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Prognostic significance of infections in critically ill adult patients with acute liver injury: a retrospective cohort study

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Abstract

Background and Aims—Patients with acute liver failure have high rates of infections, likely from defects in immune function. Whether infections are independently associated with poor outcomes is unclear. We hypothesized that patients with acute liver injury who developed infections were at increased risk of adverse outcomes.

Methods—We conducted a retrospective analysis of 150 critically ill adult patients admitted with acute liver dysfunction at a single academic institution between 2005 and 2011. We excluded patients with immunocompromised states, patients with chronic liver disease and patients who died or were discharged within 48 h of admission. Our primary endpoint was a 30-day event-free survival, with events defined as either death or liver transplantation. Our secondary endpoint was length of stay. Univariate and multivariate analyses were performed to determine associations between presence of infection and our primary and secondary endpoints.

Results—Of our cohort of 150 patients, 62 (41%) were infected and 88 (59%) were not infected. Of the infected patients, 45% died or underwent transplantation, compared to 22% for the non-infected patients ($P = 0.003$). Univariate and multivariate analyses demonstrated that infections in patients with acute liver dysfunction were an independent predictor of poor outcome (i.e. death or transplantation). In addition, specific types of infection, including pneumonia, independently led to a 48% increase in length of stay ($P = 0.002$).

Conclusions—Infections in patients with acute liver dysfunction are associated with increased risk of death or transplant and increased hospital length of stay.

Keywords

acute liver failure; infection; length of stay; mortality; orthotopic liver transplantation

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Infection is a frequent complication of both acute and chronic liver failure. Patients with liver failure have been shown to display numerous defects in the immune system, including impaired monocyte (1, 2) and neutrophil function (3–5) as well as complement deficiency (6). A recent study from our institution on patients with cirrhosis suggests that pre-transplant culture-positive septic shock is associated with poorer outcomes in liver transplant patients with high acuity (MELD > 40) (7). Although this study examined patients with chronic liver failure only, it demonstrated that severe pre-transplant infections may confer adverse effects even after liver transplantation.

Among patients with acute liver failure (ALF), however, it is unclear what impact infection has on survival (8). In addition, whether infections are independently associated with worse outcomes in patients with less severe acute liver dysfunction (e.g. acute liver injury without hepatic encephalopathy) remains unclear. Compared to earlier studies, substantial advances in critical care have occurred, including improvements in supportive care for patients with septic shock and acute respiratory distress syndrome (9, 10). Furthermore, antibiotic prophylaxis is not universally adopted in critically ill patients admitted with acute liver dysfunction, given the uncertainty of who might benefit from this practice and the potential increase in adverse effects and resistant organisms from routine antibiotic therapy. It would therefore be of prognostic and potentially therapeutic importance to determine whether infections among critically ill patients with acute liver injury independently contribute to adverse outcomes.

To examine this question, we undertook a study at our institution of all adult patients admitted to the intensive care unit (ICU) over a 7-year period with acute liver injury to examine the clinical impact of infection on outcomes, including event free survival. We also examined the incidence and types of infection in patients admitted to the adult ICUs with acute liver injury, and whether or not specific types of infections were associated with poorer outcomes. We hypothesized that patients with acute liver injury who developed infections were at increased risk of adverse outcomes, including increased mortality.

Patients and methods

Patient selection and setting

We performed a retrospective analysis of all adult patients (≥18 years) admitted to all adult ICUs, including the specialized Liver Intensive Care Unit and the Medical Intensive Care Unit, for acute liver dysfunction or acute liver failure at the University of California Los Angeles Medical Center between January 1, 2005 and December 31, 2011. UCLA Medical Center is an academic quaternary referral centre that performs an average of 200+ liver transplants annually, with a total of >6000 transplants since the inception of the program, making our institution one of the largest liver transplant centres worldwide.

