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Retrospective Study

Delayed referral for liver transplant evaluation worsens outcomes in chronic liver disease patients requiring inpatient transplant evaluation

Katherine M Cooper, Alessandro Colletta, Nicholas J Hathaway, Diana Liu, Daniella Gonzalez, Arslan Talat, Curtis Barry, Anita Krishnarao, Savant Mehta, Babak Movahedi, Paulo N Martins, Deepika Devuni

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Abstract

BACKGROUND

Indications to refer patients with cirrhosis for liver transplant evaluation (LTE) include hepatic decompensation or a model for end stage liver disease (MELD-Na) score ≥ 15 . Few studies have evaluated how delaying referral beyond these criteria affects patient outcomes.

AIM

To evaluate clinical characteristics of patients undergoing inpatient LTE and to assess the effects of delayed LTE on patient outcomes (death, transplantation).

METHODS

This is a single center retrospective cohort study assessing all patients undergoing inpatient LTE ($n = 159$) at a large quaternary care and liver transplant center between 10/23/2017-7/31/2021. Delayed referral was defined as having prior indication (decompensation, MELD-Na ≥ 15) for LTE without referral. Early referral was defined as referrals made within 3 mo of having an indication based on practice guidelines. Logistic regression and Cox Hazard Regression were used to evaluate the relationship between delayed referral and patient outcomes.

RESULTS

Many patients who require expedited inpatient LTE had delayed referrals. Misconceptions regarding transplant candidacy were a leading cause of delayed referral. Ultimately, delayed referrals negatively affected overall patient outcome and an independent predictor of both death and not receiving a transplant. Delayed referral was associated with a 2.5 hazard risk of death.

CONCLUSION

Beyond initial access to an liver transplant (LT) center, delaying LTE increases risk of death and reduces risk of LT in patients with chronic liver disease. There is substantial opportunity to increase the percentage of patients undergoing LTE when first clinically indicated. It is crucial for providers to remain informed about the latest guidelines on liver transplant candidacy and the transplant referral process.

Key Words: Liver transplantation; Liver transplant evaluation; Liver transplant referral; Patient access; Equity; Patient outcomes

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Core Tip: There are many system and provider-level barriers to liver transplant evaluation. However, the effect of late transplant evaluations remains unclear. We demonstrate delayed liver transplant evaluation is independently associated with death prior to transplant in patients undergoing liver transplant evaluation.

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INTRODUCTION

The global impact of chronic liver disease is increasing. Liver transplantation is the only definitive treatment for decompensated cirrhosis. Guideline recommended indications to refer patients with cirrhosis for liver transplant evaluation (LTE) include hepatic decompensation or a Model for End Stage Liver Disease score (MELD) ≥ 15 [1,2]. While the progression cirrhosis usually occurs over multiple years [3], many patients go un-diagnosed prior to overt hepatic decompensation[3,4]. Thus, many patients have progressed disease when they begin receiving care[5]. Further delays entering the transplant care pathway can result in delayed referral and need for expedited LTE in the setting of acute decompensation. While there is emerging literature on what qualifies as late referral or urgent transplant evaluation[6,7], there is little data regarding the influence of delayed transplant evaluation on outcomes. In this retrospective analysis, we evaluate clinical characteristics of patients undergoing inpatient LTE to identify risk factors for delayed LTE and assess the effect of delayed LTE on patient outcomes.

MATERIALS AND METHODS

Study design and definitions

This is a single center retrospective cohort study analyzing patients undergoing LTE at a large quaternary care and liver transplant center. Medical records were obtained for patients with a transplant evaluation encounter between October 2017 and July 2021 using our center's liver transplant database. Patients with diagnosis of cirrhosis who underwent LTE for chronic liver disease (CLD) as an inpatient in this time period were identified as potential subjects. Patients were excluded if they: (1) Were undergoing re-transplantation; (2) being evaluated for acute liver failure; and (3) were completing evaluation in the outpatient setting. Patients with hepatocellular carcinoma were also excluded due to differences in candidacy and referral criteria[8]. Study data were collected and managed using a 255-field form with an electronic data capture tool hosted at UMass Chan Medical School. Research Electronic Data Capture (REDCap) is a secure, web-based software platform designed to support data capture for research studies, providing: (1) An intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources[9,10].

All clinical and laboratory data including Model for End Stage Liver Disease -Sodium (MELD-Na) score were collected at the time of LTE. Available clinical documentation collected during LTE was closely reviewed and evaluated. Cirrhosis etiologies included chronic alcohol (ETOH) associated liver disease, non-alcoholic steatohepatitis (NASH), Hepatitis C (HCV), cholestatic liver disease (primary sclerosing cholangitis, primary biliary cirrhosis), inherited/genetic disease (hereditary hemochromatosis, alpha-1 anti-trypsin deficiency), and cryptogenic/other. Clinical decompensations included hepatic encephalopathy, jaundice, ascites, hepato-renal syndrome, spontaneous bacterial peritonitis (SBP), and variceal bleed[2,11]. Patients were considered to have a cardiac diagnosis if their past medical history included diagnosis or treatment of a cardiac arrhythmia, coronary artery disease, or cardiomyopathy with heart failure. Malnutrition was diagnosed by registered dietitians on the multidisciplinary transplant team using the ASPEN criteria[12]. Cause of death was recorded when available.

