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Long-term outcome in patients with acute liver failure

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Abbreviations

ALF: acute liver failure; MOF: multi-organ failure; ELT: emergency liver transplantation; KCH: King's College Hospital; LT: liver transplantation; SS: spontaneous survivors; APAP: acetaminophen; INR: international normalised ratio; HE: hepatic encephalopathy; ES : early survivors, ALF patients who survived after 90 days from ICU admission; APAP ELT: acetaminophen overdose ALF patients treated with liver transplantation; APAP SS: acetaminophen overdose ALF patients treated conservatively (spontaneous survivors); nAPAP ELT: non acetaminophen overdose ALF patients treated with liver transplantation; nAPAP SS: non acetaminophen overdose ALF patients treated conservatively (spontaneous survivors); ICU: intensive care unit; ED: early deaths, ALF patients who died within 90 days from ICU admission; AIH: auto-immune hepatitis; HBV: hepatitis B virus; WCC: white cell count; MAP: mean arterial blood pressure; CRP: c-reactive protein; PT: prothrombin time; ALT: alanine transaminase; GCS: glasgow coma scale; RRT: renal replacement therapy; APACHE2: acute physiology and chronic health evaluation II; MELD: Model for End Stage Liver Disease; SOFA: sequential organ failure assessment; UKELD: United Kingdom Model for End Stage Liver Disease; DBD: donor after brain-death, heart beating donor; DCD donor after circulatory death, non-heart beating donor; CIN: cervical intraepithelial neoplasia; CNS: central nervous system; ESKD: end stage kidney disease;.

Conflicts of interest and disclosures: Rajiv Jalan has research collaborations with Takeda, Ocera, and Yaqrit, and consults for Ocera and Yaqrit. Rajiv Jalan is the founder of Yaqrit Limited, which is developing UCL inventions for treatment of patients with cirrhosis. Rajiv Jalan is an inventor of ornithine phenylacetate, which was licensed by UCL to Ocera Therapeutics. He is also the inventor of Yaq-001, DIALIVE and Yaq-005, the patents for which

have been licensed by his University into a UCL spinout company, Yaqrit Ltd. No other authors declared conflicts of interest.

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ABSTRACT

Background and aims: Acute liver failure patients who meet poor prognostic criteria have high early mortality without emergency liver transplantation. A recent study however, reported that patients that survive spontaneously have a poorer outcome compared with patients undergoing transplantation. In this single center study, we aimed to confirm or refute this observation.

Methods: Early survivors (patients who survived 90 days) were assessed for long term outcomes in 4 distinctive cohorts, incorporating aetiology (Acetaminophen overdose or non-Acetaminophen overdose related acute liver failure), and management strategy (conservative or liver transplantation). Chi Squared or Fisher test were used to compare outcomes among the 4 cohorts ($p<0.05$) and Kaplan Meier curve (Log Rank test) to represent cumulative survival.

Results: 200 consecutive acute liver failure patients between 1990 and 2014 were included; mean age 38.3, ± 12.8, male 70, 35%. 124/200 (62%) early survivors were identified; 13/124 (10.5%) acetaminophen patients underwent transplantation and 48/124 (38.7%) survived spontaneously; 36/124 (29.0%) non-acetaminophen underwent transplantation and 27/124 (21.8%) survived spontaneously. 11/124 (8.9%) died subsequently (median survival 5.3 ± IQR 9.1); three spontaneous survivors and 8 transplanted patients ($p=0.025$); of the 8 transplanted patients, six died of transplant related complications and two of suicide.

Conclusion: The results of this study suggest that although liver transplantation is a life-saving operation for acute liver failure patients, they have a worse long-term outcome compared with spontaneous survivors. Novel therapies to increase the percentage of spontaneous survivors are urgently needed.

Key Words: Emergency Liver Transplantation, Spontaneous Survivors, Acetaminophen Overdose, Early Survivors, Early Deaths.

LAY SUMMARY/KEY POINTS BOX

- Emergency liver transplantation (ELT) is a lifesaving procedure for patients with acute liver failure (ALF) who are unlikely to recover spontaneously.
- Over the past 30 years, rates of spontaneous survival of patients with ALF have improved considerably, but data about long-term outcomes of patients that undergo ELT or survive spontaneously are not well documented.
- The data in the present study show that ALF patients recovering spontaneously have better long-term outcomes compared to patients treated with ELT.
- ELT in ALF patients should be rationalized, strategies to increase spontaneous survivors should be defined and criteria for selecting candidates for ELT should be improved.

INTRODUCTION

Acute liver failure (ALF) in patients requiring ICU admission is associated with high mortality. The cause of death in the majority of patients is related to multi-organ failure (MOF) and sepsis. [1-3] Emergency Liver transplantation (ELT) has emerged over the years as the gold standard treatment for patients who are unlikely to survive with standard medical treatment

alone. [4,5] The determination of prognosis and listing for transplantation is assessed on the basis of prognostic tools of which the King's College Hospital (KCH) and the modified KCH criteria (since 2005) are currently the most widely used worldwide. [6,7]

In light of the mounting evidence supporting the trend of a continuously improving spontaneous survival rates (without ELT) decade after decade, [8] consequent upon an improved understanding of the disease itself, the potential reversibility of liver injury in the absence of a pre-existing disease, in particular for acetaminophen overdose ALF, [9] with the enhanced standards of medical management, [10] the actual role and the timing of ELT in ALF, once again, has been in the spotlight, raising questions about the additional benefit of ELT in some categories of patients and about the ability of the KCH criteria in selecting patients to candidate to Liver Transplantation (LT). This is particularly relevant given the shortage of organs available for transplantation, the emergency nature of the surgery, which could compromise the short-term outcome, and the long-term complications associated with a LT.

The short-term survival from an ELT is decidedly poorer compared with an elective transplant procedure for chronic liver disease. [11-13] The long-term outcomes, defined as survival at 3- and 5- year in most studies, have similarly been reported to be better in those who recovered spontaneously, an observation, which is intuitively predictable as potential spontaneous survivors (SS) would not be exposed to the late complications of a major surgery and immunosuppressive therapy. [14] However, a recent large multi-centre study by Fontana et al [15] has reported an exactly opposite finding, the one of poorer long-term outcomes for the SS, even within the acetaminophen overdose (APAP) ALF group. They concluded that, wherever possible and indicated by the current transplantation criteria, the treatment in ALF patients should preferably be surgical. The long-term follow up data for many of the patients in this

study were missing. Therefore, the aims of this study were to determine the long term (post ELT or spontaneous recovery) outcomes in a cohort of ALF patients admitted to a single large tertiary liver center equipped with transplantation facility and an established process of following up these patients over time, in order to confirm or refute this observation.

PATIENTS AND METHODS

Data for this study were retrospectively obtained through archived patient notes in the hospital and the follow up data retrieved through a combination of follow up clinic notes, patient's general physicians and direct telephone contact with patients themselves. This database is updated at regular intervals and has been analysed for other purposes previously. Ethical approval was obtained through Royal Free Hospital NHS Trust ethics review board.