We screened patients to include in our study using the ICD-9 codes for all forms of liver failure (570–573), viral hepatitis (070) and various drug toxicities (962–981). We automatically excluded patients with ICD-9 codes for cirrhosis (571) and liver cancer (155). We then reviewed the hepatology notes to determine each patient’s clinical diagnosis, and

we confirmed this diagnosis with review of pathology reports (when available). To be included in this study, the patient had to have: (i) no known prior liver disease, (ii) hepatology specialist documentation of acute hepatitis or acute liver failure and (iii) where available, pathology consistent with acute liver injury. We did not include patients with immunocompromised states (e.g. active malignancy, immunosuppressive medications, HIV, etc.), and patients who died or were discharged within 48 h of admission. A total of 150 patients met our inclusion criteria.

The Institutional Review Board (IRB) at UCLA reviewed and approved this study; informed consent was waived by the IRB because of the following criteria: this was a retrospective study, involving no more than minimal risk to the subjects; waiving informed consent would not adversely affect the rights and welfare of the subjects; the research could not practicably be carried out without the waiver or alteration as some of the patients were deceased; and the research was not anticipated to generate information which would require notification of subjects.

Data collection and definitions

All data was obtained from that available in the electronic medical record. Hepatology consult notes were used when possible as the primary source of data for comorbidities, presence of hepatic encephalopathy and aetiology of liver failure. Comorbidities were included if they were listed in the past medical history or in the summary problem list. Hepatic encephalopathy was defined as absent or present (either medically controlled or refractory).

On admission, patients are routinely screened for infection with surveillance blood and urine cultures. We do not routinely initiate antibiotic or antifungal prophylaxis. Initiation of antibiotics is at the discretion of the physician for suspected sepsis or for shock. Typical coverage includes an antibiotic with MRSA coverage and an anti-pseudomonal antibiotic.

Patients were counted as ‘infected’ if they had an infection prior to transplantation. To be included as an infection, a positive microbiologic culture with likely pathogen was required from the respective site. Vital signs and medication administration records were not available for review. Thus, we were unable to use SIRS criteria, antibiotic initiation or change in antibiotics to refine our definition of infection. For respiratory cultures, growth of Candida was not counted as an infection. For patients with positive respiratory cultures, we reviewed chest X-rays obtained at the time of sample collection. X-rays were counted as ‘positive’ if the radiology impression mentioned pneumonia or an infiltrate; however, all patients had to have abnormal findings on chest imaging (e.g. atelectasis, interstitial oedema, etc.) to be counted as pneumonia.

Model for End-Stage Liver Disease (MELD) scores were calculated using the United Network for Organ Sharing (UNOS) equation. For King’s college criteria, acetaminophen and non-acetaminophen ALF patients were analysed separately. Of note, for non-acetaminophen patients, we did not use time to onset of coma as one of the criteria. American Association of the Study of Liver Disease (AASLD) ALF criteria were used as described in Lee *et al.* (11).

Outcomes

For our primary endpoint, we used the composite of death or orthotopic liver transplantation (OLT). We reasoned that patients who underwent OLT for liver failure would have died without transplant. Secondary endpoints included hospital length of stay.