Transplant evaluation indications were defined using the American Association for the Study of Liver Disease (AASLD) guidelines and included: (1) Hepatic decompensation OR; and (2) MELD ≥ 15 AND (3) absence of active alcohol or illicit drug use[13]. Time for sobriety required for evaluation at our institution is 3 mo. Subjects were dichotomized to either “delayed referral” or “early referral.” “Delayed referral” indicated that subjects had an indication for transplant evaluation but were not referred within three months, while “early referral” meant that subjects were referred within three months of having an indication for transplant evaluation. Three months was chosen as this is the timeline of clinical improvement in patients expected to recover once cirrhosis trigger is withdrawn (e.g., alcohol cessation) [14]. In terms of transplant outcomes, there are multiple potential outcomes of LTE and many of these can occur interchangeably. For example, patients can be approved but not yet listed, or listed but inactive on the wait list. For analytical simplicity, our selected outcomes included: not approved, died on waitlist, off list, on list, and transplanted. For statistical analysis, subjects were further dichotomized as “approved” or “not approved,” “dead” or “not dead,” and “transplanted” or “not transplanted” at the time of data collection.

Endpoints and data analysis

Normally distributed continuous data is reported as “mean (standard deviation)” and were compared with two-sample *t*-test. Non-normally distributed continuous data is reported as “median [inter-quartile range]” and were compared using Wilcoxon rank sum tests. Categorical variables are reported as “percentage” and were compared using pair-wise *z* testing. Correlations are reported using Pearson’s bivariate correlation coefficient. Associations are reported as odds ratios with 95% confidence intervals and were evaluated with logistic regression.

Demographic, psychosocial, and clinical variables were compared between delayed and early referral (Tables 1-3). Comparisons were also made between: (1) Dead and not dead; and (2) transplanted and not transplanted within the delayed referral group to identify potential markers of mortality within this cohort (Supplementary Table 1).

Backward logistic regression modeling was used to identify risk factors for delayed referral with the following starting variables: Age, race, sex, ethnicity, time since diagnosis (months), malnutrition (as defined by ASPEN guidelines), depression, trauma history, number of prior hospitalizations, sobriety period, smoking history, lives with family, married/stable partner, stable housing, employed within 1 year, military service history, non-English first language, education, proximity to transplant center, regular outside gastroenterologist, regular outpatient labs.

Backward logistic regression was also used to evaluate if delayed referral was an independent predictor of transplant status and death amongst other relevant clinical markers (for full list see Tables 4 and 5, respectively). We created a multi-variable logistic regression model utilizing this data and other variables known to affect outcomes in the liver transplantation pathway including but not limited to sex [15], age[16], height[17], acute on chronic liver failure (ACLF) grade[18], and laboratory markers that comprise MELD-Na and represent hepatic function. The final model was created to optimize goodness of fit using the Hosmer and Lemeshow test.

Cox proportional hazard regression modeling was used to evaluate the impact of delayed referral on risk of dead in patients undergoing inpatient LTE. Participants were censored on the day of transplant and the last known well if lost to follow up. An unadjusted model was performed using “delayed” as the sole independent variable; the adjusted model incorporated the following additional variables: age, sex, ethnicity, etiology, MELD-Na, and blood type. Data is reported as hazard ratios (HRs) with 95% confidence intervals.

The threshold for statistical significance was set at $P < 0.05$. For all backward logistic regression model threshold to enter was 0.05 and threshold to remove was 0.10. All statistical analysis was conducted using SPSS version 29. This study was reviewed and approved by the institutional review board at our medical center.

RESULTS

We identified 160 patients undergoing inpatient LTE for cirrhosis (49% delayed referral and 51% early

Table 1 Baseline and demographics, %

Characteristic	Delayed referral (n = 78)	Early referral (n = 82)	P value
Portion of sample	49	51	-
Age (yr)	59 (10)	57 (9)	0.19
Distance to center (miles)	43.0 [20.5–59.5]	43.5 [19.3–67.3]	0.74
Time since diagnosis (mo)	30 [12.3–60]	11 [3.75–55.5]	< 0.01
Gender			0.59
Female	39.7	43.9	
Male	60.3	56.1	
Race			0.49
Asian	1.3	3.7	
Black or African American	1.3	1.2	
Other/Unknown	17.9	12.2	
White	79.5	82.9	
Ethnicity			0.11
Hispanic/other	19.2	9.8	
Non-Hispanic	80.8	90.1	
Etiology			0.88
Autoimmune	5.1	4.9	
Alcohol	43.6	53.7	
Cryptogenic/cholestatic	5.1	6.1	
Genetic	7.7	4.9	
Hepatitis C	11.5	9.8	
NASH	26.9	20.7	
Blood type			0.36
A	37.2	27.2	
B	16.7	19.8	
AB	1.3	4.9	
O	44.9	48.1	

Demographic and clinical data for delayed referral (left) versus early referral (right) patients undergoing inpatient liver transplant evaluation. Data reported as percentages of total group for categorical data; as average (standard deviation) for normally distributed continuous data, and as median [IQR] for non-normally distributed continuous data. NASH: Non-alcoholic steatohepatitis.

referral). Participants were predominately a male, white, and non-Hispanic with a mean age of 58 +/- 10. Over half of subjects had a high school level education or less (50.7% early *vs* 62.7% delayed, $P = 0.14$). The most common etiologies of cirrhosis were ETOH, NASH, and HCV. Subjects with delayed referral had been diagnosed with liver disease more months on average than those with early referral ($P < 0.01$). Subjects with early referral were diagnosed within the preceding year more often than subjects with delayed referral (50.7% *vs* 30.8%, $P = 0.02$) (See [Table 1](#) for summary of demographics).