Acute Liver Failure and Transplantation definition

ALF was defined by the presence of coagulopathy (INR> 1.5) and hepatic encephalopathy (HE) in patients with no previous liver disease, stratified into the sub-categories of hyperacute, acute and sub-acute liver failure on the basis of the length of the time interval between development of jaundice and progression to encephalopathy (J-E period) of 1, 4, and 12 weeks respectively. For APAP related ALF, where jaundice is rare, this would refer to the interval between the first presentation of symptoms to development of HE.

All the patients were treated with intravenous infusion of N-Acetylcysteine during the first 72 hours after ALF diagnosis. Longer periods of treatment were used for patients with ischemic hepatitis and APAP related ALF, according to response. Fresh Frozen Plasma was administered only to patients who fulfilled the KCH criteria when an invasive procedure was necessary. KCH criteria, or UK modified KCH Criteria since 2005, were used to assess poor prog-

nosis and for listing for ELT. [6,7] All the patients were regularly assessed in order to determine the best strategy for ALF management, whether conservative (organ support) or surgical (ELT). Patients were considered for ELT only when they fulfilled the KCH criteria, which was dynamically applied. For difficult cases where ambiguity existed around issues related to listing for ELT, a multidisciplinary approach was adopted to identify those who would be unlikely to benefit from ELT, taking into account the clinical characteristics, severity of illness and psychosocial factors that would preclude ELT despite patients meeting the KCH criteria. When patients fulfilled eligibility and transplantation criteria, they were listed on the UK National Register for Liver Transplantation. On the contrary, they were delisted if, despite fulfilling KCH criteria, their clinical condition significantly improved or deteriorated.

Long Term immunosuppression was managed following the same strategy for all the patients, according with Royal Free Hospital internal protocol. In general, Tacrolimus was used as the first line drug. Prednisolone was used at a dose of 20mg per day and tapered and stopped within the first 3 months. In patients with autoimmune hepatitis or early rejection episodes, additional mycophenylate mofetil or azathioprine was administered. In patients with renal dysfunction post-transplantation, additional Basiliximab was used for the first week. In patients not able to tolerate Tacrolimus, Cyclosporine was used. Episodes of cellular rejection were treated with 3 boluses of IV methylprednisolone (1g/day for 3 consecutive days).

Patient Selection, clinical characteristics and data collection

All adult (over 18 years of age) patients with ALF admitted to ICU or the liver unit at the Royal Free Hospital between January 1990 and September 2014 were included. Individual case notes were reviewed by 2 investigators independently and data collected for patient demographics, aetiology of ALF, relevant laboratory and clinical parameters including organ

system support, severity of illness assessment (including KCH criteria) on the day of admission and then daily (until spontaneous recovery, death or ELT), management (spontaneous survival or ELT) and short-term (90 days) and long-term outcome. In order to assess the long-term mortality without any bias related to the acute condition, only patients that were alive after 90 days from the ICU admission were considered for this study (early survivors, ES). Patients were followed up for long-term outcomes until May 2015, the end of study period. ES were grouped into 4 cohorts: APAP ELT (acetaminophen overdose patients treated with liver transplantation), APAP SS (acetaminophen overdose patients managed conservatively or spontaneous survivors), nAPAP ELT (non-acetaminophen overdose patients treated with liver transplantation) and nAPAP SS (non-acetaminophen overdose ALF patients managed conservatively or spontaneous survivors).

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (Spss Inc., Chicago, IL). Mean and standard deviation for parametric and median and range for non-parametric descriptive variables, Chi Square or Fisher test (categorical variables) and ANOVA or Kruskal Wallis test (continuous variables) to compare baseline characteristics between 4 cohorts and to compare differences in their outcomes, were applied. To estimate the cumulative survivals, Kaplan Meier analysis (Log Rank test) was used. Threshold value $p < 0.05$ was considered for 95% confidence interval.

RESULTS

Patients Selection

200 patients with ALF were admitted to the Royal Free Hospital ICU (London, UK) between January 1990 and September 2014. The mean age was 38.3 (DS ± 12.8), male 70 (35%). 98 patients had an APAP related ALF (49%). Among the nAPAP patients, 42 had an indeterminate cause of ALF (21%), 18 had drug induced ALF (9%) and 13 had ALF due to autoimmune hepatitis (6.5%). 162/200 patients fulfilled the KCH criteria (81%), but only 90/162 patients (55.6%) were listed, and 70/90 (77.8%) transplanted. Reasons for management alternative to ELT are explained in Figures 1 and 2.

In total, 87/200 patients died (43.5%). The majority of deaths, 76/87 (87.4%), occurred within the first 90 days of ICU admission (called Early Deaths, ED) and 70.1% within 21 days of ICU admission (Supplementary Figure 1). The median survival time was 6.5 days (range 0-57 days, IQR 15 days). The causes of death in the patients who died within 90 days (ED) were related to the severity of the acute condition (Supplementary Table 1). For the ED, the cause of death was related to persistent MOF in 67% of cases (one third with evidence of sepsis) and to brain oedema in 10.5%. Thirty one percent of the transplanted patients (21/70) died within 90 days but only 10/21 within 21 days of ICU admission. The main cause of death in the ED who had been transplanted was persistence of MOF despite surgery (14/21, 66.7%), 57% with evidence of sepsis.

Early Survivors

The remaining 124/200 survived past 90 days, called ES. The median waiting time for the transplanted patients from ICU admission to ELT was 2 days (Range 0 - 27). Among the ES, 92/124 patients (74.2%) fulfilled KCH criteria for ELT during the ICU stay (Figure 2), and among them 77/124 (62.1%) from the time of ICU admission. Of these, only 49/92 patients

(53.3%) underwent ELT (p<0.001), 13/49 for APAP related ALF (26.5%) and 36/49 for nAPAP (73.5%) (p<0.001). All the transplanted patients fulfilled the KCH criteria.

The remaining 43 patients who also fulfilled KCH criteria, survived despite conservative management (Figure 2). Among them, 38 (88.4%) were not transplanted because of early improvement, 7/38 (18.4%) in spite of having already being listed (Figure 2). 13/124 APAP ELT (10.5%), 48/124 APAP SS (38.7%), 36/124 nAPAP ELT (29.0%) and 27/124 nAPAP SS (21.8%) were identified (p<0.001). Routine diagnostic liver biopsy was not performed for all the patients but mainly when biological data alone were not helpful and a diagnostic doubt regarding the diagnosis of ALF aetiology persisted. Histological data were available for 56/124 (45.2%) patients. Only 7/56 biopsies were performed in patients who did not undergo ELT, showing "non contributory" results in 4/7 (57.1%) patients. Explant analysis of the liver was available for 49 transplanted patients. 17 of these 49 (34.7%) transplanted patients also had liver biopsy in the pre-ELT workup. Details are provided in Supplementary Table 2.