Statistical analysis

Descriptive statistics such as mean, standard deviation, count and percentage were used to summarize patients' demographic and admission clinical characteristics. Comparison of these characteristics between pre-transplant infected and non-infected groups was carried out using unpaired *t* tests (for continuous variables) and chi-square tests/Fisher's exact tests (for categorical variables). The primary endpoint, event-free survival (EFS), was calculated from the date of adult ICU admission to the date of death or orthotopic liver transplantation, whichever came first. The Kaplan–Meier estimates (12) and the log-rank test (13) were used to describe and compare EFS between patients with and without infections. To adjust for additional risk factors that might confound the EFS differences noted, univariate and multivariate Cox proportional hazard regression (14) analyses were performed. Hazard ratios and their 95% confidence intervals were reported. Multivariate linear regression was used to associate hospital length of stay (secondary endpoint) with infection and other potential risk factors. All statistical hypothesis testings were two-tailed, and a *P*-value less than 0.05 was considered to be statistically significant. All statistical analyses were carried out using SAS version 9.3 and JMP®, Version 10 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and baseline characteristics are listed in Table 1. A total of 150 patients who met inclusion criteria were separated into pre-transplant infected and non-infected groups. Patients who were infected but did not subsequently undergo liver transplant were included in the 'pre-transplant infected' group. Both groups had similar baseline characteristics such as age, race, number of comorbidities and aetiology of liver failure. When compared to patients who were not infected, patients in the pre-transplant infected group were more likely to be female (76% vs. 60%, $P = 0.05$). In addition, patients with infection had a significantly higher admission MELD (UNOS) score (29.7 vs. 24.8, $P = 0.003$), were more likely to meet King's college criteria (23% vs. 8%, $P = 0.02$), were more likely to have hepatic encephalopathy on admission (56% vs. 30%, $P = 0.002$), and were more likely to meet AASLD criteria for acute liver failure (48% vs. 25%, $P = 0.003$).

Timing and types of infections

Sixty two patients developed infections in the setting of acute liver dysfunction. Of these, 52 patients developed their first infection within 3 days of hospital admission. 37 patients had one site of infection, while 25 had more than one site of infection. There were 40 patients with pneumonia, 34 with urinary tract infections, 11 with bacteraemia and nine with an infection in a different site. Of the 40 patients with culture-positive pneumonia, 24 had infiltrates on chest imaging interpreted as being consistent with pneumonia, although all patients had abnormal chest X-ray findings.

Effect of infections on OLT and survival

To evaluate the clinical significance of having a acute liver injury-associated infection, we first examined survival to hospital discharge. The majority of patients (138 of 150) survived to hospital discharge (92%), 35 of whom received an OLT. Among the 111 patients who did not receive an OLT, 40 had an infection, while 71 were not infected. Sixty-nine of the 71 uninfected patients (97%) survived to hospital discharge, whereas only 34 of 40 patients (85%) with infection survived. Patients with acute hepatic dysfunction who did not undergo OLT were significantly more likely to survive if they did not have an infection (Fisher's exact test, two-tailed $P = 0.025$). In addition, patients with pre-transplant infections were also more likely to undergo OLT (35% vs. 19% of uninfected; Pearson's $\chi^2 = 0.026$, Fisher's two-tailed $P = 0.037$) suggesting that infection is associated with the severity of the clinical presentation in patients with acute liver dysfunction.

We next examined 30-day event-free survival (Fig. 1). 55% of patients who had an infection survived to 30 days without a transplant, compared to 78% of patients who did not have an infection. Of the infected patients, 60% died or underwent transplantation, compared to 40% for the non-infected patients (Fisher's two tail, $P = 0.003$). Univariate analysis revealed that pre-transplant infection, admission MELD score, King's college criteria and presence of hepatic encephalopathy were all significantly associated with death or OLT (Table 2). The type of infection was not significantly associated with the primary outcome, although there was a trend towards worsened outcomes with pneumonia patients.

To investigate the relationship between infection and event-free survival, we performed a multivariate Cox regression analysis (Table 3). Infection was associated with the presence of hepatic encephalopathy, and the interaction between infection and hepatic encephalopathy was included as a variable in our model. Although age did not turn out to be a significant factor for determining outcome, MELD score, pre-transplant infection and hepatic encephalopathy significantly increased the risk of death or transplant. As expected, hepatic encephalopathy even in the absence of infection was the most significant determinant of outcome, underscoring the poor prognosis of patients who present with acute liver failure. However, infection, with or without the presence of hepatic encephalopathy on admission, was also significantly associated with death or OLT compared to patients who had neither.