Laboratory evaluation collected at time of LTE did not differ between groups ([Supplementary Table 2](#)). Most subjects had MELD-Na scores between 25–34 with an average score of 27 in each group ($P = 0.91$). A similar proportion of subjects had Grade 1, Grade 2, and Grade 3 ACLF ($P = 0.56$). The mean number clinical decompensations present during LTE was 4 and the number decompensations positively correlated with MELD-Na score ($r(157) = 0.390$, $P < 0.01$). One third of subjects were diagnosed with malnutrition during LTE (23.1% delayed referral *vs* 43.9% early referral, $P \leq 0.001$). Infection was recorded 40% of patients (42.3% delayed *vs* 35.4% early, $P = 0.39$) and blood pressure support occurred in 30% of patients (34.6% delayed *vs* 26.8% early, $P = 0.29$). About half the subjects in each group (48%) required an intensive care unit (ICU) stay during LTE with no differences in days of ICU stay ($P = 0.44$). Trans-jugular intrahepatic portosystemic shunt during admission was 2.3 times

Table 2 Liver transplant evaluation data, %

	Delayed	Early	P value
Transferred to center	48.7	51.2	0.75
MELD-Na (points)	27.2 (7)	27.0 (9)	0.87
TIPS placed	15.4	7.3	0.22
ICU stay	51.3	43.9	0.35
ICU d (#)	10 (9)	8 (7)	0.44
Pressor support	34.6	26.8	0.29
Declined for LT listing	17.9	15.9	0.72
Reasons declined			
Psychosocial	30.0	12.5	0.38
Medical	20.0	25.0	
Death	30.0	12.5	
Other	20.0	50.0	
Decompensations			
Ascites	94.9	96.3	0.65
Jaundice	64.1	72.0	0.29
EVB	21.8	24.4	0.70
HE	70.7	70.5	0.98
HRS	59.8	62.8	0.69
HHT	21.8	14.6	0.24
SBP	21.8	18.3	0.58
ACLF grade			
Grade 1	34.6	42.7	0.56
Grade 2	50.0	42.7	
Grade 3	15.4	14.6	
ACLF bilirubin			
< 15 mg/dL	82.1	76.8	0.28
15-25 mg/dL	9.0	17.1	
> 25 mg/dL	9.0	6.1	
ACLF INR			
< 1.8	62.8	62.2	0.78
1.8-2.5	28.2	25.6	
> 2.5	9	12.2	
ACLF lactate			
< 1.5 mmol/L	73.1	80.5	0.16
1.5-2.5 mmol/L	15.4	6.1	
> 2.5 mmol/L	11.5	13.4	
ACLF creatinine			
< 0.7 mg/dL	7.3	7.3	0.64
0.7-1.5 mg/dL	32.9	32.9	
> 1.5 mg/dL	52.6	59.8	

Clinical data from index admission and liver transplant evaluation. Data reported as percentages of group for categorical data; as average (standard deviation) for normally distributed continuous data. Comparisons were made using students T tests and comparison of proportions test. ACLF: Acute on chronic liver failure; LT: Liver transplant; ICU: Intensive care unit; MELD: Model for end stage liver disease; TIPS: Trans-jugular intrahepatic portosystemic shunt; EVB: Esophagogastric variceal bleeding; HRS: Hepatorenal syndrome; HHT: Hepatic hydrothorax; SBP: Spontaneous bacterial peritonitis; LTE: Liver transplant evaluation; INR: International normalized ratio; HE: Hepatic encephalopathy.

more common in delayed referrals (95%CI: 0.92-8.25, $P = 0.11$). Most subjects (83%) were accepted as candidates for liver transplant with no differences between groups ($P = 0.78$). However, it took 6-8 d longer to complete LTE for subjects with delayed referral compared to early referral ($P = 0.07$) (See [Table 2](#) for summary of clinical data).

Pre-LTE: Identifying risk factors for delayed referral

Psychosocial factors: A similar proportion of participants resided with family ($P = 0.75$) and had stable housing in each group ($P = 0.68$). Interestingly more subjects with delayed referral had an established partner compared to early referral ($P = 0.05$). Slightly more subjects with a delayed referral reported English as a second language, though this failed to meet statistical significance 20.5% *vs* 13.6%, $P = 0.24$). In terms of education, almost two thirds of the delayed referral group had a high school education or less compared to one half of the early referral group ($P = 0.14$). Employment within the last year ($P < 0.01$) and having an identifiable source of income ($P = 0.01$) were more common in subjects with early referral. Smoking history ($P = 0.15$) and alcohol use history was similar in each group ($P = 0.12$). However, for those patients who reported prior regular alcohol consumption, early referral subjects were closer to their last drink compared to delayed referral ($P < 0.01$). Specifically, more patients in the early group were evaluated with sobriety of 3-6 mo (39.3% early *vs* 22.4% delayed, $P = 0.05$) while more patients in the delayed group were referred with sobriety of 1-2 years (30.6% delayed *vs* 8.2% early, $P < 0.01$) (See [Table 3](#) for summary of psychosocial factors).