Baseline characteristics of ES patients detected at the time of ICU admission are described in Table 1. In 61/124, 49.2% ES, APAP was the cause of ALF. nAPAP SS cohort was younger. Organ failures and need for organ support were similar between the groups, except for renal replacement therapy (RRT). The need for mechanical ventilation at the time of ICU admission was more frequent for the APAP ELT cohort (92.3%), but no differences were noted according to the ventilatory settings and gas exchange parameters, compared to the other cohorts. Serum creatinine values were higher and need for RRT more frequent in APAP patients. All the transplanted patients, independently of ALF aetiology, had more deranged coagulation parameters and higher serum bilirubin. Metabolic impairment and acid-base disturbance was more severe in APAP ELT patients and WCC was significantly higher in nAPAP SS patients. Patients treated with ELT, at the time of ICU admission, had a higher

MELD score and more frequently fulfilled the KCH criteria. APACHE2 and SOFA scores at the time of ICU admission were higher in APAP ELT patients.

Long-term outcome of the ES patients

11/124 ES patients died during the follow up (8.9%), 8/11 (72.7%) were treated with ELT (p=0.025) (Figure 2). For the patients who died, the median survival was 5.3 years (range 92 days - 12.4 years, IQR 9.1 years). The first non-ELT death was registered after 8.2 years of follow up. Figure 3 represents the estimated overall survival, using the Log Rank test, which shows a significantly higher expected mortality in ELT patients. Figure 3a, compares the total ELT with the SS patients in those that survived 90-days (ES), confirming a better outcome for SS patients (p=0.029). Considering the ES stratified according to ALF aetiology and management (Figure 3b), KM survival curves confirms a worse outcome for APAP patients managed with ELT, and a better outcome for APAP patients treated conservatively (p=0.003). These findings were confirmed when patients were analysed separately according to ALF aetiology (p=0.005 and 0.160 respectively for APAP and nAPAP aetiology, Figure 3c and 3d). The worse survival of patients undergoing ELT was confirmed even when considering only the APAP patients fulfilling the KCH criteria (Figure 4, p=0.014). In nAPAP patients the trend confirmed a worse outcome for transplanted patients although the difference was not statistically significant (Figure 3d). However, subgroup analysis considering the ALF type (hyperacute/acute/subacute) showed that only the patients with subacute ALF (12/124, 9.7%) had benefits from ELT (11/12, 91.7%,) in 90-day and overall survival (p=0.024 respectively, no patient dying after the 90th day from ICU admission, data not shown) compared to those managed conservatively.

Causes of death in ES patients

Table 2 shows the main features of ES patients who died. All the ALF events were homogeneously distributed between 1994 and 2010. 3/11 patients were older than 45 and 7/11 were female. 8/11 patients (72.7%) who died had an APAP related ALF (Figure 2); 3/11 had an indeterminate cause of ALF. The cause of death was related to graft failure or immunosuppression in 6/8 LT patients (Table 3a), including two end-stage renal failure. According to table 3b, only good quality grafts were used for the management of ELT patients who died. 7/8 transplanted patients developed post LT long-term comorbidities. In 2/8 transplanted patients no complications were observed in the post operative period but one of them developed biliary strictures after the discharge. In total, 5/8 transplanted patients developed biliary complications requiring surgery or endoscopic interventional procedure. 2/8 ELT patients were not compliant with immunosuppression, which was based, on Tacrolimus (N=5) and Cyclosporin (N=3). 4/8 ELT patients developed graft failure. One of these patients underwent a re-transplant, 5 years after the first one. 2 deaths were related to suicide.

Among the 3 non-transplanted patients who died, 2/3 had a severe psychiatric history (Table 4). 1/3 did not meet KCH and died from suicide. 2/3 had not been transplanted in spite of meeting KCH because of clinical improvement and ineligibility respectively. One of these patients died from an unknown cause and the second from suicide (APAP intoxication).

DISCUSSION

ALF can rapidly evolve into multi organ failure and lead to death through multiple mechanisms. [1-3] ELT is often a lifesaving option for some patients, [4] but it is a high-risk procedure, both in the immediate perioperative period and in the longer-term, mainly due to complications of immunosuppression. [16-19] The short-term outcomes have improved over the years

from less than 20% hospital survival in the pre-transplantation era to up to more than 70% currently. [8,10,20] Similar improvements with time have also been registered for those treated conservatively. [8,10,20,21] Consequently, it is important to be able to identify the sub-cohort of the patient who might recover without ELT amongst those deemed at high risk of death without ELT. [6,21] KCH Criteria has been the most widely validated score and the most widely used criteria in clinical practice and in the UK is used to define the group of patients with ALF that may benefit from ELT. [6, 22,23]

Several studies have shown a better long-term outcome for ALF patients treated with ELT once they survive the acute post-operative period compared to patients transplanted for chronic liver failure, [17,19,24] but data about the long-term mortality of SS are limited. Consequently, considerations about the long-term outcome are currently not taken into account in the decision-making process for ALF management. In contrast to the recently published study, [15] the present study suggests that the long-term outcome for ALF patients who survive at the first 90 days from the ICU admission is better for the SS compared to the patients treated with ELT.

In order to evaluate the long-term outcomes, Fontana et al. [15] enrolled ALF patients who survived 3 weeks from the onset of the syndrome. Their study suggested that the mortality of SS over the long-term was higher than those that underwent ELT. The first main differences of the paper of Fontana et al. stems from the multicenter nature of the study that did not allow determination of the cause of mortality for more than 50% of the patients and the second from the choice of the timing of starting the analysis, i.e. from 3-weeks of the onset of ALF. As previously described [5,12,17,19,25] and confirmed by this study (Supplementary Figure 1 and Supplementary Table 1), ALF mortality is very high during the first 90 days from ICU ad-

mission and related to events derived from the condition of the acute phase response developed during the SIRS, often persistent in spite of ELT. Thus, the mortality that occurs in this early period following diagnosis of ALF, both for SS and ELT ALF patients, is a potential confounder to assess long-term outcomes, and should be considered as mortality related to the illness itself or the effect of surgery. For this reason, we decided to define ES at 3-months and determine long-term outcome from this point forward.

This study suggests a greater likelihood of mortality over the long-term in the patients that underwent ELT compared with the SS patients (Figure 3a). Considering ALF aetiology and management together, the long-term survival confirms a higher mortality rate in APAP patients treated with ELT, even when considering only the patients fulfilling poor prognostic criteria (Figure 3b, Figure 3c and Figure 4). In contrast, the outcome of nAPAP treated with ELT was not significantly different to the SS patients, probably due to the low prevalence of deaths in this category (Figure 3d). However, subgroup analysis showed that ELT improves the survival rate in patients presenting a subacute liver failure.

