

Recipient ineligibility after liver transplantation assessment: a single centre experience

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Background: Candidacy for liver transplantation is determined through standardized evaluation. There are limited data on the frequency and reasons for denial of transplantation after assessment; analysis may shed light on the short-term utility of the assessment. We sought to describe the frequency and reasons for ineligibility for liver transplantation among referred adults.

Methods: We studied all prospectively followed recipient candidates at a single centre who were deemed unsuitable for liver transplantation after assessment. Inclusion criteria were age 18 years and older and completion of a standard liver transplantation evaluation over a 3-year period. Patients were excluded if they had a history of prior assessment or liver transplantation within the study period. Demographic and baseline clinical data and reasons for recipient ineligibility were recorded.

Results: In all, 337 patients underwent their first liver transplantation evaluation during the study period; 166 (49.3%) fulfilled inclusion criteria. The mean age was 55.4 years, and 106 (63.9%) were men. The 3 most common reasons for denial of listing were patient too well ($n = 82$, 49.4%), medical comorbidities and/or need for medical optimization ($n = 43$, 25.9%) and need for addiction rehabilitation ($n = 28$, 16.9%).

Conclusion: Ineligibility for transplantation after assessment was common, occurring in nearly half of the cohort. Most denied candidates could be identified with more discriminate screening before the resource-intensive assessment; however, the assessment likely provides unforeseen positive impacts on patient care.

Contexte : Les candidats à une greffe du foie sont sélectionnés au moyen d'une évaluation standardisée. On dispose de peu de données au sujet de la fréquence et des motifs des refus de transplantation consécutifs à cette évaluation. Une analyse pourrait faire la lumière sur l'utilité de l'évaluation à court terme. Nous avons voulu décrire la fréquence de ces refus et les raisons pour lesquelles des adultes adressés pour consultation se voient refuser la greffe.

Méthodes : Nous avons étudié tous les candidats à la greffe suivis prospectivement dans 1 seul centre et à qui, après évaluation, la greffe du foie a été refusée. Les critères d'inclusion étaient l'âge de 18 ans et plus et les résultats de l'évaluation standard en vue de la greffe du foie sur une période de 3 ans. Les patients étaient exclus s'ils avaient déjà subi une évaluation ou une greffe du foie au cours de la période de l'étude. Les données démographiques et cliniques de départ, de même que les raisons de l'exclusion des candidats ont été consignées.

Résultats : En tout, 337 patients ont subi leur première évaluation en vue d'une greffe du foie au cours de la période de l'étude; 166 (49,3 %) répondaient aux critères d'inclusion. L'âge moyen était de 55,4 ans et 106 (63,9 %) étaient des hommes. Les 3 raisons les plus souvent invoquées pour refuser l'accès à la greffe chez ces candidats étaient qu'ils étaient suffisamment bien ($n = 82$, 49,4 %), qu'ils présentaient des comorbidités et(ou) qu'ils devaient améliorer leur état de santé ($n = 43$, 25,9 %) ou qu'il leur fallait une cure de désintoxication ($n = 28$, 16,9 %).

Conclusion : De nombreux patients, soit près de la moitié de la cohorte, ont été jugés mauvais candidats à la greffe après l'évaluation. Il serait possible de reconnaître les patients qui sont mauvais candidats à la greffe en faisant un dépistage plus précis avant même d'aller de l'avant avec l'évaluation standard, qui draine d'importantes ressources. Toutefois, l'évaluation a probablement des répercussions positives imprévues sur le soin des patients.

In well-selected recipients, liver transplantation is a highly efficacious and cost-effective surgery for which there are established indications and contraindications.^{1,2} The discord between the number of patients who require liver transplantation and the number of suitable hepatic grafts available for

transplantation necessitates an organ allocation system and has bearing on exclusion criteria.³⁻⁵ To determine suitability for liver transplantation, candidates undergo an intensive multidisciplinary work-up, including hepatic, renal, cardiac, pulmonary, psychosocial, nutrition and functional status assessments.² Eligibility determination is based on objective evidence of hepatic dysfunction and the consensus of the transplant team comprising specialists in a multitude of disciplines, including hepatology, hepatobiliary surgery, anesthesiology, cardiology, psychology, nursing, social work, nutrition and physical therapy.