Clinical care- outpatient providers, medication, and gastrointestinal provider notes: There were no significant differences in pre-LTE hepatic decompensations between groups ([Table 3](#)). Average body mass index was slightly higher in missed group (32.5 $\pm$ 10 *vs* 30.1 $\pm$ 8; $P = 0.09$). Malnutrition was more common amongst early referrals and was associated with a 2/3 Lower chance of having a delayed referral (OR: 0.34, CI: 0.14-0.78, $P = 0.01$). The number of patients receiving routine medications for ascites and hepatic encephalopathy when applicable based on decompensation history did not differ between groups. Interestingly, of the 35.6% of patients with known diabetes, insulin use was more common in delayed referrals, but not to a statistically significant degree (33.3% delayed *vs* 16.7%, $P = 0.15$). Of patients with regular laboratory evaluation available, previously documented hypercoagulability and transaminitis was noted between groups; hypoalbuminemia was slightly more common amongst those with delayed referral ([Table 3](#)). Considering only patients with outside documentation from gastroenterologist, there were no differences in proportion of patients with low albumin, elevated international normalized ratio, or abnormal liver enzymes between early and delayed referral (data not shown) (See [Table 3](#) for summary of outpatient care factors).

Risk factors for delayed referrals: Backward logistic regression model using 20 psychosocial or demographical variables identified female sex and trauma history to be predictors of delayed referral while malnutrition, work within the prior year, and prior smoking history were predictors of early referral ([Supplementary Table 3](#)). The most common theme identified in clinical documentation leading to delayed referral was poor understanding about indications for transplant referral, which was identified in 20% of the subjects with delayed referrals. Specifically, outpatient providers cited inaccurate contraindications to transplant, such as age or weight, or incorrect sobriety periods required for referral. Other frequently identified themes included failure to obtain or calculate MELD-Na labs (10%), lack of care continuity (18%), insurance or financial barriers (9%), or patient reluctance to pursue transplant (10%). However, one in three patients had no clear reason for lack of referral.

Effects of referral time on patient outcomes

Primary outcome measures differed between those with delayed compared to early referral. Delayed referrals were transplanted less often (28% *vs* 48%) and died prior to transplant more often than those with early referral (42% *vs* 21%). Predictors of transplant identified on backward logistic regression include age, ACLF grade, platelets, neutrophil-lymphocyte ratio, albumin, sex, months since diagnosis, weight, blood type, and delayed referral. On a multivariable regression model created using clinical data optimized for goodness of fit, early referral was associated with 2.3 increased odds of receiving a transplant (95%CI: 1.02-4.57; $P = 0.045$) ([Supplementary Table 4](#)). Of those transplanted, over 80% of each group was one year post transplant at the time of data collection, and about 50% were two years post-transplant. There were no differences in survival at either the one-year ($P = 0.650$), or two-year ($P = 1.000$) time points (data not shown).

Table 3 Pre-transplant clinical and demographic factors, %

	Delayed	Early	P value
Education			0.14
Highschool or less	62.6	50.7	
College degree or more	14.7	23.4	
Substance use			
Smoking history	55.1	57.3	0.15
Drinking history	62.8	74.3	0.12
Sobriety period			< 0.01
< 6 mo	22.4	59.0	
6 mo – 2 yrs	53.0	26.2	
> 2 yrs	23.6	14.8	
Psychosocial factors			
Depression history	39.7	28.0	0.12
Trauma history	9.0	2.4	0.07
Public insurance	50.0	50.0	1.00
Non-English first language	20.5	13.6	0.24
Lives with family	78.2	80.2	0.75
Married/stable partner	67.5	52.4	0.05
Unstable housing	6.4	4.9	0.68
Military service history	3.8	8.6	0.21
Worked within 1 mo	7.7	22.2	<0.01
Worked within 1 yr	24.4	49.4	<0.01
Clinical care			
Outpatient GI documentation	83.3	78.0%	
Ascites on diuretics	90.7	90.3	0.94
Ascites with regular paracentesis	32.0	25.0	0.35
On lactulose/rifaximin	85.0	90.5	0.39
Midodrine	42.9	46.0	0.81
Regular labs	<i>n</i> = 59	<i>n</i> = 40	
Low albumin	89.8	77.5	0.09
High ALT/AST	93.2	87.5	0.31
High INR	84.7	72.5	0.14
Prior decompensations			
Ascites	96.2	87.8	0.05
Jaundice	66.7	68.3	0.83
Variceal bleed	35.9	29.3	0.37
Hepatic encephalopathy	78.2	64.2	0.06
Hepatorenal syndrome	35.9	31.7	0.58
Hepatic hydrothorax	11.5	9.8	0.72
Spontaneous bacterial peritonitis	21.8	24.4	0.68

Comparison of psychosocial and clinical data from prior to liver transplant evaluation (LTE) in patients with delayed compared to early LTE. Psychiatric

comorbidities including depression and trauma occurred more in delayed LTE. Working history was strongly associated with timely referral. Data reported as percentages of group for categorical data; as average (standard deviation) for normally distributed continuous data. Comparisons were made using students T tests and comparison of proportions test. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GI: Gastrointestinal; INR: International normalized ratio.

Predictors of death on backward logistic regression include Age, hematocrit, neutrophil to lymphocyte ratio, albumin, months since diagnosis, weight, decompensation number, and delayed referral (Table 5). Within the delayed LTE cohort patients who died were older ($P = 0.04$), had an outpatient gastrointestinal (GI) provider less often ($P = 0.03$), had SBP more often ($P = 0.04$) and required an ICU stay and blood pressure support more often (< 0.01) (Supplementary Table 1). On univariable Cox Regression, the HR of death was 2.2 (95%CI: 1.2–2.9) in for delayed referral compared to early referral over average follow up period of 269 d. When adjusting for age, sex, ethnicity etiology, and MELD-Na, the HR for increased to 2.5 (95%CI: 1.3–4.7) for delayed referral compared to early referral (Figure 1).