The main cause of death in the 3 patients in the SS group of ES patients was suicide in 2 and unknown cause in one, with no significant morbidity in the post recovery period. This was not surprising as all these patients had serious underlying psychiatric diseases and suicide resulted in 2 despite close follow up. In contrast, the ELT group of ES patients frequently died from graft related causes of death (graft failure or immunosuppression complication; 6/8, 75%). Additionally, the ELT patients had a longer ICU stay and 7/8 developed in-hospital and/or long-term post-LT co-morbidities, including requirement for re-transplantation, renal dialysis and need for kidney transplantation. Graft failure was registered in four patients and related to poor compliance with immunosuppressive therapy in two patients. All these data

suggest that APAP patients require on-going psychological support in the community. Factors predictive of poor long-term outcomes include use of marginal donors and the use of extended criteria donor graft features. [11,27,30] As shown in Table 3b, only good quality grafts were used with only 2 patients being over 65 years in the patients that died**.** In the SS group, the first death was registered after 8-years from the ALF episode suggesting complete regeneration and recovery of liver function in this group of patients. [24,28,29] These findings are particularly relevant given the high risks of performing unnecessary LT. As shown in Figure 2, 38/92 patients fulfilling KCH criteria (41%), mainly APAP related, were not transplanted because of clinical improvement, suggesting lack of specificity of the criteria.

Although the low number of long term deaths does not allow definitive conclusions and in-depth statistical analysis to search for predictors of long-term mortality, the availability of sequential data in all ALF patients admitted to a single ICU provides robust evidence to question the previous observation of high rate of long-term mortality in SS. The analysis of the causes of death shows that a cut-off of 21 days is inappropriate in defining the long-term mortality, as this is likely to reflect the acute phase of the illness. In conclusion, the results of this study suggest that beyond the first 90-days following the occurrence of ALF, patients treated with SS have a better long-term outcome compared with those treated with ELT. This data underlines the importance of identifying new tools to select patients for ELT as well as the urgent need for novel therapies to increase the proportion of spontaneous survivors.

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FIGURE LEGEND

Figure 1. Acute liver failure patients, according to 90-day outcome.

ALF: acute liver failure; ED: early deaths, ALF patients who died within 90 days from ICU admission; ELT: emergency liver transplantation; ES: early survivors, ALF patients who survived after 90 days from ICU admission; SS: spontaneous survivors; KCH: King's College Hospital Criteria; APAP: acute liver failure induced by acetaminophen overdose; nAPAP: acute liver failure not induced by acetaminophen overdose.

Figure 2. Overall outcome of Early Survivors, according to King's College Hospital criteria, ALF aetiology and management.

ALF: acute liver failure; ED: early deaths, ALF patients who died within 90 days from ICU admission; ELT: emergency liver transplantation; ES: early survivors, ALF patients who survived after 90 days from ICU admission; SS: spontaneous survivors; KCH: King's College Hospital Criteria; APAP: acute liver failure induced by acetaminophen overdose; nAPAP: acute liver failure not induced by acetaminophen overdose.

Figure 3. Estimated cumulative survival.

(A) Early survivors patients (N=124) according to acute liver failure management alone (p=0.029).

Black=ELT; Grey=SS.

(B) Early survivors patients (N=124) according to acute liver failure aetiology and management (p=0.003).

Black=APAP ELT; Dark Grey=nAPAP SS; Grey=APAP SS; Light Grey=nAPAP ELT.

(C) Early survivors patients with acetaminophen intoxication (APAP, N=61) according to acute liver failure management (p=0.005).

Black=ELT; Grey=SS.

(D) Early survivors patients without acetaminophen intoxication (nAPAP, N=63) according to acute liver failure management (p=0.160).

Black=ELT; Grey=SS.

ES: Early Survivors; ALF: Acute Liver Failure; ELT: Emergency Liver Transplantation; SS: Spontaneous Survivors; APAP: acute liver failure induced by acetaminophen overdose; nAPAP: acute liver failure induced by other causes. Statistical Long-rank test

Figure 4. Estimated cumulative survival in Early Survivors patients with acetaminophen intoxication (APAP) fulfilling the KCH criteria (N=46), according to the management finally performed (p=0.014)

ES: Early Survivors; ALF: Acute Liver Failure; ELT: Emergency Liver Transplantation; SS: Spontaneous Survivors; APAP: acute liver failure induced by acetaminophen overdose; KCH: King's College Hospital Criteria

Supplementary Figure 1. Timing of mortality of the totality of patients who died (N=87)

Table 1. Baseline characteristics of Early Survivors

		N	Total ES (N=124)	ES stratified according to aetiology and management				
				APAP ELT (N = 13)	APAP SS (N = 48)	nAPAP ELT (N = 36)	nAPAP SS (N = 27)	P value
Demographics								
	Male sex - N (%)	124	40 (32.2%)	2 (15.4%)	16 (33.4%)	14 (38.9%)	8 (29.6%)	NS (p = 0.470)
	Age (years)	124	34.7 (14.6 - 68.9)	37.8 (16.9 - 52.2)	35.5 (14.6 - 68.9)	36.4 (17.1 - 60.3)	31.3 (18.8 - 52.6)	NS (p = 0.632)
ALF History								
	ALF type - N (%) *Hyperacute* *Acute* *Subacute*	124	 101 (81.4%) 11 (8.9%) 12 (9.7%)	 13 (100%) 0 0	 48 (100%) 0 0	 21 (58.4%) 4 (11.1%) 11 (30.5%)	 19 (70.4%) 7 (25.9%) 1 (3.7%)	p < 0.001
	ALF etiology - N (%) *APAP* *AIH* *HBV* *Ischemic* *Indeterminate* *Other drugs* *Other virus* *Other cause*	124	 61 (49.2%) 8 (6.5%) 7 (5.6%) 2 (1.6%) 23 (18.5%) 12 (9.7%) 1 (0.8%) 10 (8.1%)	 13 (100%) / / / / / / /	 48 (100%) / / / / / / /	 / 8 (22.3%) 4 (11.1%) 1 (2.8%) 12 (33.4%) 7 (19.4) 0 4 (11%)	 / 0 3 (11.1%) 1 (3.7%) 11 (40.7%) 5 (18.5%) 1 (3.7%) 6 (22.3%)	p < 0.001
	Year of ALF development - N (%) *1990-1999* *2000-2014*	124	 23 (18.5%) 101 (81.5%)	 4 (30.8%) 9 (69.2%)	 9 (18.8%) 39 (81.2%)	 6 (16.7%) 30 (83.3%)	 4 (14.8%) 23 (85.2%)	NS (p = 0.655)
	ICU stay (days)	124	8 (0 - 102)	12 (5 - 102)	4 (0 - 23)	9 (1 - 45)	8 (0 - 29)	p < 0.001
	Follow up period (days)	124	2745 (92 -7822)	2899 (92 - 7355)	3087 (358 - 7704)	2745 (92 - 7378)	1847 (361 - 7822)	NS (p = 0.216)