In theory, liver transplantation is indicated for decompensated end-stage liver disease, acute liver failure, early hepatocellular carcinoma (HCC) and certain metabolic disorders. Contraindications to liver transplantation include select causes of pulmonary or cardiac dysfunction (e.g., severe pulmonary hypertension, advanced coronary artery disease), uncontrolled systemic infection, active extrahepatic malignancy, poor prognosis from other medical comorbidities, severe psychiatric or neurologic disorders that can interfere with compliance, lack of adequate social supports and advanced HCC with or without vascular invasion.^{2,6-9}

Surprisingly few studies have evaluated the frequency of and reasons for rejection of candidacy after the liver transplantation assessment. Such data could help optimize the use of resources required for the evaluation, particularly given the anticipated increased need for liver transplantation owing to the growing burden of liver disease and HCC in many populations.¹⁰⁻¹³ In a study of 150 patients deemed unsuitable for liver transplantation at the University of British Columbia, Alali and colleagues³ reported that medical contraindications were the most common reason for denial, and the proportion of ineligible patients in their series was relatively small. It is unclear whether rates of denial of candidacy for liver transplantation relate to appropriateness of referrals from providers and/or to effectiveness of screening of referrals by the liver transplantation program. It is also unclear how early referrals (i.e., referrals made before a recipient candidate has sufficient hepatic decompensation to theoretically achieve a survival benefit from liver transplantation) impact on clinical outcomes and liver transplantation programs. Further observational data — particularly in the current era where candidates are older and have more comorbidities and hepatic dysfunction — is needed to explore outcomes from the liver transplantation assessment. We sought to describe the demographic characteristics and reasons for denial of transplantation in referred adults over a 3-year period.

METHODS

As part of a quality assurance project approved by the Institutional Review Board, all patients assessed for a primary liver transplantation at Western University (London,

Ont.) from Jan. 1, 2009, to Dec. 31, 2011, were prospectively followed. We collected demographic and baseline clinical data on patients who were denied candidacy for liver transplantation and not ultimately listed for liver transplantation during the study period. The model for end-stage liver disease (MELD) score was calculated using laboratory parameters ascertained during the week of the assessment, and for the purposes of this analysis, we did not use MELD exception criteria. In patients who had more than 1 disease causing liver dysfunction, we attributed the etiology of the liver disease to the dominant component. Patients with primary biliary cirrhosis, primary sclerosing cholangitis and/or autoimmune hepatitis were collectively categorized as having “autoimmune liver disease.” Reasons for ineligibility of patients were categorized as follows: too well, requires addiction rehabilitation, medical comorbidities and/or need for medical optimization, advanced HCC, or other. The distance between the primary residence of the patient and the transplant centre was assessed as a variable. We approximated the distance from the patient’s residence to the transplant centre using Google Maps; patients residing in the same city as the transplant centre were assigned a distance of 0 km. Local patients were arbitrarily defined as those residing within 200 km of the transplant centre.

Statistical analysis

We report categorical variables as frequencies with percentages and continuous variables as means with standard deviations (SD). To assess the associations between the distance of the patient’s primary residence and the transplant centre with both MELD score and underlying cause of liver disease, we used the χ^2 test, Armitage test for proportions and/or analysis of variance. Statistical analyses were performed using STATA software version 11.0 (StataCorp.).

RESULTS

Participant demographic and baseline clinical characteristics are summarized in Table 1. In all, 337 adults were assessed for liver transplantation during the study period, and 166 patients (49.3%) were declined. Of those who

Table 1. Demographic and baseline clinical characteristics of study population

Characteristic	Mean (SD) or no. (%)
Age at assessment, mean (SD) yr	55.4 (9.8)
Male sex, no. (%)	106 (63.9)
Proximity from transplant centre, mean (SD) km	345.4 (510.7)
MELD score, mean (SD)	12.4 (5.3)
Hepatocellular carcinoma, no. (%)	24 (14.5)
Diabetes mellitus, no. (%)	44 (26.5)

MELD = model for end-stage liver disease; SD = standard deviation.

were denied candidacy, the mean age was 55.4 years, and 106 (63.9%) were men. The mean MELD score was 12.4 (SD 5.3, range 6–29). Patients resided a mean distance of 345.4 (SD 510.7) km from the transplant centre.

Figure 1 shows the causes of liver disease in the study population. The 4 most common causes were hepatitis C ($n = 51, 30.7\%$), alcohol ($n = 50, 30.1\%$), autoimmune liver disease ($n = 26, 15.7\%$) and nonalcoholic fatty liver disease ($n = 18, 10.8\%$).