DISCUSSION

Our study assessed clinical characteristics of patients with decompensated cirrhosis undergoing inpatient LTE and examined the effect of delayed referral on patient outcomes. We observed that a significant proportion of patients could have been referred earlier and built on this notion by demonstrated delayed LTE was associated with worse patient outcomes in patients already undergoing urgent LTE. These relationships persisted when controlling for key variables and backward logistic regression identified delayed referral as an independent risk factor for death and not receiving a liver transplant. We identified risk factors for death within the patients who had a delayed LTE to identify the most vulnerable cohorts and found death to be most common in patients with delayed referral and (1) Had no regular documentation from an outside GI provider; and (2) were critically ill in the ICU with SBP and requiring blood pressor support.

The high proportion of patients with delayed referrals is consistent with previous studies that report poor adherence to liver transplant referral guidelines in patients with cirrhosis[19]. We sought to identify demographical risk factors for delayed LTE but observed no differences in basic demographics between cohorts in our study. Patients in our study resided within similar proximity to the transplant center, which is inconsistent with previous literature reporting that increased distance from a transplant site is a barrier to transplant related care[20]. However, we believe this suggests distance may be more related to the ability to attend health care appointments and not play a role in the referral decision itself. For example, a recent study that identified LTE within 30 d of LT referral was associated with better outcomes and that distance from the transplant center reduced odds of completing LTE within the 30-d window[21]. While we anticipated group differences in health insurance[6,22,23], we observed approximately 50% of each cohort having publicly funding insurance. It is possible that this is due to the robust public health and insurance funding in Massachusetts.

There were notable psychosocial differences between cohorts including education and employment status. Lower education attainment and lack of employment within the preceding year were more common in patients with delayed referral. This data supports that lower degrees of financial stability and health literacy may act as barriers to early evaluation. Identifying patients with limited health literacy could reduce the number of delayed evaluations by improving patients' understanding of their disease[24]. In addition, we found that being married or having a stable partner was more common in patients with delayed referrals but did not affect transplant or death. We found this point interesting as typically psychosocial support is associated with improved outcomes in the transplant pathway; it remains unclear the role of having a spouse or stable partner on referral and care seeking in this population.

We utilized clinical history and provider written medical documentation to inform understanding of barriers to access to liver transplantation referral and evaluation. First, specific hepatic decompensations did not differ between groups, which is consistent with recent research reporting that clinical manifestations of CLD may be poor markers of the timeliness of transplant evaluation[7]. Conversely, malnutrition was protective against of delayed evaluation which may suggest that frailty is a conspicuous manifestation of CLD that is more readily recognized compared to more obscure manifestations of CLD, such as mild hepatic encephalopathy, or that physicians associate frailty with poor outcomes and are more likely to refer. Differences in time from diagnosis to transplant evaluation may reflect this as well, as data suggests providers have different thresholds for referral. Conversely it may be explained by lack of care continuity amongst patients with delayed referrals. Care continuity may reflect poor understanding of disease severity, and it is possible that targeting patient understanding of liver disease may improve the follow up rate in this cohort.

Table 4 Predictors of transplant

	Initial multivariate regression				Backward logistic regression			
	Wald	P value	OR	95%CI	Wald	P value	OR	95%CI
Age (yr)	3.45	0.06	0.94	0.9-1.0	4.62	0.03	0.95	0.9-1.0
Education (HS)	2.41	0.12	1.49	0.9-2.5	-	-	-	-
ICU stay (+)	1.12	0.29	0.38	0.1-2.3	-	-	-	-
ACLF grade (G3)	2.67	0.10	2.76	0.8-9.3	4.75	0.03	2.13	1.1-4.2
MELD (points)	0.58	0.45	1.07	0.9-1.3	-	-	-	-
Creatinine (mg/dL)	0.08	0.78	0.90	0.4-1.9	-	-	-	-
Sodium (mmol/L)	1.28	0.26	0.90	0.8-1.0	-	-	-	-
Bilirubin (mg/dL)	1.06	0.30	1.05	1.1-1.1	-	-	-	-
INR	1.28	0.26	0.42	0.1-1.9	-	-	-	-
WBC ($\times 10^9/L$)	0.03	0.86	0.99	0.8-1.2	-	-	-	-
Hematocrit (%)	1.34	0.25	0.94	0.9-1.0	-	-	-	-
Platelets ($\times 10^9/L$)	1.73	0.19	0.99	1.0-1.0	5.50	0.02	0.99	1.0-1.0
N-L ratio	3.65	0.06	0.89	0.8-1.0	5.15	0.02	0.90	0.8-1.0
Albumin (g/dL)	6.79	< 0.01	3.58	1.4-9.4	9.04	< 0.01	3.32	1.5-7.3
Malnutrition (+)	0.30	0.59	1.39	0.4-4.6	-	-	-	-
Cardiac dx (+)	0.06	0.82	0.83	0.2-3.9	-	-	-	-
Sex (Male)	7.29	< 0.01	14.8	2.1-105	3.02	0.08	2.38	0.9-6.3
Race (White)	1.24	0.27	0.42	0.1-1.9	-	-	-	-
Depression (+)	4.17	0.04	4.24	1.1-17	-	-	-	-
Time since dx (mo)	2.44	0.12	1.01	1.0-1.0	2.69	0.10	1.01	1.0-1.0
Pressor need (+)	0.28	0.60	0.56	0.1-4.8	-	-	-	-
Height (cm)	2.37	0.12	0.94	0.9-1.0	-	-	-	-
Weight (kg)	1.22	0.27	0.99	1.0-1.0	4.72	0.03	0.98	1.0-1.0
Transferred (+)	0.00	1.0	1.00	0.3-3.5	-	-	-	-
Refer to LTE (d)	0.04	0.85	1.00	1.0-1.0	-	-	-	-
Delayed referral (+)	2.67	0.10	0.32	0.1-1.2	3.51	0.06	0.40	0.2-1.0
Decompensations (#)	0.11	0.73	0.91	0.5-1.6	-	-	-	-
Etiology (ETOH)	0.00	0.98	1.00	0.7-1.5	-	-	-	-
TIPS (+)	1.36	0.24	0.52	0.2-1.6	-	-	-	-
Blood type (A)	2.50	0.11	0.62	0.3-1.1	2.71	0.01	0.65	0.4-1.1
Constant	3.26	0.07	5000	-	0.745	0.38	6.54	-