		N	Total ES (N=124)	ES stratified according to aetiology and management				
				APAP ELT (N = 13)	APAP SS (N = 48)	nAPAP ELT (N = 36)	nAPAP SS (N = 27)	P value
	Hospital Outcome - N (%) *Alive* *Dead*	124	 123 (99.2%) 1 (0.8%)	 13 (100%) 0	 48 (100%) 0	 35 (97.3%) 1 (0.7%)	 27 (100%) 0	NS (p = 0.482)
	Overall Outcome - N (%) *Alive* *Dead*	124	 113 (91.1%) 11 (8.9%)	 8 (61.5%) 5 (38.5%)	 45 (93.8%) 3 (6.3%)	 33 (91.7%) 3 (8.3%)	 27 (100%) 0	p = 0.001
ALF severity								
	KCH Criteria - N (%) *Yes* *No*	124	 92 (74.2%) 32 (25.8%)	 13 (100%) 0	 33 (68.8%) 15 (31.2%)	 36 (100%) 0	 10 (37%) 17 (63%)	p < 0.001
	MELD score	124	34.8 (3.3 - 47.8)	36.5 (33.2 - 40.7)	32.9 (3.3 - 42.7)	36.7 (16.2 - 47.8)	27.6 (17 - 39.1)	p < 0.0001
	UKELD score	124	69 (45 - 84)	73 (64 - 81)	69 (45 - 81)	70 (58 - 84)	64 (55 - 82)	p = 0.003
	APACHE2 score	124	19.5 (4 - 37)	29 (11 - 36)	20 (4 - 35)	14.5 (8 - 35)	18 (7 - 37)	p = 0.002
	SOFA score	124	10 (3 - 20)	12 (3 - 20)	9 (3 - 20)	9 (4 - 16)	11 (3 - 20)	p = 0.033
Laboratory at ITU admission								
	White cell count (x10*9/L)	124	11.3 (0.8 - 38.4)	15.9 (0.8 - 24.8)	9.5 (1.6 - 25.5)	12.9 (4.5 - 38.1)	11 (2.9 - 38.4)	p = 0.015
	Platelets (x10*9/L)	124	102 (6 - 335)	52 (25 - 239)	104 (6 - 288)	124 (20 - 248)	98 (11 - 335)	NS (p = 0.124)
	Creatinine (µmol/L)	124	128.5 (31 - 825)	278 (46 - 693)	158 (43 - 825)	100 (31 - 528)	203 (38 - 658)	p = 0.002
	Total Bilirubin (µmol/L)	124	116 (3 - 693)	88 (43 - 187)	78 (3 - 581)	392 (47 - 693)	88 (19 - 604)	p < 0.0001
	Albumin (mg/L)	121	26 (9 - 45)	22.5 (16 - 45)	29 (9 - 43)	24 (11 - 43)	22 (15 - 40)	P = 0.001

		N	Total ES (N=124)	ES stratified according to aetiology and management				
				APAP ELT (N = 13)	APAP SS (N = 48)	nAPAP ELT (N = 36)	nAPAP SS (N = 27)	P value
	C-reactive protein (mg/L)	93	10 (1 - 273)	5 (1 - 10)	10.5 (1 - 67)	10 (1 - 39)	14 (1 - 273)	p = 0.012
	INR	124	5.8 (1.2 - 15.3)	8 (6.6 - 15.3)	5.9 (1.8 - 8.0)	5.3 (1.7 - 11.8)	3.0 (1.5 - 9.0)	p < 0.0001
	Sodium (mEq/L)	124	132.7 (110 - 147)	127 (121 - 142)	131 (112 - 141)	135 (110 - 147)	133 (115 - 147)	NS (p = 0.053)
	Lactate (mmol/L)	124	3.6 (0.8 - 23.5)	5.7 (2.9 - 13.1)	3.6 (0.8 - 14.6)	3.01 (1.1 23.5)	3.43 (1.2 - 14.2)	p = 0.039
Clinical Characteristics, Organ Failures and Organ support at ITU admission								
	Temperature (ºC)	124	36.9 (31 - 39.2)	34.8 (32.6 - 37.4)	37 (31 - 39.2)	36.9 (31.9 - 38)	37 (33.8 - 38.7)	p = 0.029
	Glasgow Coma Scale	124	12 (3 - 15)	8 (3 - 13)	13 (3 - 15)	12 (3 - 15)	8 (3 - 15)	NS (p = 0.51)
	Encephalopathy Grade - N (%)	124						
	1		18 (14.5%)	2 (15.4%)	4 (8.3%)	6 (16.7%)	6 (22.2%)	NS (p = 0.606)
	2		22 (17.7%)	3 (23.1%)	9 (18.8%)	6 (16.7%)	4 (14.8%)	
	3		41 (33.1%)	2 (15.4%)	15 (31.3%)	15 (41.6%)	9 (33.4%)	
	4		43 (34.7%)	6 (46.1%)	20 (41.6%)	9 (25%)	8 (29.6%)	
	Mechanical Ventilation - N (%)	124						p = 0.026
	Yes		70 (56.5%)	12 (92.3%)	23 (47.9%)	18 (50%)	17 (63%)	
	No		54 (43.5%)	1 (0.7%)	25 (52.1%)	18 (50%)	10 (37%)	
	Renal Replacement Therapy - N (%)	124						p = 0.005
	Yes		52 (41.9%)	9 (69.2%)	26 (54.2%)	9 (25%)	8 (29.6%)	
	No		72 (58.1%)	4 (30.8%)	22 (45.8%)	27 (75%)	19 (70.4%)	

For Non Parametric Variables, values are described by median (± range).

ES: Early Survivors; APAP ELT: acetaminophen overdose ALF patients treated with liver transplantation; APAP SS: acetaminophen overdose ALF patients treated conservatively (spontaneous survivors); nAPAP ELT: non acetaminophen overdose ALF patients treated with liver transplantation; nAPAP SS: non acetaminophen overdose ALF patients treated conservatively (spontaneous survivors); ALF: acute liver failure; APAP: acetaminophen overdose; ICU: intensive care unit; AIH: auto-immune hepatitis; HBV: hepatitis B virus; KCH: King's College Hospital; MELD: model for end stage liver disease; UKELD: United Kingdom model for end stage liver disease; SOFA: sequential organ failure assessment; APACHE2: acute physiology and chronic health evaluation II; CRP: c-reactive protein; INR: international normalised ratio.