Infections and length of stay

Little has been reported on the impact of infections on hospital length of stay among patients with acute liver disease. In our patient population, among patients who survived to discharge, median length of stay (LOS) for all infected patients was 18 days (IQR, 10–33 days), vs. 7 days (IQR, 4–11 days) for non-infected patients ($P < 0.0001$), Fig. 2). For patients who did not undergo transplantation, median LOS for infected patients was 12 days (IQR, 7–19 days), vs. 6 days (IQR 4–8 days) for non-infected patients ($P < 0.0001$). Patients who underwent OLT also had substantially longer LOS (median 28 days vs. 7 days for no OLT, $P = <0.0001$). Multivariate analysis demonstrated that hepatic encephalopathy, pneumonia alone, any 'other' infection (i.e. non-pneumonia, UTI and bacteraemia), and liver transplantation were all independently associated with increased length of stay (Table 4).

Discussion

Among patients with acute liver failure, the incidence of bacterial infections ranges from 38 to 80% (15–17), while the incidence of fungal infections is around 30% (18). Infections have also been associated with the development of SIRS (systemic inflammatory response syndrome) and progression of hepatic encephalopathy, particularly in patients with acetaminophen-induced liver failure (8, 19). We performed an in-depth retrospective analysis of 150 adult patients admitted to all critical care units at our institution with acute liver dysfunction or failure, and found that infections in these patients were significantly associated with worsened outcomes, including decreased survival without transplantation and decreased overall event-free survival. In addition, whether examined as a group or by individual type, infections were independently associated with an increased length of stay in our population, whether or not patients underwent OLT. We believe our study is the first to demonstrate this association between infections and either death or liver transplantation, as well as an increased length of stay.

In addition, we also examined whether specific types of infections were associated with poorer outcomes. While bacteraemia was not associated with mortality in ALF patients at King's College (20), association between outcomes and other types of infection, such as pneumonia, have not been reported. In our study, no specific infection was associated with worsened event-free survival, but pneumonia alone was close to demonstrating statistical significance.

Many of our patients with acute liver dysfunction-associated infection did not have hepatic encephalopathy on admission. Patients with hepatic encephalopathy on admission (i.e. met criteria for acute liver failure) but who did not develop a pre-transplant infection had the highest hazard ratio for our composite endpoint (OLT and/or death). This was largely driven by OLT, underscoring the severity of patients who present with ALF. However, consistent with current aggressive management for ALF, we observed a low overall death rate in our cohort. Notably, however, infection also was associated with increased risk of death and OLT, regardless of the presence of encephalopathy on admission. Among patients who did not have hepatic encephalopathy on admission, infection may either contribute to worsening liver failure with resultant encephalopathy or exacerbate encephalopathy in those patients who progress to acute liver failure. Both scenarios could then lead to increased rates of transplantation or death. Our results support previous studies demonstrating higher rates of progression of hepatic encephalopathy in patients with ALF and infection (8) and higher incidence of infection in patients with hepatic encephalopathy (21).

Our study was limited by the retrospective nature and relatively small number of subjects. However, having a single centre study enabled us to avoid any confounding factors introduced by differences in styles of ICU management, referral patterns and antimicrobial management. For example, our centre routinely checks admission blood, urine and sputum (if present) cultures on all admissions for acute liver failure. We do not routinely use prophylactic antibiotics in the absence of suspected infection at the time of admission. We were unable to analyse variables associated specifically with mortality because of the low event rate; however, given current practices, very few patients with acute liver failure would

be expected to die without OLT. Also, given the limited number of subjects, we cannot make definitive conclusions about the specific type of infection and impact on outcomes. Despite the small sample size, we were still able to demonstrate statistical significance with respect to the group of infected patients and our primary endpoint and length of stay.