Multivariable logistic model with backward logistic regression to identify predictors of receiving transplant in patients undergoing inpatient liver transplant evaluation (LTE). Starting with 30 potential variables that may predict hepatic encephalopathy, backward regression identified 10 potential independent predictors for transplant including age, ACLF grade, platelets, N-L ratio, serum albumin, sex, time since diagnosis, weight blood type, and having a delayed LTE. Regression complete in SPSS using backward regression conditional model; probability to enter 0.05 and probability to remove 0.10. Units recorded in parenthesis for continuous variables; reference variable recorded in parenthesis for categorical variables where “+” indicates the variable is present in the patient. ACLF: Acute on chronic liver failure; ICU: Intensive care unit; WBC: White blood cell count; MELD: Model for end stage liver disease; INR: International normalized ratio; N-L ratio: Neutrophil to lymphocyte ratio; dx: Diagnosis; TIPS: Trans-jugular intrahepatic portosystemic shunt.

Documentation for 1 in 5 patients with delayed referral included misconceptions about candidacy and referenced inaccurate contraindications to transplant. This was especially evident in subjects with alcohol use disorder, where providers noted longer sobriety periods than truly required to enter the transplant care pathway. These findings are consistent with literature showing provider level factors

Table 5 Predictors of death

	Initial multivariate regression				Backward logistic regression			
	Wald	P value	OR	95%CI	Wald	P value	OR	95%CI
Age (yrs)	5.51	0.02	1.12	1.0-1.2	6.24	0.01	1.10	1.0-1.1
Education (HS)	0.72	0.40	0.75	0.4-1.5	-	-	-	-
ICU stay (+)	0.03	0.86	0.84	0.1-5.8	-	-	-	-
ACLF grade (G3)	0.06	0.81	1.19	0.3-4.9	-	-	-	-
MELD (points)	4.58	0.03	0.73	0.5-1.0	-	-	-	-
Creatinine (mg/dL)	2.85	0.09	2.46	0.9-7.0	-	-	-	-
Sodium (mmol/L)	5.25	0.02	0.82	0.7-1.0	-	-	-	-
Bilirubin (mg/dL)	0.04	0.84	0.99	0.9-1.1	-	-	-	-
INR	3.06	0.08	8.85	0.8-101	-	-	-	-
WBC ($\times 10^9$ /L)	0.02	0.88	1.02	0.8-1.3	-	-	-	-
Hematocrit (%)	1.57	0.21	1.11	0.9-1.3	2.67	0.10	1.09	1.0-1.2
Platelets ($\times 10^9$ /L)	0.09	0.76	1.00	1.0-1.0	-	-	-	-
N-L ratio	5.90	0.02	1.22	1.0-1.4	5.47	0.02	1.11	1.0-1.2
Albumin (g/dL)	5.07	0.02	0.18	0.0-0.8	2.67	0.10	0.49	0.2-1.2
Malnutrition (+)	0.04	0.85	0.84	0.1-5.1	-	-	-	-
Cardiac dx (+)	1.71	0.19	3.53	0.5-23	-	-	-	-
Sex (Male)	4.43	0.04	0.08	0.0-0.8	-	-	-	-
Race (White)	1.06	0.30	0.32	0.0-2.8	-	-	-	-
Depression (+)	1.72	0.19	3.07	0.6-16	-	-	-	-
Time since dx (mo)	5.84	0.02	0.97	1.0-1.0	3.52	0.06	0.99	1.0-1.0
Pressor need (+)	0.36	0.55	0.44	0.0-6.5	-	-	-	-
Height (cm)	4.04	0.05	1.13	1.0-1.3	-	-	-	-
Weight (kg)	3.83	0.05	1.04	1.0-1.1	7.01	< 0.01	1.02	1.0-1.0
Transferred (+)	1.53	0.22	0.36	0.1-1.8	-	-	-	-
Refer to LTE (d)	0.65	0.42	0.99	1.0-1.0	-	-	-	-
Delayed referral (+)	6.75	0.01	8.40	1.7- 42	7.27	< 0.01	4.51	1.5-14
Decompensations (#)	3.61	0.06	2.08	1.0-4.4	6.33	0.01	1.49	1.1-2.0
Etiology (ETOH)	1.22	0.27	1.30	0.8-2.1	-	-	-	-
Blood type (A)	4.98	0.03	3.01	1.1-7.9	-	-	-	-
TIPS (+)	0.44	0.51	1.45	0.5-4.4	-	-	-	-
Constant	0.09	0.76	0.02	-	0.75	0.38	6.54	-