Table 2. Clinical Characteristics of Early Survivors who died

	Sex	Age (years)	Year of ALF	Year of death	Follow up (days)	Cause of ALF	ELT	ICU in-stay (days)
Pt 1	Male	60.3	2010	2011	92	Indeterminate	Yes	10
Pt 2	Female	16.9	2010	2012	899	APAP	Yes	74
Pt 3	Female	43.8	2008	2008	92	APAP	Yes	8
Pt 4	Male	40.5	2001	2005	1418	APAP	Yes	18
Pt 5	Female	43.3	1995	1996	314	Indeterminate	Yes	12
Pt 6	Female	30.0	2008	2014	1936	APAP	Yes	10
Pt 7	Female	36.7	2001	2011	3547	APAP	No	11
Pt 8	Female	37.8	1998	2011	4523	APAP	Yes	8
Pt 9	Male	63.4	1998	2006	3016	APAP	No	16
Pt 10	Male	60.2	1997	2009	4275	APAP	No	1
Pt 11	Female	17.7	1994	2004	3630	Indeterminate	Yes	4

ALF: Acute Liver Failure; ELT: Emergency Liver Transplantation; ICU: Intensive Care Unit; APAP: Acetaminophen Overdose.

Table 3. Characteristic of Early Survivors who died after liver transplantation

Table 3a. Complications and causes of death

	ELT	Post ALF complications	Psychiatric comorbidities prior to ALF	Cause of death
Pt 1	Yes	Repeated Septic events	No	Septic shock (pneumonia)
Pt 2	Yes	Post ELT abdominal bleeding Hemothorax *C. Difficilis* colitis Pulmonary embolism Pneumothorax Biliary stenosis Severe keloid	No	Graft failure (ductopenic rejection)
Pt 3	Yes	Biliary stenosis	Yes	Suicide
Pt 4	Yes	Chest infection (*P. Aeruginosa, E. Fecium*) Biliary stenosis	Yes	Graft Failure (fibrosing cholestasis)
Pt 5	Yes	Post ELT Bleeding (Arterial anastomosis) Biliary fistula	No	Graft failure (chronic rejection)
Pt 6	Yes	Infected peri hepatic hematoma Ischemic optic neuropathy	Yes	Suicide
Pt 8	Yes	Chest infection ESKD Biliary stenosis Hypertension Malnutrition	Yes	Cardiac arrythmia - ESKD
Pt 11	Yes	ESKD Chronic pyelonephritys Graft Failure (2nd liver transplantation) Kidney transplantation (failure) CIN cervix	No	Cardiac arrythmia - ESKD

ELT : Emergency Liver Transplantation; ALF: Acute Liver Failure; ESKD: End Stage Kidney Disease; CIN: cervical intraepithelial neoplasia.

Table 3b. Graft features

	Donor	Cava Anastomosis	Waiting time from listing (days)	Cold Ischemia Time	Blood group matching	Donor age (years)	Graft steatosis	Split liver
Pt 1	DBD	Piggy Back	1	10 hr 42 min	0+/0+	79	no	no
Pt 2	DBD	Piggy Back	0	6 hr 47 min	0+/0+	42	mild	no
Pt 3	DBD	Cava replacement	1	11 hr 0 min	B+/B+	78	no	no
Pt 4	DBD	Cava replacement	1	11 hr 17 min	A+/A+	57	no	no
Pt 5	DBD	Cava replacement	1	6 hr 30 min	0+/0+	21	no	no
Pt 6	DBD	Cava replacement	1	8 hr 22 min	0+/0+	33	no	no
Pt 8	DBD	Cava replacement	0	7 hr 07 min	B+/B+	41	no	no
Pt 11	DBD	Cava replacement	1	10 hr 40 min	0+/0+	30	no	no

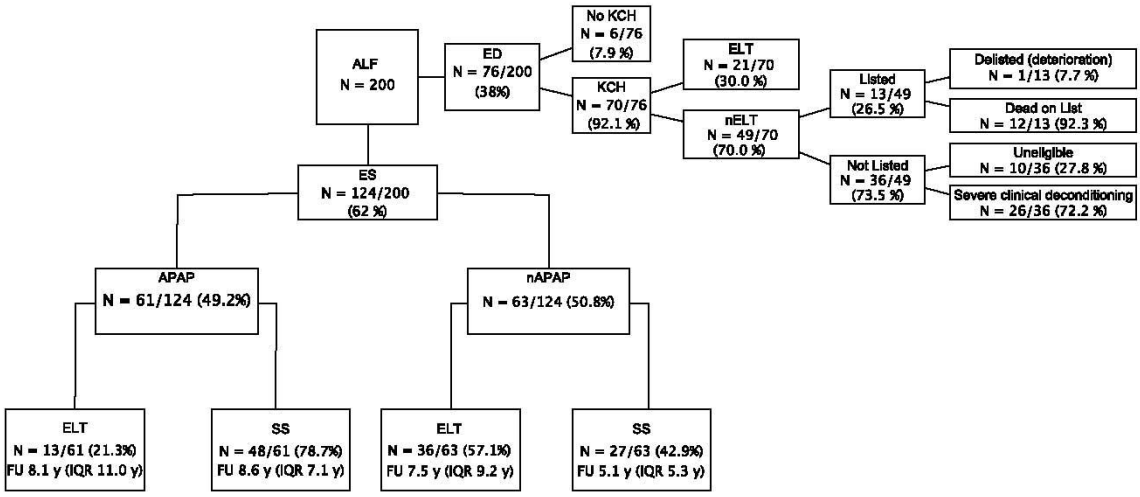
DBD: donor after brain-dead, heart beating donor; DCD: Donor after circulatory death, non-heart beating donor.

Table 4. Causes of death in Spontaneous Survivors

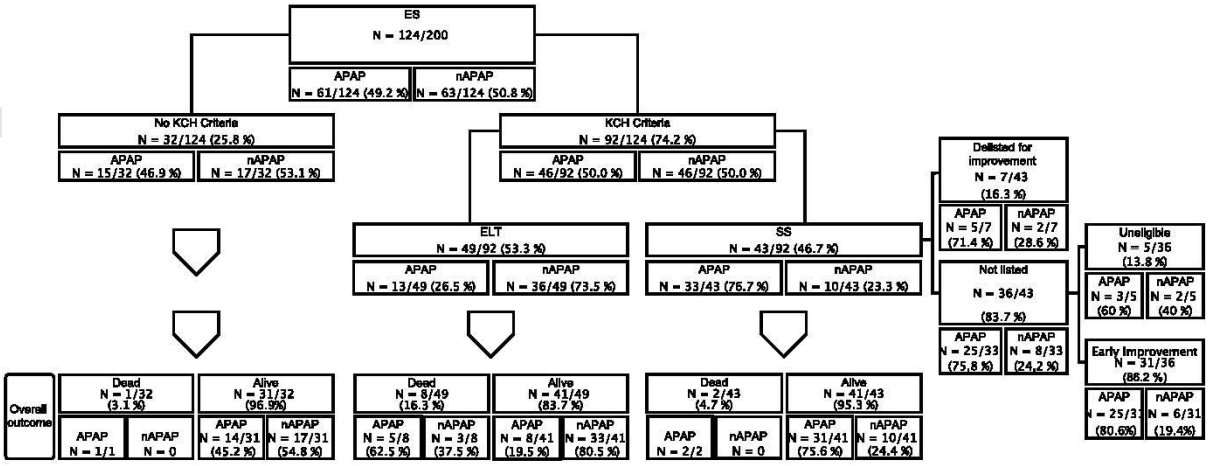
	Post ALF complications	Psychiatric comorbidities prior to ALF	Cause of death
Pt 7	None	yes	Suicide
Pt 9	None	yes	Suicide
Pt 10	None	no	Unknown

ALF: Acute Liver Failure.