Our study did not permit us to make definitive conclusions about the causal relationship between infection and severity of liver failure. However, other investigators have shown a temporal relationship between infection and worsened encephalopathy and SIRS in patients with acute liver failure (8). In our cohort, we found that frequently, infection was discovered at the time of clinical deterioration from liver disease, which rapidly led to transplantation. Given the immunosuppression associated with acute liver dysfunction, many patients may not be able to mount clinical signs and symptoms of acute infection, making early identification of infection difficult. Hence, it would be difficult to determine whether infection causes worsened liver disease, or if infection simply reflects the severity of the underlying liver disease. Certainly, the severity of illness could be driven by the development of severe hepatic encephalopathy and coagulopathy in some patients with acute liver failure, independent of infectious complications. Also, we elected to choose only culture positive infections to have a more stringent, better defined infected population, since ‘clinical judgment’ of whether an infection is present varies among practitioners, due to the non-specificity of symptoms and signs. Although we may introduce selection bias by only choosing culture positive infections, we believe that our results can be more consistently applied to other centres. Nonetheless, given the clear association between culture positive infections and poor outcomes in our study, there may exist a subset of patients for whom infectious complications lead to a vicious cycle of SIRS or immune dysregulation, further worsening the liver dysfunction and multisystem organ failure (19, 22). These findings underscore the need for larger studies to determine which biomarkers can identify infected patients with poorer outcomes, and whether giving antibiotics prophylactically in critically ill patients admitted with acute liver dysfunction may improve outcomes. Although earlier studies have not demonstrated a clear improvement in survival with routine prophylactic antibiotics, many of these studies were smaller, older studies focused on patients with acute liver failure (20, 21), who may already be on an irreversible course of decline. It remains to be determined whether in patients presenting with severe liver dysfunction without overt failure whether antibiotic prophylaxis might be beneficial.

With the improvements in supportive care and the high rates of pre-transplant infections, this is an issue worth reexamining. Furthermore, given the shortage of organs and the long-term complications of transplant, we believe that the need to undergo OLT represents a poor outcome. In the light of the interaction between infection and hepatic encephalopathy, future prospective studies on prophylactic antibiotics should examine other clinically important non-mortality endpoints, such as rates of transplantation or length of stay. The true benefit of prophylactic antibiotics in this population may be avoidance of liver transplantation and shorter hospital stays or perhaps improved post-operative outcomes in those who do require liver transplantation.

In summary, we found that infection in the setting of acute hepatic dysfunction was associated with increased death and OLT in a population of acute liver injury patients treated

in an ICU at an academic quaternary referral centre. In addition, we found an association between infection and increased hospital length of stay. Our findings underscore the need for clinical trials to determine whether prophylactic antibiotics would improve event-free survival and decrease hospital length of stay, particularly among patients with acute liver injury.

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Abbreviations

AASLD	American association for the study of liver disease
ALF	acute liver failure
EFS	event free survival
H.R	hazard ratio
HIV	human immunodeficiency virus
ICD-9	international classification of diseases, 9th revision
ICU	intensive care unit
IQR	interquartile range
IRB	institutional review board
LOS	length of stay
MELD	model for end-stage liver disease
OLT	orthotopic liver transplantation
OSH	outside hospital
SD	standard deviation
SIRS	systemic inflammatory response syndrome
UNOS	united network for organ sharing
UTI	urinary tract infection)

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Key Points

- The prognostic significance of infectious complications in critically ill adults with acute hepatic dysfunction is unclear.
- In patients with acute liver injury, infection, MELD score and hepatic encephalopathy are independently associated with death or OLT.
- In acute liver injury patients, specific types of infections, hepatic encephalopathy and liver transplantation result in increased length of stay.
- Further investigation should examine whether prophylactic antibiotics in critically ill patients with acute liver dysfunction will improve outcomes, or whether the presence of infection simply reflects the severity of liver disease and associated immune dysfunction.

