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Retrospective Study

Delayed referral liver transplant evaluation is associated with worse outcomes in patients with chronic liver disease requiring inpatient liver 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

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 liver transplant evaluation (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 LT center, delaying LTE increases risk of death and reduces risk of LT in patients with CLD. 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.

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 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. REDCap (Research Electronic Data Capture) 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 (HE), jaundice, ascites, hepato-renal syndrome (HRS), spontaneous bacterial peritonitis (SBP), and variceal bleed (EVB) [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 dieticians 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 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 4).

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-values <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 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 1). 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) = .390, p<0.01). One third of subjects were diagnosed with malnutrition during LTE (23.1% delayed referral vs. 43.9% early referral, p=<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 ICU stay during LTE with no differences in days of ICU stay ($P = 0.44$). Trans-jugular intrahepatic portosystemic shunt (TIPS) during admission was 2.3 times 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 days 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 patents 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 GI 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 +/-10 vs. 30.1 +/- 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 INR, 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 2). 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 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 3). 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*).

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 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 4). 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 days. When adjusting for age, sex, ethnicity etiology, and MELD-Na, the HR for increased to 2.5 (95% 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 days of LT referral was associated with better outcomes and that distance from the transplant center reduced odds of completing LTE within the 30-day window [21]. While we anticipated group differences in health insurance [6, 22, 23], we observed ~ 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.

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 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 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.

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