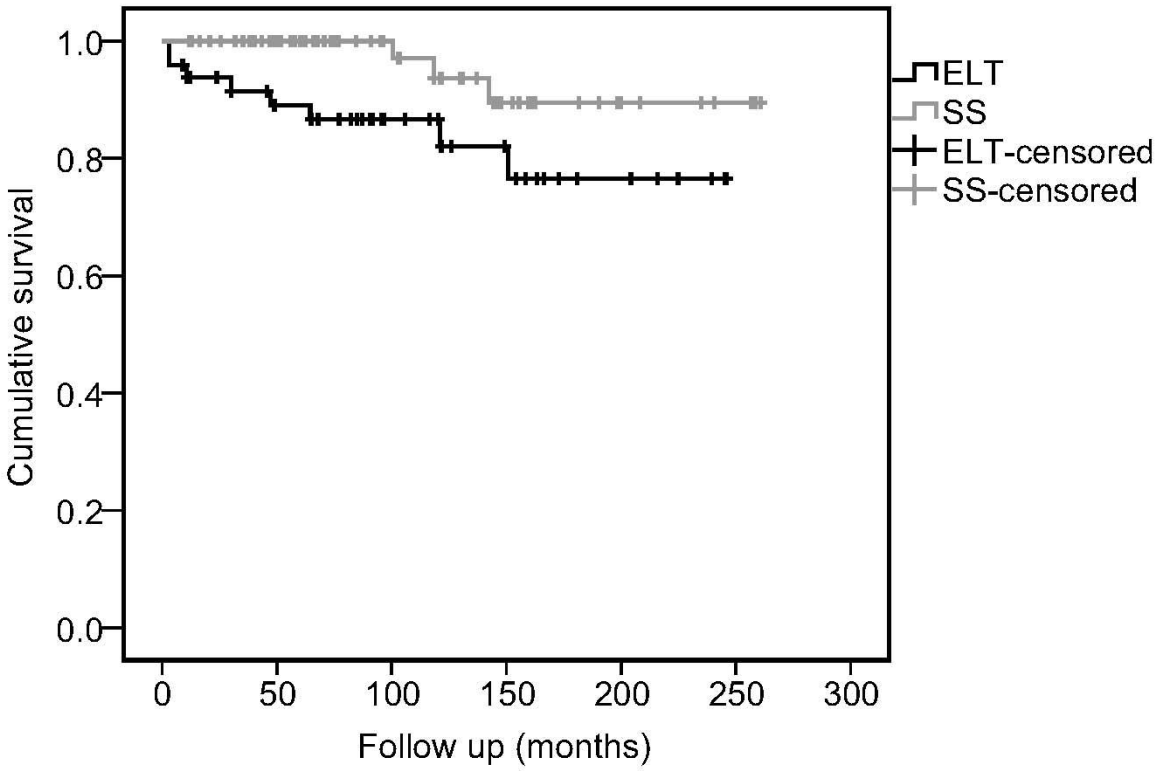
(FIGURE 1) ACUTE LIVER FAILURE PATIENTS, ACCORDING TO 90-DAY OUTCOME



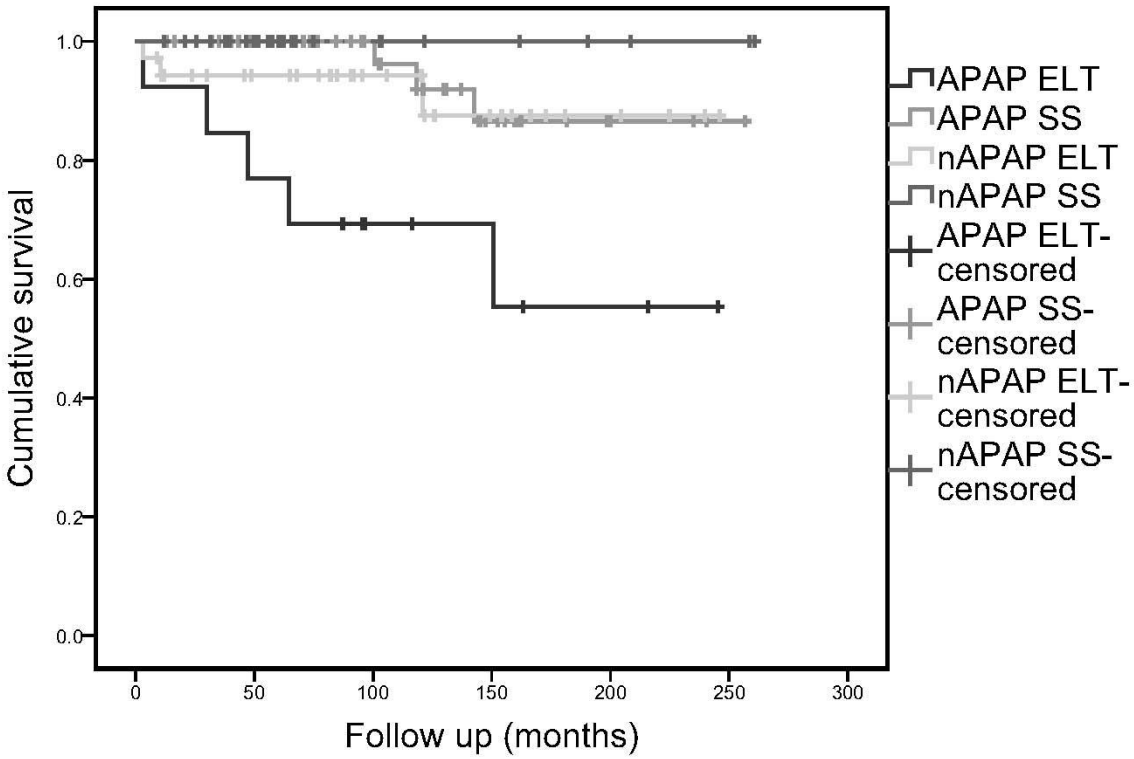
(FIGURE 2) OVERALL OUTCOME OF EARLY SURVIVORS, ACCORDING TO KING'S COLLEGE HOSPITAL CRITERIA, ACUTE LIVER FAILURE AETIOLOGY AND MANAGEMENT



