

Referral to Liver Transplant: A National Survey from Portugal

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Keywords

Access · Selection · Barriers · Obstacles · Liver transplantation

Abstract

Introduction: The referral of patients with cirrhosis to liver transplant (LT) is a multi-stage, complex process. There is a lack of data on potential challenges to this process. We aimed to characterize challenges faced by Portuguese referring clinicians. **Methods:** This was a cross-sectional survey from Curry Cabral Hospital, Lisbon, Portugal. The survey was open for 90 days, from August to November 2024. The survey included 13 questions: characterization of participants with 5 questions and characterization of the process of referral to LT with 8 questions. **Results:** Overall, 56 clinicians responded to the survey (response rate of 46.7%). Their median (IQR) age was 38.1 (33.2–42.1) years. Their level of training was specialist grade for 47 (83.9%) and fellow or intern grade for 9 (16.1%) individuals. The responders were from 21 different hospitals in Portugal; 8 (38.1%) provided tertiary care and 2 (9.5%) were LT centers. Among responders, there was heterogeneity regarding the following topics: referring criteria to LT, liver-related prognostic scores, contact channels with the LT center, tests and visits part of the LT workup. Many of them suggested the following improvements to develop national or regional referral

criteria, to expedite communication with the LT team, to accelerate access to the tests or visits part of the LT workup, and to shorten the time to the first appointment with the LT team. **Conclusion:** Portuguese clinicians identified several challenges and improvements to the referral of patients with cirrhosis to LT. These findings may inform future strategies to streamline the referral to LT.

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Referenciação a transplante hepático: um inquérito nacional em Portugal

Palavras Chave

Acesso · Selecção · Barreiras · Obstáculos · Transplantação hepática

Resumo

Introdução: A referenciação de doentes com cirrose para transplante hepático (TH) é um processo complexo em várias fases. Faltam dados sobre potenciais desafios a este processo. Pretendeu-se caracterizar os desafios enfrentados pelos médicos referenciadores portugueses. **Métodos:** Tratou-se de um estudo transversal do Hospital Curry Cabral, Lisboa, Portugal. O inquérito esteve aberto

durante 90 dias, de agosto a novembro de 2024. O inquérito contou com 13 questões: caracterização dos participantes com 5 questões; e caracterização do processo de referência para LT com 8 questões.

Resultados: No geral, 56 médicos responderam ao inquérito (taxa de resposta de 46.7%). A idade mediana (IQR) foi de 38.1 (33.2–42.1) anos. O nível de formação foi: especialista para 47 (83.9%) e interno para 9 (16.1%) indivíduos. Os inquiridos eram de 21 hospitais diferentes em Portugal, 8 (38.1%) prestavam cuidados terciários e 2 (9.5%) eram centros de TH. Entre os inquiridos, verificou-se heterogeneidade em relação aos seguintes temas: critérios de referência para TH; índices prognósticos relacionadas com o fígado; canais de contacto com o centro de LT; testes e visitas parte da avaliação para LT. Muitos deles sugeriram as seguintes melhorias: desenvolver critérios de referência nacionais ou regionais; agilizar a comunicação com a equipa de LT; acelerar o acesso aos testes e visitas parte da avaliação para TH; e encurtar o tempo para a primeira consulta com a equipa de LT. **Conclusão:** Médicos portugueses identificaram vários desafios e melhorias na referência de doentes com cirrose para TH. Estes dados podem informar estratégias futuras para agilizar o encaminhamento para TH.

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Introduction

The proportion of patients referred for liver transplant (LT) has been found to be low in different geographies [1, 2]. Several barriers may delay or preclude timely referral to LT. These may be categorized as patient-related, practice-related, or provider-related [3].

The severity of liver disease and portal hypertension, hepatocellular carcinoma, and extrahepatic comorbidities have been established as primary factors to consider in LT candidacy [4, 5]. However, aspects such as patient frailty, access to addiction specialist support, financial hardship, or distance to the LT center remain difficult to weigh in decisions regarding referral to transplant [6].

Additionally, there is perceived variability regarding LT practices among centers [7, 8]. For example, different centers may be more or less selective regarding patients with alcohol-associated liver disease, especially those with alcoholic hepatitis, or liver cancer (e.g., hepatocellular carcinoma, cholangiocarcinoma, liver metastasis from colorectal cancer). Moreover, organ availability may change substantially over time, with geography, or with

country-specific legislation on donation. Finally, living donor programs are available in certain regions but less so in others. Thus, there remains an almost permanent imbalance between the need for and the availability of organs for transplant [9]. At a time of aging populations and strained healthcare systems across the globe, this known organ scarcity surely impacts access to LT [6].