Multivariable logistic model with backward logistic regression to identify predictors of receiving transplant in patients undergoing inpatient liver transplant evaluation (LTE). Starting with 30 potential variables that may predict hepatic encephalopathy, backward regression identified 8 potential independent predictors for transplant including age, Hematocrit, N-L ratio, serum albumin, sex, time since diagnosis, weight, number of decompensations, and having a delayed LTE. Regression complete in SPSS using backward regression conditional model; probability to enter 0.05 and probability to remove 0.10. Units recorded in parenthesis for continuous variables; reference variable recorded in parenthesis for categorical variables where “+” indicates the variable is present in the patient. ACLF: Acute on chronic liver failure; ICU: Intensive care unit; WBC: White blood cell count; MELD: Model for end stage liver disease; INR: International normalized ratio; N-L ratio: Neutrophil to lymphocyte ratio; dx: Diagnosis; TIPS: Trans-jugular intrahepatic portosystemic shunt.

affect LT access[19,25] and may suggest bias has a negative impact on referral. Patients in our study who were referred within the first year of sobriety had improved outcomes. Patients in the delayed evaluation were more likely to have 1-2 years of sobriety than early referral. Patients who have continued hepatic decompensation after 3 mo of sobriety are less likely to recompensate and our data

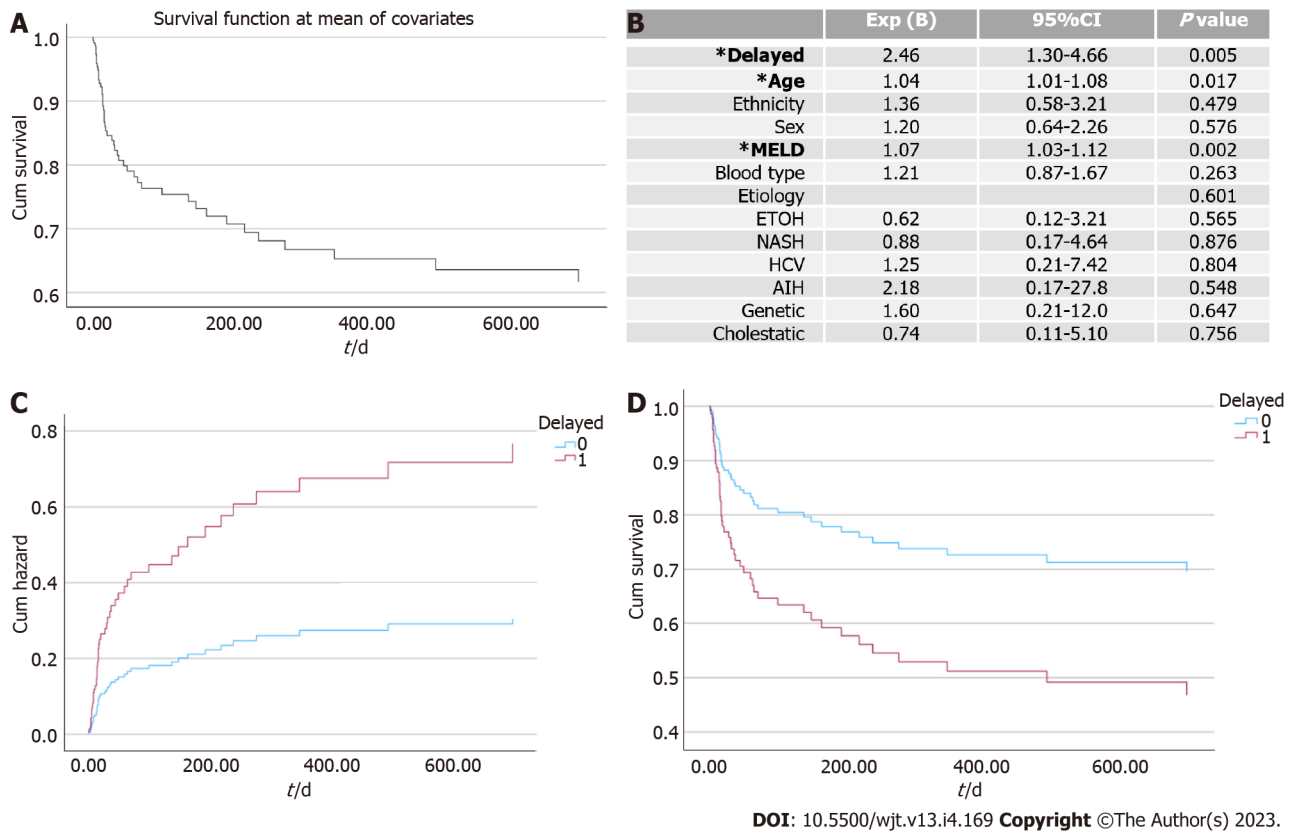


Figure 1 Multivariable Cox regression model assessing the effect of delayed referral on death when accounting for age, ethnicity, patient sex, MELD score, and disease etiology. Patients were censored if lost to follow up or at the time of transplant. A: Total survival curve for patients undergoing inpatient liver transplant evaluation (LTE); B: Cox hazard regression output with hazard ratio (HR) with 95% CI and p values are reported from multivariate analysis. (*) indicates variables that are significant with $P < 0.05$; C: Hazard function plotted for risk of death since time of LTE start where "0" is early LTE and "1" is delayed LTE; D: Cumulative survival function since time of LTE start where "0" is early LTE and "1" is delayed LTE. Delayed LTE was associated with increased mortality amongst patients undergoing inpatient LTE.

supports the growing trend for early LTE referral in patients with alcohol liver disease. Our results demonstrate that providers need have increased awareness of patients who have not been referred to a transplant center at this point in sobriety as they may be at increased risk of precipitous decompensation and require urgent LTE. Beyond alcohol, reducing bias toward cirrhosis in general may help as almost one-third of patients did not have an identifiable reason for delayed referral. Further research is needed to characterize referral patterns for LTE. While nationwide and database research can help improve this, there is also the need for regionally based research given practices and attitudes likely vary by geographic location.