The reasons for patient ineligibility for liver transplantation are shown in Figure 2. The reasons were as follows: too well ($n = 82, 49.4\%$), medical comorbidities and/or need for medical optimization ($n = 43, 25.9\%$), need for addiction rehabilitation ($n = 28, 16.9\%$) and advanced HCC ($n = 7, 4.2\%$). Among patients declined owing to

medical comorbidities and/or need for medical optimization, 20 (46.5%) had medical comorbidities, 13 (30.2%) required medical optimization, 6 (14.0) had a body mass index (corrected for ascites) greater than 40 and 4 (9.3%) had severe malnutrition.

There was no correlation between patient distance from the transplant centre and underlying cause of liver disease (Fig. 3). There was a trend toward a greater prevalence of hepatitis C among local patients (i.e., residing 200 km or less from the transplant centre), but this association was not significant ($p = 0.08$; Fig. 3B).

The mean MELD scores, stratified by distance from the transplant centre, are listed in Table 2. There was no

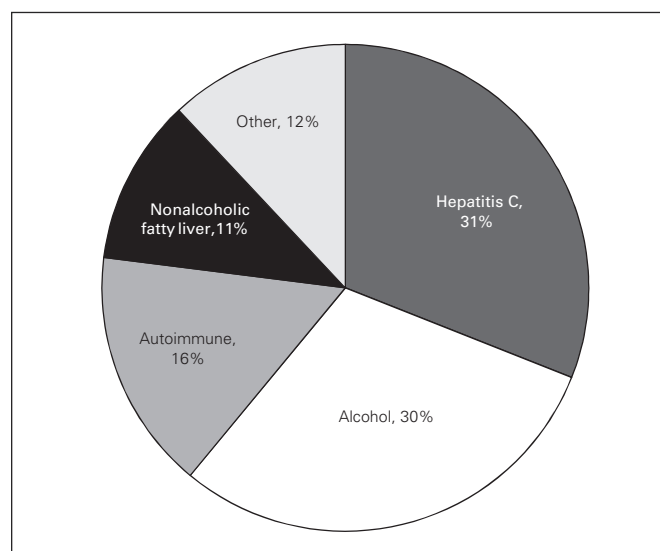


Fig. 1. Etiology of liver disease in the study population.

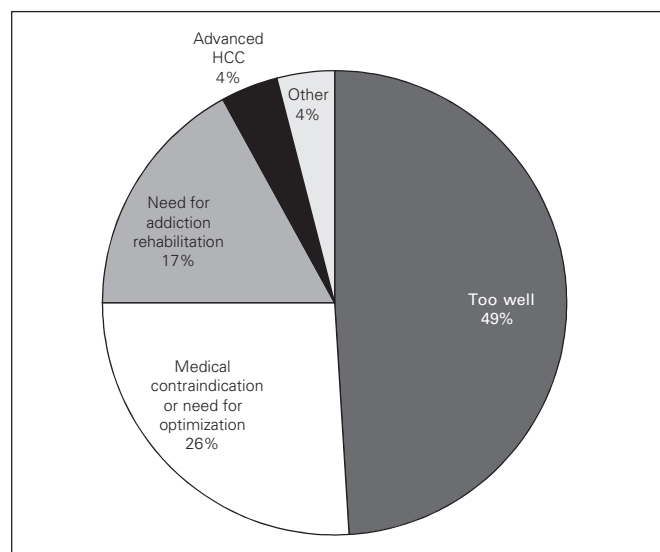


Fig. 2. Reasons for ineligibility for transplantation candidacy of patients referred for assessment.