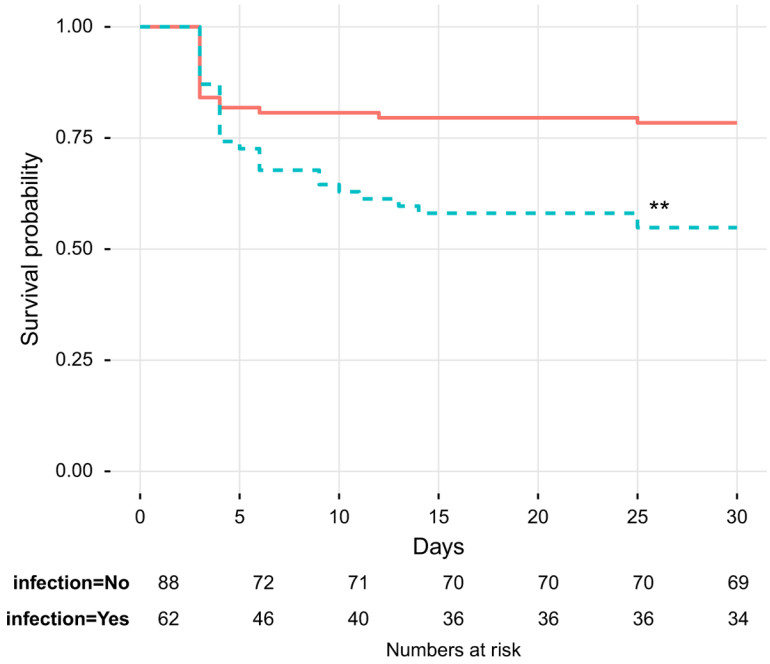

Fig. 1.

Kaplan–Meier event-free survival. Time to composite endpoint of in-hospital death or liver transplant in ALF patients with (blue dashed line) and without (red solid line) infections. The analysis was censored at 30 days (**$P < 0.01$).

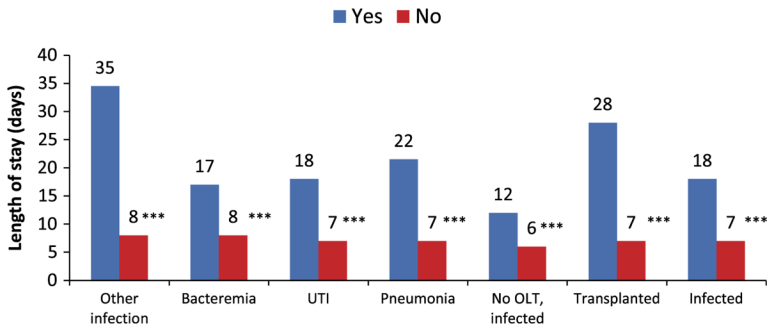

Fig. 2.

Median length of stay. Median length of stay (LOS) for patients with or without infection, transplant, or infection without transplant and individual types of infection. All comparisons were statistically significant on univariate analysis (***$P < 0.001$).

Table 1

Patient demographics and baseline clinical characteristics

	All patients (N = 150)		Infected (N = 62)		Not infected (N = 88)		
	Mean/Freq	**SD/Per cent**	**Mean/Freq**	**SD/Per cent**	**Mean/Freq**	**SD/Per cent**	***P*-value**
Age	41.5	15.3	43.5	14.7	40.0	16.1	0.18
Female sex	100	66.7%	47	75.8%	53	60.2%	0.05
Race							0.42
Caucasian	79	52.7%	35	56.5%	44	50.0%	
Other	45	30.0%	15	24.2%	30	34.1%	
Unknown	26	17.3%	12	19.4%	14	15.9%	
Prior location							0.08
OSH	137	91.3%	58	93.5%	79	88.5%	
Home/ED	11	7.3%	2	3.2%	9	10.2%	
Other	2	1.3%	2	3.2%	0	0.0%	
Co-morbidities							0.54
One	41	27.3%	13	21.0%	28	31.8%	
Two	40	26.7%	18	29.0%	22	25.0%	
Three	27	18.0%	12	19.4%	15	17.0%	
Four or more	42	28.0%	19	30.6%	23	26.1%	
Aetiology of liver failure							0.17
Acetaminophen	99	66.0%	42	67.7%	57	64.8%	
Non-acetaminophen drug	25	16.7%	10	16.1%	15	17.0%	
Non-drug	11	7.3%	7	11.3%	4	4.5%	
Unknown	15	10.0%	3	4.8%	12	13.6%	
Admission data							
Total bilirubin	7.0	8.2	7.5	8.8	6.6	7.8	0.52
INR	2.7	2.5	3.1	3.1	2.4	1.9	0.10
Creatinine	1.8	1.5	2.0	1.6	1.7	1.4	0.24
MELD	26.9	10.2	29.7	10.1	24.8	10.1	0.003
King’s college							0.01
Met criteria	21	14.0%	14	22.6%	7	8.0%	

