	298 (55.5%)	61	35 (57.4%)	0.78
21 day overall survival	537	354 (65.9%)	61	41(67.2%)	0.84
Non-acetaminophen					
Transplanted	596	212 (35.6%)	36	11 (30.6%)	0.54
21 day spontaneous survival	598	148 (24.8%)	36	9 (25%)	0.90
21 day overall survival	598	325 (54.3%)	36	19 (52.8%)	0.85

*When comparing arrhythmias following initiation of TH, there was no significant difference between the two groups (control 27% vs. TH 28%, p=0.9).

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Table 3

Multivariable Analysis: Predictors of 21-day spontaneous survival in 582 patients with acetaminophen-induced Acute Liver Failure.

	Univariate (N=598)			Multivariate (N=582, c=0.812)		
	Odds ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Age	0.998	0.986 – 1.011	0.79			***
Male	0.766	0.514 – 1.143	0.19	1.350	0.815 – 2.239	0.24
Mechanical ventilation	0.199	0.096 – 0.413	<0.0001*			
Renal replacement therapy	0.491	0.354 – 0.682	<0.0001*			
Vasopressors	0.154	0.108 – 0.221	<0.0001	0.164	0.111 – 0.244	**<0.0001**
MELD	0.912	0.893 – 0.931	<0.0001	0.913	0.893 – 0.935	**<0.0001**
Hypothermia	1.075	0.629 – 1.836	0.79			***
*Age*hypothermia*						**0.024**

- *Ventilator and Renal replacement therapy were co-linear with vasopressors and MELD and not included in final model

- Final model included age, gender, vasopressors, MELD and hypothermia

- 16 patients had missing data

- Variables included in final model if significant on univariable logistic regression included MELD on admission and vasopressors during 7 days in study

- The multivariable model had a c-statistic of 0.812, Hosmer-Lemeshow p=0.9125

- When adjusting for other confounding factors, younger APAP patients were more likely to spontaneously survive to 21 days when treated with TH and older APAP patients were less likely to spontaneously survive when treated with TH. The odds ratio is > 1 (protective, does not cross unity) for those aged 18–25 (Age 25: OR: 2.735 (1.001 – 7.467)). The odds ratio is < 1 (deleterious, does not cross unity) for those over 64 (Age 64: OR: 0.167 (0.028 – 0.999)) (*see* Supplementary file eTable 1)

Table 4

Multivariable Analysis: Predictors of 21-day spontaneous survival in 613 patients with non-acetaminophen-induced Acute Liver Failure.

Variable	Univariate (N=632)			Multivariate (N=613, c=0.700)		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Age	0.984	0.972 – 0.996	0.0086	0.99	0.977 – 1.002	0.11
Male	1.291	0.893 – 1.867	0.17	1.618	1.083 – 2.416	**0.019**
Mechanical ventilation	0.837	0.518 – 1.350	0.47			
Renal replacement therapy	0.861	0.592 – 1.253	0.44			
Vasopressors	0.519	0.355 – 0.757	0.0007	0.602	0.4 – 0.904	**0.014**
MELD	0.929	0.907 – 0.952	<0.001	0.929	0.906 – 0.952	**<0.0001**
Hypothermia	1.051	0.481 – 2.293	0.90	0.962	0.394 – 2.347	0.93

- Final model included age, gender, vasopressors, MELD and hypothermia

- 19 patients had missing data

- The multivariable model had a c-statistic of 0.70, Hosmer-Lemeshow p=0.1577