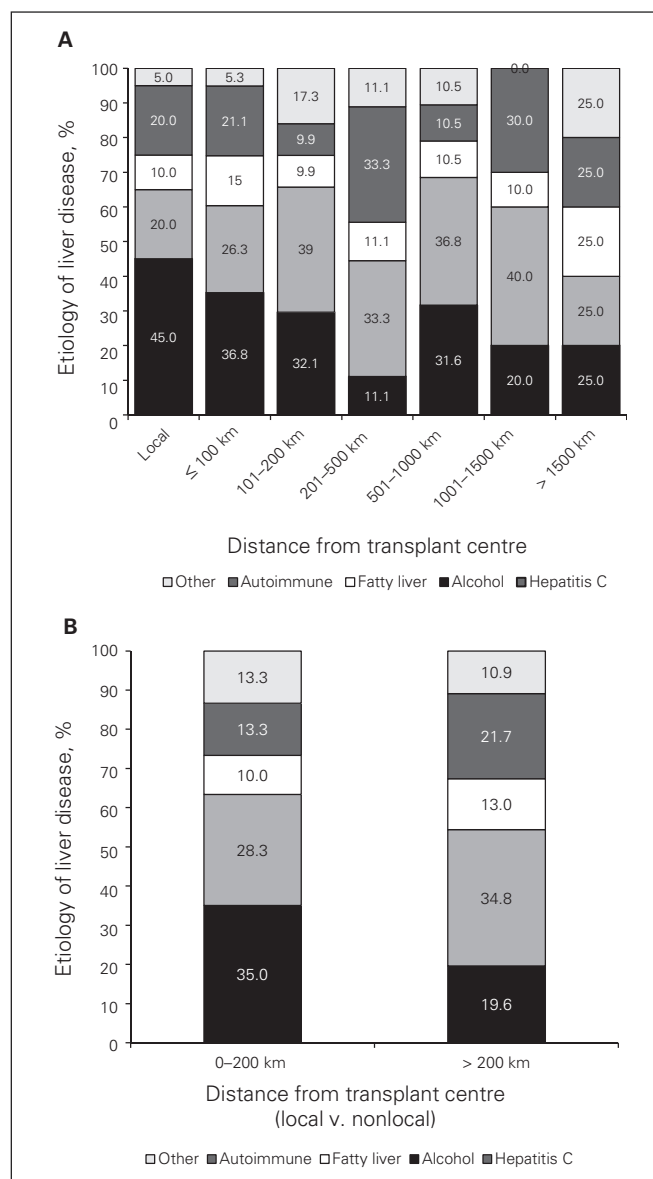


Fig. 3. (A) Association between patients' distance from the transplant centre and underlying cause of liver disease. (B) Association between patients' distance from the transplant centre, stratified by local versus nonlocal status, and underlying cause of liver disease.

correlation between distance of the patient's primary residence from the transplant centre and MELD score (correlation coefficient = 0.09, $p = 0.25$).

Proportions of patients ineligible for transplant were similar across varying distances from the transplant centre ($p = 0.78$; Fig. 4).

DISCUSSION

In our study, nearly half of the patients were deemed unsuitable for liver transplantation after assessment, raising the possibility of inappropriate and/or premature referrals by providers or of liberal screening practices of referred patients. The most common reason for ineligibility was that the patient was too well from a liver standpoint. This is supported by the observation that the mean MELD score in the study population was only 12.4. Although our centre does not subscribe to a minimal listing criterion, candidates are generally not listed if they have a MELD score below 14 unless they satisfy other exceptional criteria (e.g., hepatopulmonary syndrome, HCC within transplant criteria) in consideration of a lack of survival benefit in this patient group.¹⁴ Although our centre prescreens referred patients, we postulate that a substantial number of liver transplantation assessments could have been avoided through careful consideration of updated MELD scores and/or detailed knowledge of patients' medical comorbidities and psychosocial issues before assessment. In light of the high rate of ineligibility, it is clear that a substantial proportion of our centre's transplant referrals may be better suited to treatment at a general hepatology clinic. We postulate that a standardized transplant referral form prompting the referring provider to submit all updated pertinent information might facilitate the dissemination of clinical data from the referring provider to the transplantation program. Given the increased burden of HCC and end-stage liver disease, a growing demand for liver transplantation can be anticipated, and hence liver transplantation programs require strategies to systematically avert unnecessary assessments. Nonetheless, there may be potential benefits of an early

assessment for transplantation. Given that many etiologies of end-stage liver disease progress slowly, a transplant referral at the compensated stage of liver disease may permit transplantation programs to intervene earlier in patient care to avert morbidity and liver-related death. Furthermore, early referral may strengthen the provider-patient relationship between transplantologists and potential recipients by extension of the care period before transplantation. In addition, patients may benefit from a pre-emptive referral through an enhanced understanding of the surgery.

In the present study, 16.9% of declined patients were denied candidacy because of failure to complete an addiction rehabilitation program and/or demonstrate a longer period of sustained sobriety. At our centre, listing criteria for alcoholic liver disease includes a minimum of 6 months of abstinence, successful completion of an alcohol rehabilitation program and the presence of an adequate social support network. Our centre does not perform transplants in patients who actively use illicit substances, but we do not reject patients on the basis of marijuana and/or methadone use provided that social supports and medical compliance are demonstrated. Confirmation of completion of a rehabilitation program or ascertainment of the duration of sobriety by the referring physician before the resource-intensive liver transplantation assessment might prevent the need for assessment in some cases. However, details of the addiction history and relevant aspects of the patient's psychosocial wellbeing and psychiatric comorbidities often cannot be sufficiently evaluated without a face-to-face interview with the liver transplantation candidate, and this accounts for the liberal policy of assessment of such candidates. Moreover, a pre-emptive liver transplantation