In Portugal and Europe, there is a paucity of data regarding challenges to the process of referral to LT [10, 11]. However, aggregate LT-related outcomes have been similarly improving over time in almost every European region [10, 11]. In this context, we aimed to identify possible modifiable factors that may influence the referral of patients with cirrhosis to LT in Portugal.

Materials and Methods

Design, Setting, and Participants

This was a cross-sectional survey developed at Transplant Unit, Curry Cabral Hospital, Lisbon, Portugal, to assess potential obstacles to referral of patients with cirrhosis to LT in the country. In Portugal, LT is provided by the Public National Health System at 3 hospitals. The Health Ministry budget covers all expenses related to surgery, perioperative care, and long-term care. The Curry Cabral Hospital runs the largest LT program in the country with >2,500 procedures performed since 1992 [11]. The Portuguese legislation on organ donation makes every citizen a possible donor unless one has previously stated formally otherwise.

The survey was open to responses for 90 days, from August to November 2024. Participation was anonymous and voluntary. Individual consent was implied by survey completion. Given that no patient data was involved, local ethics approval was not deemed necessary.

The survey was developed and disseminated using the online platform Microsoft Forms[®]. The survey included 13 questions with the following categories: characterization of participants with 5 questions; characterization of the process of referral to LT with 8 questions (online suppl. File 1; for all online suppl. material, see <https://doi.org/10.1159/000545593>). The number of questions was kept short to minimize response time. Questions were mostly of a closed model with multiple answers allowed.

The survey was pilot tested for correction, comprehension, and response time among 3 elements belonging to the Transplant Unit's Medical Team. After minor adjustments, the survey was sent to 120 potential responders by email. All potential responders were clinicians of different levels of training known to have referred patients for LT

before. This was intended to better capture real challenges faced in clinical practice. The reporting of this survey followed the principles of the CROSS checklist [12].

Statistical Analysis

A descriptive analysis was performed using IBM SPSS® Version 19.0 (IBM Corp., Armonk, NY, USA). Continuous variables were described by median and interquartile range (IQR). Categorical variables were described by absolute frequency and percentage. Missing data across all variables were 1.4% across all values.

Results

Characterization of Participants

Overall, 56 clinicians responded to the survey (response rate of 46.7%). The median (IQR) response time was 3.5 (2.8–4.4) min. The median (IQR) age of responders was 38.1 (33.2–42.1) years. Their core specialties were the following: gastroenterology for 31 (55.4%), internal medicine for 17 (30.4%), surgery for 4 (7.1%), and other for 4 (7.1%) individuals. The level of training of responders was the following: specialist grade for 47 (83.9%) and fellow or intern grade for 9 (16.1%) individuals.

The monthly average number of patients with cirrhosis treated by clinicians was characterized as follows: <5 for 11 (19.6%), 5–10 for 5 (8.9%), 10–15 for 10 (17.9%), 15–20 for 12 (21.4%), and >20 for 18 (32.1%) individuals. The responders were from 21 different hospitals in Portugal. Their geographical distribution along the country was the following: 6 (28.6%) in the Northern regions, 10 (47.6%) in the Central regions, 3 (14.3%) in the Southern regions, and 2 (9.5%) in the Azores Islands. Among these hospitals, 8 (38.1%) were considered to provide tertiary clinical care and 2 (9.5%) were LT centers.

Characterization of Referral to the LT Team

Most responders referred patients for LT if there was difficulty to control portal hypertension (89.3%), hepatocellular carcinoma (82.1%), or worsening liver-related prognostic scores (75.0%) (Table 1). However, less than 2 fifths of clinicians referred patients for LT due to poor quality of life (37.5%).

The liver-related prognostic scores more frequently used to refer patients for LT were the following: Model for End-Stage Liver Disease with sodium correction (MELD-Sodium) (70.9%); Child-Pugh (67.3%); Chronic Liver Failure (CLIF-C) for Acute Decompensation (AD) or Acute-on-Chronic Liver Failure (ACLF) (50.9%); and

biochemical MELD (43.6%). Additionally, just less than one fifth of clinicians (16.4%) reported using the newly developed MELD 3.0 score.