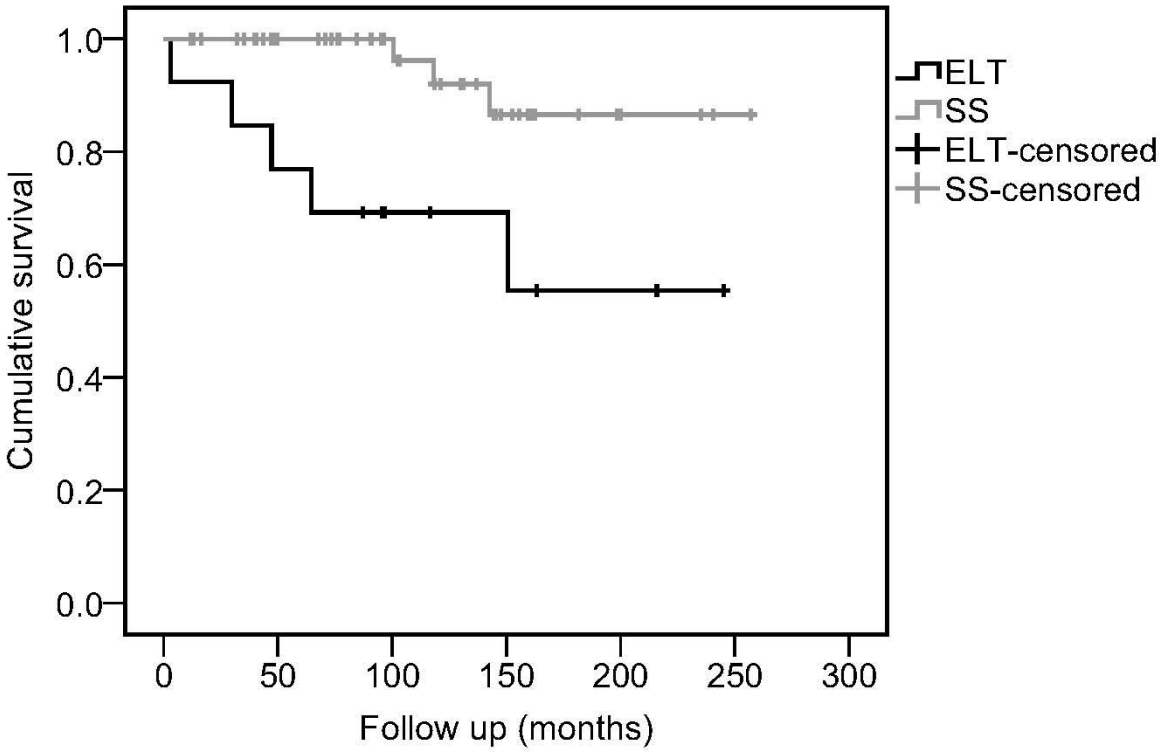
(FIGURE 3) ESTIMATED CUMULATIVE SURVIVAL (A) EARLY SURVIVORS PATIENTS (N=124) ACCORDING TO ACUTE LIVER FAILURE MANAGEMENT ALONE (P=0.029)



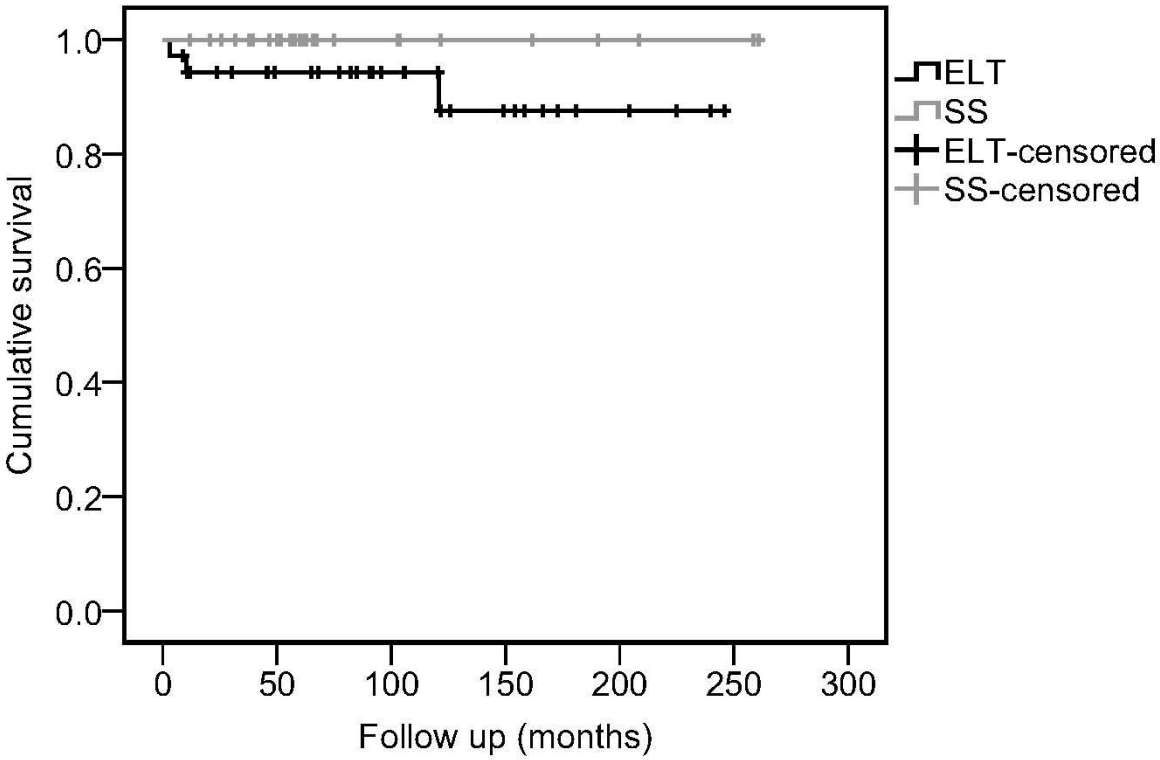
(FIGURE 3) ESTIMATED CUMULATIVE SURVIVAL (B) EARLY SURVIVORS PATIENTS (N=124) ACCORDING TO ACUTE LIVER FAILURE AETIOLOGY AND MANAGEMENT (P=0.003)



(FIGURE 3) ESTIMATED CUMULATIVE SURVIVAL (C) EARLY SURVIVORS PATIENTS WITH ACETAMINOPHEN INTOXICATION (APAP, N=61) ACCORDING TO ACUTE LIVER FAILURE MANAGEMENT (P=0.005)



(FIGURE 3) ESTIMATED CUMULATIVE SURVIVAL (D) EARLY SURVIVORS PATIENTS WITHOUT ACETAMINOPHEN INTOXICATION (nAPAP, N=63), ACCORDING TO ACUTE LIVER FAILURE MANAGEMENT (P=0.160)



(FIGURE 4) ESTIMATED CUMULATIVE SURVIVAL IN EARLY SURVIVORS PATIENTS WITH ACETAMINOPHEN INTOXICATION (APAP) FULFILLING THE KING'S COLLEGE HOSPITAL CRITERIA (N=46), ACCORDING TO THE MANAGEMENT FINALLY PERFORMED (P=0.014)