Table 2. Model for end-stage liver disease score, stratified by patients' distance from the transplant centre

Distance from transplant centre, km	No.	MELD score, mean (SD) [range]
London, Ontario	20	12.3 (1.2) [7–26]
≤ 100	19	13.1 (1.2) [7–26]
101–200	81	12.3 (0.6) [6–29]
201–500	9	11.8 (1.8) [6–18]
501–1000	19	10.7 (1.2) [7–19]
1001–1500	10	16.6 (1.7) [9–32]
> 1500	8	11.1 (2.0) [6–17]

MELD = model for end-stage liver disease; SD = standard deviation.

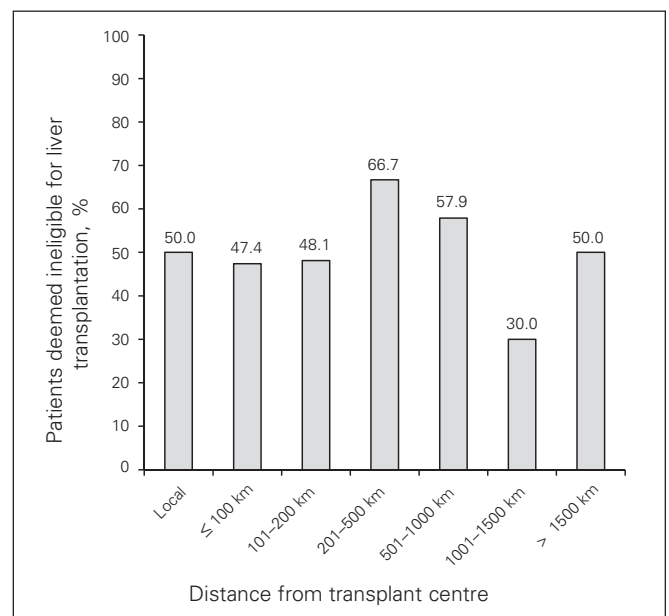


Fig. 4. Proportions of patients deemed ineligible for liver transplantation, stratified by their distance from the transplant centre.

assessment in this patient population, among others, can also provide patients with reinforcement for ongoing psychosocial treatment and additional insight into the nature of their addiction. A visit to the transplant centre where patients receive education on the extensive nature of the transplantation surgery might also serve as motivation for prolonged abstinence and offer the transplant team a greater opportunity to appraise long-term compliance. It should be noted that although no patients in our cohort had human immunodeficiency virus, positive patients would have been referred to an alternative centre, as our program does not presently perform liver transplantations in this population.

Our study suggests a need for cost-effectiveness and cost-utility data on the liver transplantation assessment. Such analyses would have to account for the substantial travel expenses and time off work incurred by accompanying family members during the liver transplantation evaluation. However, it is probable that there are unforeseen benefits on patient care following a liver transplantation assessment, and these benefits may be difficult to study or measure. Many patients, especially those from rural communities far from tertiary health facilities, may not otherwise have access to subspecialized care from a hepatologist or hepatobiliary surgeon, for example. Despite the fact that our centre previously determined that patients residing closer to our institution had improved access to liver transplantation,¹⁵ we found no association between distance of patients' primary residence from the transplant centre and MELD score or underlying liver disease in the present study. This observation suggests similarities in transplantation referral patterns between local and nonlocal referring providers, thus accounting for comparable rates of ineligibility of patients after transplantation assessment.

CONCLUSION

Further studies are required to explore the potential benefits of the liver transplantation assessment on patient care and clinical outcomes. There may also be theoretical advantages for transplantation centres to assess candidates early, although this remains unproven. Our analysis also indicates the need to better understand patient and referring provider satisfaction after the liver transplantation assessment, as this may impact referral decision-making. Furthermore, the practice patterns and settings of referring providers, including access to hepatobiliary expertise in their jurisdictions, undoubtedly require analytic consideration in the context of studying the utility of the transplantation assessment. In addition, more data are needed on optimal ways for transplantation programs to receive and screen referred patients and to best use the extensive resources required for transplantation assessments.

Competing interests: None declared.

Contributors: A. Arya, P. Marotta and N. Chandok designed the study. A. Arya acquired the data, which J. Uhanova and N. Chandok analyzed. A. Arya, R. Hernandez-Alejandro, P. Marotta and N. Chandok wrote the article. All authors reviewed the article and approved its publication.

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