	All patients (N = 150)		Infected (N = 62)		Not infected (N = 88)		
	Mean/Freq	SD/Per cent	Mean/Freq	SD/Per cent	Mean/Freq	SD/Per cent	*P*-value
Did not meet criteria	129	86.0%	48	77.4%	81	92.0%	
Hepatic encephalopathy*							
Present	60	40.3%	34	55.7%	26	29.5%	0.001
Absent	89	59.3%	27	44.3%	62	70.5%	
AASLD ALF							
Met criteria	52	32.7%	30	48.4%	22	25.0%	0.003
Did not meet criteria	98	67.4%	32	51.6%	66	75.0%	

*No data on mental status for one patient.

Table 2

Univariate Cox regression analysis for composite endpoint and selected characteristics

	Hazard ratio	***P*-value**
Demographics		
Age – average	1.00	0.84
Sex		
Male	Reference	
Female	1.21	0.55
Race		0.57
Caucasian	Reference	
Other	1.34	0.36
Unknown	0.92	0.84
Prior location		
OSH	1.54	0.47
Other	Reference	
Aetiology of liver failure		0.97
Tylenol	Reference	
Non-Tylenol drug	1.12	0.76
Non-drug	0.82	0.74
Unknown	1.07	0.89
Admission data		
MELD – average	1.07	<.0001
Met King's College criteria	2.71	0.002
Did not meet KC criteria	Reference	
Hepatic encephalopathy		
Absent	Reference	
Present	3.29	<.0001
Infected pre-transplant	2.22	0.01
Not infected pre-transplant	Reference	
Type of infection		
Pneumonia	1.78	0.06
No pneumonia	Reference	
UTI	1.19	0.60
No UTI	Reference	
Bacteraemia	1.56	0.35
No bacteraemia	Reference	
Other infection	1.45	0.48
No other infection	Reference	

Table 3

Multivariate Cox regression analysis for composite end point and selected characteristics

Variable	Hazard ratio (95% C.I.)	*P*-value
Age(per year increase)	1 (0.98–1.02)	0.95
MELD (per 10 unit increase)	1.67 (1.30–2.15)	<0.001
Infected pre-transplant		0.007
Hepatic encephalopathy		<0.001
Infected × hepatic encephalopathy		0.002
Not Infected and H.E. absent (n = 62)	Reference	
Infected and H.E. absent (n = 27)	4.40 (1.51–12.85)	0.007
Not infected and H.E. present (n = 26)	8.31 (2.95–23.40)	<0.001
Infected and H.E. present (n = 34)	4.85 (1.72–13.67)	0.002

Table 4

Multivariate linear regression analysis for length of stay and selected characteristics

Variable	Effect (% change in LOS) (%)	*P*-value
Age (per year increase)	0.3	0.340
Infected pre-transplant (yes vs. no)	8.6	0.531
Hepatic encephalopathy (present vs. absent)	35.4	0.001
Transplant (yes vs. no)	120.4	<0.0001
Pneumonia (yes vs. no)	47.8	0.002
Other infection (yes vs. no)	67.8	0.003