Most responders used the following criteria to preclude or delay referral to LT: out of criteria malignancy (75.0%); active alcohol intake (67.9%); or perceived psychological, social, or financial obstacles (58.9%). Nevertheless, only up to a quarter of clinicians considered a MELD score <15 (25.0%) or progressive sarcopenia (21.4%) as criteria to preclude or delay referral to LT.

Most responders (81.5%) reported that the first LT appointment usually occurred less than 6 weeks after their initial referral. Moreover, most clinicians stated that their preferred methods of contact with the LT team were either personal contact with LT doctors (58.2%) or institutional email (47.3%). Yet, less than a quarter of responders used alternative methods of contact with the LT team, namely, the institutional telephone or fax machine or an institutional letter ($\leq 20.0\%$).

When asked about what could improve the process of referral to LT, the most common suggestions made by clinicians were the following: availability of regional or national formal referral criteria (79.2%); easier communication with LT doctors (52.8%); faster access to diagnostic tests part of the transplant workup (49.1%); and faster access to the first appointment with the LT team (35.8%).

Regarding transplant workup tests or visits requested by referring clinicians before the initial referral to LT, the most frequently reported were the following: liver computed tomography or magnetic resonance (92.4%); gastroscopy (81.1%); electrocardiogram (79.2%); colonoscopy (75.5%); and transthoracic echocardiogram (75.5%). Notably, only less than a quarter of responders requested nutrition (22.6%), dental (9.4%), or dermatology (3.8%) appointments before referring patients for LT.

When asked about which vaccines to consider before the referral to LT, most responders reported the following: hepatitis B (85.5%), influenza (76.4%), hepatitis A (72.7%), *Streptococcus pneumoniae* (72.7%), and COVID-19 (72.7%). Differently, only less than a fifth of clinicians recommended the varicella-zoster vaccine (16.4%). Complete data on all variables analyzed are depicted in Table 1.

Discussion

Main Findings and Comparisons with Literature

Using the responses from clinicians across Portugal, we described heterogeneity regarding the following issues in the referral of patients with cirrhosis to LT: referring

Table 1. Characteristics of referral to LT in Portugal

Questions	Responders, n (%)
Which criteria do you use to refer patients with cirrhosis for the LT team?	n = 56
Difficult to control portal hypertension	50 (89.3)
Hepatocellular carcinoma	46 (82.1)
Prognostic scores (e.g., Child-Pugh, MELD, or CLIF-C AD/ACLF)	42 (75.0)
Poor quality of life (e.g., pruritus or unable to work or study)	21 (37.5)
Other	4 (7.1)
Which prognostic scores do you use to refer patients with cirrhosis for the LT team?	n = 55
MELD-Sodium	39 (70.9)
Child-Pugh	37 (67.3)
CLIF-C AD/ACLF	28 (50.9)
MELD (biochemical)	24 (43.6)
MELD 3.0	9 (16.4)
Other	1 (1.8)
Which criteria do you use to preclude or delay the referral of patients with cirrhosis to the LT team?	n = 56
Out of criteria liver malignancy (e.g., tumor size, vascular invasion, or extrahepatic involvement)	42 (75.0)
Active alcohol intake	38 (67.9)
Perceived psychological, social, or financial obstacles	33 (58.9)
MELD (biochemical) <15	14 (25.0)
Progressive sarcopenia	12 (21.4)
How much time on average does it take from referral to first appointment with the LT team?	n = 54
<2 weeks	13 (24.1)
2–4 weeks	18 (33.3)
4–6 weeks	13 (24.1)
6–8 weeks	4 (7.4)
>8 weeks	6 (11.1)
How do you use to contact the LT team for any referral?	n = 55
Personal contact with transplant doctors	32 (58.2)
Institutional email	26 (47.3)
Institutional telephone/fax	11 (20.0)
Institutional letter	8 (14.5)
Other	4 (7.3)
What could improve the referral of patients with cirrhosis to the LT team?	n = 53
Availability of regional or national formal referral criteria	42 (79.2)
Easier communication with transplant doctors	28 (52.8)
Faster access to diagnostic tests part of the transplant workup	26 (49.1)
Faster access to the first appointment at the LT center	19 (35.8)
Other	1 (1.9)
Which tests do you request as part of the transplant workup at your hospital before referral to the LT team?	n = 53
Liver computed tomography or magnetic resonance	49 (92.4)
Gastroscopy	43 (81.1)
Electrocardiogram	42 (79.2)
Colonoscopy	40 (75.5)
Transthoracic echocardiogram	40 (75.5)
Lung spirometry	35 (66.0)
Thorax computed tomography	29 (54.7)
Prostate ultrasound	28 (52.8)
Chest X-ray	28 (52.8)
Mammogram	25 (47.2)
Thyroid ultrasound	25 (47.2)
HOLTER	19 (35.8)
Ovaries/uterus ultrasound	19 (35.8)
Nutrition appointment	12 (22.6)
Dental appointment	5 (9.4)
Dermatology appointment	2 (3.8)