We believe our paper has multiple strengths. To our knowledge, this is the first study stratifying inpatient liver transplant candidates based on presence or absence of previously missed opportunities for transplant evaluation and compared outcomes. Study staff had full access to the electronic medical record and were able to conduct a comprehensive chart review that included both discrete/categorical data and more qualitative information from clinical documentation. This offers advantages compared to large databases studies which can analyze large amounts of data, but do not consider the clinical context in which medical decisions are taken. Statistically, we used a variety of modeling methods and used backward logistic regression to demonstrate delayed LTE is an independent predictor of death. This was further supported with Cox regression to demonstrate the strength of this relationship over time.

There are also limitations to our study. Its retrospective and single center nature with a small sample limits the elimination of biases and statistical analysis. Our study population is predominantly white and non-Hispanic which limited our ability to control for the effect of race and ethnicity[26] without disrupting the statistical strength of our models. In effort to account for this, we incorporated language status into the model which improved overall representation of our data. This study included evaluations performed during the SARS-2 Coronavirus pandemic, which universally impacted organ transplantation. However, overall patient outcomes did not differ before and after the onset of the pandemic in our study population (data not shown).

In this paper we build on existing literature that demonstrates many patients experience delays in access to LTE care and demonstrate that delayed referral for LTE has a negative impact on patient survival and transplant outcomes even in patients receiving expedited and high-level care at a tertiary

liver transplant center. There is substantial opportunity to increase the percentage of patients undergoing transplant evaluation when first clinically indicated. Providers should aim to consistently adhering to referral guidelines to limit provider bias and allow determinations about candidacy to be made by dedicated transplant center. For this to occur, providers need to remain up to date on guidelines regarding liver transplant candidacy, the transplant referral process, and routine work up in patients with CLD. Efforts to increase awareness of this information is critical in general gastroenterology and primary care providers. In future studies, we hope to strengthen the understanding of these phenomena by studying patients who are evaluated through routine outpatient visits.

CONCLUSION

Delayed LTE negatively impacts patient care. There are both provider and patient level factors that contribute to delayed LTE and may act as actionable targets to improve patient outcomes.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation is the only definitive treatment for end stage liver disease, which has an increasing prevalence world wide. Despite this, there are many barriers to accessing liver transplant related care.

Research motivation

Barriers to timely liver transplant evaluation (LTE) are poorly understood and likely differ by geographic location.

Research objectives

We sought to perform a granular assessment of patients who completed inpatient LTE at our center and to identify risk factors for delayed LTE.

Research methods

We performed a single center retrospective cohort study analyzing patients with cirrhosis who completed LTE over 4 years. Patients were categorized as early or delayed LTE based on their clinical history. The electronic medical record was extensively reviewed to identify risk factors for delayed evaluation. Logistic regression was utilized to determine the effect of delayed evaluation on patient outcomes and to identify risk factors for delayed LTE.

Research results

Delayed referral increased the risk of death and decreased the odds of receiving a liver transplant. Female sex and trauma history to be predictors of delayed referral while malnutrition, work within the prior year, and prior smoking history were predictors of early referral. Documentation for 1 in 5 patients with delayed referral included misconceptions about candidacy and referenced inaccurate contraindications to transplant.

Research conclusions

Many patients undergo delayed LT which is associated with poor patient outcomes. Provider bias and patient psycho-social circumstances are both affect the timeliness of LTE and are targets for interventions aiming to improve access to liver transplantation.

Research perspectives

The use of granular data may improve the ability to identify patients at risk at individual centers.

FOOTNOTES

Author contributions: Cooper KM, Colletta A, Hathaway NJ, and Devuni D contributed to analysis and interpretation of data; Cooper KM, Talat A, and Devuni D contributed to study concept and design; Cooper KM, Colletta A, Liu D, Gonzalez D, Barry C, Krishnarao A, Mehta S, Movahedi B, and Martins PN contributed to acquisition of data; Cooper KM and Colletta A contributed to drafting of the manuscript; Cooper KM, Martins PN, and Devuni D contributed to critical revision of the manuscript for important intellectual content; Cooper KM and Hathaway NJ contributed to statistical analysis; Barry C, Krishnarao A, Mehta S, Movahedi B, and Martins PN contributed to material support; Devuni D contributed to study supervision.

Institutional review board statement: This study was reviewed and approved by the institutional review board at our medical center (IRB Docket: Study00000016, approved 10/24/21).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed care with informed consent. This study received a Health Insurance Portability and Accountability Act (HIPAA) waiver for informed consent at our institution through the IRB review process.

Conflict-of-interest statement: All authors have no conflicts of interest related to this study to report.

Data sharing statement: This study was reviewed and approved by the institutional review board at our medical center with a waiver of consent due to the retrospective nature of this study.

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