Table 1 (continued)

Questions	Responders, n (%)
Which vaccines do you consider for patients before referral to the LT team?	n = 55
Hepatitis B	47 (85.5)
Influenza	42 (76.4)
Hepatitis A	40 (72.7)
Streptococcus pneumoniae	40 (72.7)
COVID-19	40 (72.7)
Varicella-zoster	9 (16.4)
Only those in the mandatory National Vaccination Program	7 (12.7)

MELD, Model for End-Stage Liver Disease; CLIF-C AD/ACLF, Chronic Liver Failure Consortium Acute Decompensation/Acute-on-Chronic Liver Failure.

criteria to LT; liver-related prognostic scores; contact channels with the LT center; and tests and visits part of the LT workup. Many of the responders suggested the following improvements to this process: to develop national or regional referral criteria, to expedite communication with the LT team, to accelerate access to the tests or visits part of the LT workup, and to shorten the time to the first appointment with the LT team.

Our survey attempted to better characterize the process of referral to LT in Portugal. We were able to capture answers on some topics about this process from 56 clinicians, a reasonably good response rate (46.7%) [3, 13]. Most of them were experienced doctors as they had a specialist grade (83.9%) and were used to see >10 patients with cirrhosis per month on average (71.4%). These clinicians worked at 21 different hospitals across the country, encompassing almost all regions, and including 2 of the 3 existent regional LT centers. Considering all these demographic features, we believe the survey was successful in capturing data from experienced providers referring patients with cirrhosis to LT across the nation [3, 14].

Regarding the criteria used to refer patients with cirrhosis to the LT team, our data suggested that clinicians were likely referring these patients based on some of their most common complications, namely, portal hypertension, hepatocellular carcinoma, or progressive chronic liver dysfunction [6]. Moreover, data also implied that responders were cautious about referring patients with any potential contra-indications for LT, namely, out of criteria liver malignancy, active alcohol intake, or perceived psychological, social, or financial obstacles [1–3, 6]. Nonetheless, we could speculate that patients with cirrhosis without the previously described complications but with poor quality of life may have been under-referred to the LT team. Examples of patients fitting into this description

could be those with primary biliary cholangiopathy or primary sclerosing cholangiopathy living with a preserved liver function, no portal hypertension or malignancy, but with incapacitating pruritus [6, 15]. Additionally, data also suggested that clinicians may have been underestimating the impact of progressive sarcopenia on these patients' prospects of getting an LT [6, 16]. These characteristics are not usually captured by the MELD score, thus patients may need to be referred to LT albeit their MELD score being <15. Overall, these findings suggest that further education on topics such as quality of life metrics and sarcopenia in patients with cirrhosis being potential candidates for LT may be needed.

Regarding psychological, social, or financial obstacles, which have been reported to negatively impact referral to LT in countries such as the USA, the situation in Portugal may be different [1–3]. As the Portuguese state covers all expenses related to LT, financial hardship may not be a limiting factor for LT access as in healthcare systems based on private health insurance. Furthermore, patients with alcohol-use disorder can access free of charge, at their discretion or post-clinician-initiated referral, a nationwide network of addiction treatment teams before and after LT [17].

Concerning the use of liver-related prognostic scores in referring patients for LT, most responders claimed to apply MELD-Sodium or Child-Pugh scores. While CLIF-C AD/ACLF was in use by many clinicians, only a minority were already using the newest version of the MELD score, the one that takes into account gender and serum albumin (MELD 3.0) [18–20]. While biochemical MELD has shown to help decrease waitlist mortality overtime in many jurisdictions, newly developed prognostic scores may further help titrate the risk of death without LT. CLIF-C scores have improved 28-day overall mortality prediction, especially for patients with ACLF, as MELD

may underestimate short-term mortality among these ones [21]. For all patients on the waitlist, MELD 3.0 has shown improved discrimination for 90-day waitlist mortality in the USA, but it may require further validation in different settings [20]. Overall, liver-related prognostic scores have been evolving worldwide, but additional validation studies may be key for expanding their use in clinical practice in Portugal and Europe.

When asked about what could improve the process of referral of patients with cirrhosis to the LT team, most responders highlighted the need to make available national or regional formal referral criteria. In fact, national or regional guidelines on LT candidacy are still lacking in Portugal, which leaves clinicians with no option but to follow published European rules [6]. While the latter may suffice, many specificities of the Portuguese process of donation and transplant candidacy could be better detailed in an easily available national or regional document, potentially promoted by the competent national authority, the Portuguese Institute of Blood and Transplantation [10, 11].

Responders also advocated improving the communication with the LT team and getting faster access to the first appointment in the LT center. These claims highlight how clinicians working outside the LT center seem to value more informal and easier contact with the LT team. Thus, measures to ease the contact barriers between the referring clinicians and the LT team may streamline the overall process of referral to LT. Options to foster more direct and faster mutual engagement between referring and transplant doctors in multidisciplinary meetings, including the Transplant Committee, should be explored [3, 22, 23]. This could be achieved either by in-person encounters or by using modern telemedicine solutions.

Additionally, clinicians raised the need for better access to the tests and visits more commonly included in the LT workup. While most responders were requesting many of such tests before the initial referral to the LT center, there might be challenges in performing these tests as early as possible to avoid delaying the referral to LT [24]. In strained healthcare systems, like the Portuguese, some tests may take longer than expected to be performed, thus patients may see their appointments being postponed due to such delays. Potentially, specific channels dedicated to potential transplant candidates being followed as outpatients may be open at different institutions to improve these patients' timely access to these tests [25].

Interestingly, a minority of clinicians requested nutrition, dental, or dermatology visits before the referral to LT.

Both obesity and sarcopenia may pose additional risks to patients undergoing LT; therefore, timely interventions targeting these conditions may help improve these patients' outcomes [26]. Dental conditions may be a source of additional morbidity in patients with cirrhosis; therefore, their timely diagnosis and treatment, especially before transplant, is advised [27]. Malignant skin tumors may constitute a contra-indication for LT. Moreover, post-transplant immunosuppression may further increase the risk of skin neoplasms; thus, skin examination is important to avoid misdiagnosing potentially worrisome lesions [28]. Taking all these data into consideration, further education on the topics of nutritional, dental, and skin health among patients with cirrhosis may be warranted.

Limitations and Strengths

The results of our study need to be interpreted in the context of the following limitations. First, this was an online survey targeting clinicians used to refer patients with cirrhosis to LT; therefore, selection bias may have occurred. While potential responders were contacted only via email, the response rate was reasonably good. Moreover, we obtained answers from doctors working at 21 different institutions. This diverse survey turnout may have helped minimize the selection bias.

Second, this study was conducted in Portugal, which may have limited its generalizability to other jurisdictions. In fact, transplant practices vary widely among countries; therefore, our data may mostly reflect Portuguese clinicians' practices.

Third, the scope of this survey was largely restricted to provider-related aspects of the process of referral to LT. Consequently, there were surely many topics that may influence the overall process of referral to LT that were not covered in this study [3, 29].

Albeit these limitations, we believe our findings may add to the literature that characterizes the obstacles to the process of referral to LT. Specifically, it may inform national authorities and hospitals about some of the potential challenges faced by clinicians in a real-world scenario. Finally, it may help generate debate about the strategies to overcome these obstacles. Future studies may help analyze further variables influencing the process of referral to LT, including more at patient and practice levels [29, 30].

Conclusions

Portuguese clinicians referring patients with cirrhosis to LT reported several challenges in their daily practice. Many of them suggested the following improvements: to

develop national or regional referral criteria, to expedite communication with the LT team, to accelerate access to the tests or visits part of the LT workup, and to shorten the time to the first appointment with the LT team.

Acknowledgment

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Statement of Ethics

Given that no patient data were involved, local ethics approval was not deemed necessary. Participation was anonymous and voluntary. Individual consent was implied by survey completion.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Data Availability Statement

The data that support the findings of this study are not publicly available due to confidentiality but are available from the corresponding author upon reasonable request.

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